

SUMMARY

[0011] The present [inventiondisclosure](#) provides T cell receptors (TCRs) that were generated against a MAGE-A4 peptide antigen in the context of MHC (HLA-A2). The unique TCR sequences identified have shown specific binding to the small peptide MAGE-A4 presented in the groove of an HLA molecule and exhibited activation of T cells in a reporter assay. Furthermore, the TCRs of the [inventiondisclosure](#) do not cross-react with other “like” peptides.

[0012] Accordingly, in one aspect, the present [inventiondisclosure](#) 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 melanoma-associated antigen 4 (MAGE-A4) peptide comprising the amino acid sequence of KVLEHVVRV (SEQ ID NO:609) (MAGE-A4 286-294), 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 Formula I:

N₁-N₂-N₃-N₄-N₅-N₆-N₇-N₈-N₉-N₁₀-N₁₁-N₁₂-N₁₃-N₁₄-N₁₅ (Formula I), wherein
N₁ is a non-polar amino acid;
N₂, which may or may not be present, is Val;
N₃ is Tyr, Gly, Leu, Val, Glu, Met, Ala, or Phe;
N₄, which may or may not be present, is Arg, Glu, Ser, Asn, Gln, Lys, Asp, Gly, or Met;
N₅, which may or may not be present, is Ser, Arg, Glu, Leu, Ala, Asp, Pro, Met, Gly or Lys;
N₆, which may or may not be present, is Ala, Asp, Gly, Ser, Val, Pro, Leu, Tyr, or Thr;
N₇ is Thr, Pro, Ser, Glu, Asp, Trp, Arg, Asn, Ile, Gln, or Leu;
N₈ is His, Trp, Thr, Lys, Tyr, or Ala;
N₉ is Asn, Gly, Lys, Ile, Ser, or Arg;
N₁₀, which may or may not be present, is Gln, Lys, Gly, Thr, Leu, Asp, or Ser;
N₁₁, which may or may not be present, is Phe, Asn, Thr, Tyr, Ala, Leu, Met or Glu;
N₁₂, which may or may not be present, is Lys, Phe, Tyr, or Asp;
N₁₃, which may or may not be present, is Lys or Gly;
N₁₄, which may or may not be present, is Thr, Leu, or Tyr; and
N₁₅ is Tyr, Gln, Ile, Thr, Val, or Arg.

[0013] In one [embodimentexample](#), N₁ is Ala, Ile, or Gly.

[0013a] In another aspect, the present disclosure refers to a T cell receptor (TCR) that binds specifically to an HLA-A2 presented cancer testis antigen melanoma-associated antigen 4 (MAGE-A4) peptide comprising the amino acid sequence of KVLEHVVRV (SEQ ID NO:609) (MAGE-A4 286-294), wherein the TCR comprises a beta chain variable domain comprising complementary determining region (CDR)3, wherein the CDR3 comprises the amino acid sequence of Formula II:

$$\underline{N_1-N_2-N_3-N_4-N_5-N_6-N_7-N_8-N_9-N_{10}-N_{11}-N_{12}-N_{13}-N_{14}-N_{15}-N_{16}-N_{17}-N_{18}} \text{ (Formula II), wherein}$$

N_1 is Ala or Ser;

N_2 is Ala, Ser, or Thr;

N_3 is Ser, Gly, or Trp;

N_4 is Leu, Tyr, Trp, Asp, Phe, Gly, Pro, or His;

N_5 , which may or may not be present, is Gly or Asp;

N_6 , which may or may not be present, is Phe or Arg;

N_7 , which may or may not be present, is Trp, Phe, Asp, Pro, Tyr, Gly, Thr, Ser, or Val;

N_8 , which may or may not be present, is Pro, Arg, Asp, Tyr, Gln, Asn, or Gly;

N_9 , which may or may not be present, is Asp;

N_{10} , which may or may not be present, is Arg;

N_{11} , which may or may not be present, is Gly, Ala, or Thr;

N_{12} is Ser, Trp, Thr, Gly, Val, Leu, Arg, Met, Tyr, or Gln;

N_{13} , which may or may not be present, is Gly;

N_{14} , which may or may not be present, is Asn, Asp, Gly, Thr, Pro, Gln, or His;

N_{15} , which may or may not be present, is Thr, Ser, Glu, Asn, Tyr, Gln, Asp, or Pro;

N_{16} , which may or may not be present, is Glu, Pro, Lys, Thr, Ala, Gly, or Gln;

N_{17} , which may or may not be present, is Ala, Leu, Ile, Tyr, or Gln; and

N_{18} is Phe, His, Tyr, or Thr.

[0013b] In another aspect, the present disclosure refers to 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 MAGE-A4-associated disease or disorder.

[0013c] In another aspect, the present disclosure refers to a polynucleotide molecule encoding a T cell receptor (TCR), wherein the TCR binds specifically to an HLA-A2 presented cancer testis antigen melanoma-associated antigen 4 (MAGE-A4) peptide comprising the amino acid sequence of KVLEHVVRV (SEQ ID NO:609) (MAGE-A4 286-294), wherein the TCR has a property selected from the group consisting of: (a) does not bind to cells expressing predicted off-target peptides as determined by luminescence assay; (b) activates a T cell response about two times greater than a patient-derived MAGE-A4-specific TCR as determined by a TCR-mediated T cell signaling luminescent bioassay; and (c) activates a T cell response about two times greater than an affinity-matured (e.g., by phage display) MAGE-A4-specific TCR as determined by a TCR-mediated T cell signaling luminescent bioassay.

[0013d] 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 MAGE-A4-associated disease or disorder.

[0013h] In another aspect, the present disclosure refers to a T cell receptor (TCR) that binds specifically to an HLA-A2 presented cancer testis antigen melanoma-associated antigen 4 (MAGE-A4) peptide comprising the amino acid sequence of GVYDGREHTV (SEQ ID NO:612) (MAGE-A4 230-239), wherein the TCR comprises a complementary determining region 3 (CDR3) contained within an alpha chain variable domain of any one of SEQ ID NOs: 620, 636, 652, 668, 684, 700, 716, 732, 748, 764, 780, 796, 812, 828, 844, and 860.

[0013i] In another aspect, the present disclosure refers to a T cell receptor (TCR) that binds specifically to an HLA-A2 presented cancer testis antigen melanoma-associated antigen 4 (MAGE-A4) peptide comprising the amino acid sequence of GVDGREHTV (SEQ ID NO:612) (MAGE-A4 230-239), wherein the TCR comprises a complementary determining region 3 (CDR3) contained within a beta chain variable domain of any one of SEQ ID NOs: 628, 644, 660, 676, 692, 708, 724, 740, 756, 772, 788, 804, 820, 836, 852, and 868.

[0013j] In another aspect, the present disclosure refers to the use of the TCR as disclosed herein, the pharmaceutical composition as disclosed herein, or the isolated cell as disclosed herein in the manufacture of a medicament for treating a subject having a MAGE-A4-associated disease or disorder.

[0013k] In another aspect, the present disclosure refers to a polynucleotide molecule encoding a T cell receptor (TCR), wherein the TCR binds specifically to an HLA-A2 presented cancer testis antigen melanoma-associated antigen 4 (MAGE-A4) peptide comprising the amino acid sequence of GVDGREHTV (SEQ ID NO:612) (MAGE-A4 230-239), wherein the TCR has a property selected from the group consisting of: (a) does not bind to cells expressing predicted off-target peptides as determined by a luminescence assay; (b) does not bind to cells expressing predicted off-target peptides as determined by a flow cytometry assay; (c) activates a T cell response about two times greater than a patient-derived MAGE-A4-specific TCR as determined by a TCR-mediated T cell signaling luminescent bioassay; and (d) activates a T cell response about two times greater than an affinity-matured (e.g., by phage display) MAGE-A4-specific TCR as determined by a TCR-mediated T cell signaling luminescent bioassay.

[0013l] In another aspect, the present disclosure refers to the use of the cell as disclosed herein in the manufacture of a medicament for treating a subject having a MAGE-A4-associated disease or disorder.

[0013m] In another aspect, the present disclosure refers to a TCR that competes for binding to the TCR as disclosed herein.

[0013n] In another aspect, the present disclosure refers to a pharmaceutical composition comprising the TCR as disclosed herein and a pharmaceutically acceptable carrier or diluent.

[0013o] In another aspect, the present disclosure refers to an isolated cell presenting the TCR as disclosed herein.

[0013p] In another aspect, the present disclosure refers to an isolated polynucleotide molecule comprising a polynucleotide sequence that encodes an alpha chain variable domain of the TCR as disclosed herein.

[0013q] In another aspect, the present disclosure refers to an isolated polynucleotide molecule comprising a polynucleotide sequence that encodes a beta chain variable domain of the TCR as disclosed herein.

[0013r] In another aspect, the present disclosure refers to a vector comprising the polynucleotide molecule as disclosed herein.

[0013s] In yet another aspect, the present disclosure refers to an isolated cell expressing the vector as disclosed herein.

[0014] In another [aspectexample](#), the present [inventiondisclosure](#) provides isolated T cell receptor (TCR) that binds specifically to an HLA-A2 presented cancer testis antigen melanoma-associated antigen 4 (MAGE-A4) peptide comprising the amino acid sequence of KVLEHVVRV (SEQ ID NO:609) (MAGE-A4 286-294), wherein the TCR comprises a beta chain variable domain comprising complementary determining region (CDR)3,, wherein the CDR3 comprises the amino acid sequence of Formula II:

$N_1-N_2-N_3-N_4-N_5-N_6-N_7-N_8-N_9-N_{10}-N_{11}-N_{12}-N_{13}-N_{14}-N_{15}-N_{16}-N_{17}-N_{18}$ (Formula II),

wherein

N_1 is Ala or Ser;

N_2 is Ala, Ser, or Thr;

N_3 is Ser, Gly, or Trp;

N_4 is Leu, Tyr, Trp, Asp, Phe, Gly, Pro, or His;

N_5 , which may or may not be present, is Gly or Asp;

N_6 , which may or may not be present, is Phe or Arg;

N_7 , which may or may not be present, is Trp, Phe, Asp, Pro, Tyr, Gly, Thr, Ser,

or Val;

N_8 , which may or may not be present, is Pro, Arg, Asp, Tyr, Gln, Asn, or Gly;

N_9 , which may or may not be present, is Asp;

N_{10} , which may or may not be present, is Arg;

N_{11} , which may or may not be present, is Gly, Ala, or Thr;

N_{12} is Ser, Trp, Thr, Gly, Val, Leu, Arg, Met, Tyr, or Gln;

N_{13} , which may or may not be present, is Gly;

N_{14} , which may or may not be present, is Asn, Asp, Gly, Thr, Pro, Gln, or His;

N_{15} , which may or may not be present, is Thr, Ser, Glu, Asn, Tyr, Gln, Asp, or

Pro;

N_{16} , which may or may not be present, is Glu, Pro, Lys, Thr, Ala, Gly, or Gln;

N_{17} , which may or may not be present, is Ala, Leu, Ile, Tyr, or Gln; and

N_{18} is Phe, His, Tyr, or Thr.

[0015] In one [embodimentexample](#), 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 2 and the CDR2 independently

comprises any one of the alpha chain variable domain CDR2 amino acid sequences set forth in Table 2.

[0016] In another [embodimentexample](#), 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 2 and the CDR2 independently comprises any one of the beta chain variable domain CDR2 amino acid sequences set forth in Table 2.

[0017] 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.

[0018] In one [embodimentexample](#), 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 4; and beta chain variable domain CDR1, CDR2 and CDR3 contained within any one of the beta chain variable domain sequences listed in Table 4.

[0019] In another [embodimentexample](#), 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 4.

[0020] In yet another [embodimentexample](#), 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 4.

[0021] In one [embodimentexample](#), 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 4; 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 4.

[0022] In one [embodimentexample](#), 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, 17, 33, 49, 65, 81, 97, 113, 129, 145, 161, 177, 193, 209, 225, 241, 257, 273, 289, 305, 321, 337, 353, 369, 385, 401, 417, 433, 449, 465, 481, 497, 513, 529, 545, 561, 577, and 593; (b) an alpha chain variable domain CDR2 domain having an amino acid sequence selected from the group consisting of SEQ ID NOs: 2, 18, 34, 50, 66, 82, 98, 114, 130, 146,

162, 178, 194, 210, 226, 242, 258, 274, 290, 306, 322, 338, 354, 370, 386, 402, 418, 434, 450, 466, 482, 498 514, 530, 546, 562, 578, and 594; (c) an alpha chain variable domain CDR3 domain having an amino acid sequence selected from the group consisting of SEQ ID NOs: 3, 19, 35, 51, 67, 83, 99, 115, 131, 147, 163, 179, 195, 211, 227, 243, 259, 275, 291, 307, 323, 339, 355, 371, 387, 403, 419, 435, 451, 467, 483, 499, 515, 531, 547, 563, 579, and 595; (d) a beta chain variable domain CDR1 having an amino acid sequence selected from the group consisting of SEQ ID NOs: 9, 25, 41, 57, 73, 89, 105, 121, 137, 153, 169, 185, 201, 217, 233, 249, 265, 281, 297, 313, 329, 345, 361, 377, 393, 409, 425, 441, 457, 473, 489, 505, 521, 537, 553, 569, 585, and 601; (e) a beta chain variable domain CDR2 having an amino acid sequence selected from the group consisting of SEQ ID NOs: 10, 26, 42, 58, 74, 90, 106, 122, 138, 154, 170, 186, 202, 218, 234, 250, 266, 282, 298, 314, 330, 346, 362, 378, 394, 410, 426, 442, 458, 474, 490, 506, 522, 538, 554, 570, 586, and 602; and (f) a beta chain variable domain CDR3 having an amino acid sequence selected from the group consisting of SEQ ID NOs: 11, 27, 43, 59, 75, 91, 107, 123, 139, 155, 171, 187, 203, 219, 235, 251, 267, 283, 299, 315, 331, 347, 363, 379, 395, 411, 427, 443, 459, 475, 491, 507, 523, 539, 555, 571, 587, and 603.

[0023] In one [embodimentexample](#), 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: 7/15, 23/31, 39/47, 55/63, 71/79, 87/95, 103/111, 119/127, 135/143, 151/159, 167/175, 183/191, 199/207, 215/223, 231/239, 247/255, 263/271, 279/287, 295/303, 311/319, 327/335, 343/351, 359/367, 375/383, 391/399, 407/415, 423/431, 439/447, 455/463, 471/479, 487/495, 503/511, 519/527, 535/543, 551/559, 567/575, 583/591, and 599/607.

[0024] In one [embodimentexample](#), the TCR comprises CDR sequences contained within an alpha chain variable domain/beta chain variable domain amino acid sequence pair selected from the group consisting of SEQ ID NOs: 7/15, 23/31, 39/47, 55/63, 71/79, 87/95, 103/111, 119/127, 135/143, 151/159, 167/175, 183/191, 199/207, 215/223, 231/239, 247/255, 263/271, 279/287, 295/303, 311/319, 327/335, 343/351, 359/367, 375/383, 391/399, 407/415, 423/431, 439/447, 455/463, 471/479, 487/495, 503/511, 519/527, 535/543, 551/559, 567/575, 583/591, and 599/607.

[0025] In another [embodimentexample](#), 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: 87/31, 23/95, 231/607, 231/223, 231/591, 231/255, 231/271, 231/79, 231/47, 231/399, 599/239, 599/223, 599/591, 599/255, 599/271, 599/79, 599/47,

599/399, 215/239, 215/607, 215/591, 215/255, 215/271, 215/79, 215/47, 215/399, 583/239, 583/607, 583/223, 583/255, 583/271, 583/79, 583/47, 583/399, 247/239, 247/607, 247/223, 247/591, 247/271, 247/79, 247/47, 247/399, 263/239, 263/607, 263/223, 263/591, 263/255, 263/79, 263/47, 263/399, 71/239, 71/607, 71/223, 71/591, 71/255, 71/271, 71/47, 71/399, 39/239, 39/607, 39/223, 39/591, 39/255, 39/271, 39/79, 39/399, 391/239, 391/607, 391/223, 391/591, 391/255, 391/271, 391/79, 391/47, 439/127, 439/319, 439/287, 439/15, 439/111, 439/383, 439/191, 439/511, 439/527, 439/559, 439/207, 119/447, 119/319, 119/287, 119/15, 119/111, 119/383, 119/191, 119/511, 119/527, 119/559, 119/207, 311/447, 311/127, 311/287, 311/15, 311/111, 311/383, 311/191, 311/511, 311/527, 311/559, 311/207, 279/447, 279/127, 279/319, 279/15, 279/111, 279/383, 279/191, 279/511, 279/527, 279/559, 279/207, 7/447, 7/127, 7/319, 7/287, 7/111, 7/383, 7/191, 7/511, 7/527, 7/559, 7/207, 103/447, 103/127, 103/319, 103/287, 103/15, 103/383, 103/191, 103/511, 103/527, 103/559, 103/207, 375/447, 375/127, 375/319, 375/287, 375/15, 375/111, 375/191, 375/511, 375/527, 375/559, 375/207, 183/447, 183/127, 183/319, 183/287, 183/15, 183/111, 183/383, 183/511, 183/527, 183/559, 183/207, 503/447, 503/127, 503/319, 503/287, 503/15, 503/111, 503/383, 503/191, 503/527, 503/559, 503/207, 519/447, 519/127, 519/319, 519/287, 519/15, 519/111, 519/383, 519/191, 519/511, 519/559, 519/207, 551/447, 551/127, 551/319, 551/287, 551/15, 551/111, 551/383, 551/191, 551/511, 551/527, 551/207, 199/447, 199/127, 199/319, 199/287, 199/15, 199/111, 199/383, 199/191, 199/511, 199/527, and 199/559.

[0026] In another [embodiment example](#), the TCR comprises the CDR sequences contained within an alpha chain variable domain/beta chain variable domain amino acid sequence pair selected from the group consisting of SEQ ID NOs: 87/31, 23/95, 231/607, 231/223, 231/591, 231/255, 231/271, 231/79, 231/47, 231/399, 599/239, 599/223, 599/591, 599/255, 599/271, 599/79, 599/47, 599/399, 215/239, 215/607, 215/591, 215/255, 215/271, 215/79, 215/47, 215/399, 583/239, 583/607, 583/223, 583/255, 583/271, 583/79, 583/47, 583/399, 247/239, 247/607, 247/223, 247/591, 247/271, 247/79, 247/47, 247/399, 263/239, 263/607, 263/223, 263/591, 263/255, 263/79, 263/47, 263/399, 71/239, 71/607, 71/223, 71/591, 71/255, 71/271, 71/47, 71/399, 39/239, 39/607, 39/223, 39/591, 39/255, 39/271, 39/79, 39/399, 391/239, 391/607, 391/223, 391/591, 391/255, 391/271, 391/79, 391/47, 439/127, 439/319, 439/287, 439/15, 439/111, 439/383, 439/191, 439/511, 439/527, 439/559, 439/207, 119/447, 119/319, 119/287, 119/15, 119/111, 119/383, 119/191, 119/511, 119/527, 119/559, 119/207, 311/447, 311/127, 311/287, 311/15, 311/111, 311/383, 311/191, 311/511, 311/527, 311/559, 311/207, 279/447, 279/127, 279/319, 279/15, 279/111, 279/383, 279/191, 279/511, 279/527, 279/559, 279/207, 7/447, 7/127, 7/319, 7/287, 7/111, 7/383, 7/191, 7/511, 7/527,

7/559, 7/207, 103/447, 103/127, 103/319, 103/287, 103/15, 103/383, 103/191, 103/511, 103/527, 103/559, 103/207, 375/447, 375/127, 375/319, 375/287, 375/15, 375/111, 375/191, 375/511, 375/527, 375/559, 375/207, 183/447, 183/127, 183/319, 183/287, 183/15, 183/111, 183/383, 183/511, 183/527, 183/559, 183/207, 503/447, 503/127, 503/319, 503/287, 503/15, 503/111, 503/383, 503/191, 503/527, 503/559, 503/207, 519/447, 519/127, 519/319, 519/287, 519/15, 519/111, 519/383, 519/191, 519/511, 519/559, 519/207, 551/447, 551/127, 551/319, 551/287, 551/15, 551/111, 551/383, 551/191, 551/511, 551/527, 551/207, 199/447, 199/127, 199/319, 199/287, 199/15, 199/111, 199/383, 199/191, 199/511, 199/527, and 199/559.

[0027] In some [embodimentexamples](#), the present [inventiondisclosure](#) provides a TCR comprising the CDRs contained within an alpha chain variable domain/beta chain variable domain amino acid sequence pair selected from the group consisting of SEQ ID NOs: 668/676, 103/111, 439/447, and 503/511. In some [embodimentexamples](#), a TCR of the present disclosure comprises alpha chain variable domain complementarity determining regions (CDRs) CDR1, CDR2, and CDR3, and beta chain variable domain CDRs CDR1, CDR2, and CDR3 comprising the respective amino acid sequences of : a) SEQ ID NOs: 662, 663, 664, 670, 671, and 672; b) SEQ ID NOs: 97, 98, 99, 105, 106, and 107; c) SEQ ID NOs: 433, 434, 435, 441, 442, and 443; and d) SEQ ID NOs: 497, 498, 499, 505, 506, and 507.

[0028] The present [inventiondisclosure](#) 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 [inventiondisclosure](#).

[0029] In some [embodimentexample](#), the TCRs of the [inventiondisclosure](#) further comprise a detectable moiety.

[0030] The present [inventiondisclosure](#) further provides pharmaceutical compositions comprising any of the TCRs of the [inventiondisclosure](#), and a pharmaceutically acceptable carrier or diluent; as well as isolated cells presenting any of the TCRs of the [inventiondisclosure](#).

[0031] In one [aspectexample](#), the present [inventiondisclosure](#) provides isolated polynucleotide molecules comprising a polynucleotide sequence that encodes an alpha chain variable domain of any of the TCRs of the [inventiondisclosure](#).

[0032] In another [aspectexample](#), the present [inventiondisclosure](#) provides isolated polynucleotide molecules comprising a polynucleotide sequence that encodes a beta chain variable domain of any of the TCRs of the [inventiondisclosure](#).

[0033] The present [inventiondisclosure](#) also provides vectors comprising the polynucleotide molecule of the [inventiondisclosure](#); cells expressing the vectors of the [inventiondisclosure](#).

[0034] In one [aspectexample](#), the present [inventiondisclosure](#) provides a method of treating a subject having a MAGE-A4-associated disease or disorder. The methods include 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 [inventiondisclosure](#), thereby treating the subject.

[0035] In one [embodimentexample](#), the MAGE-A4-associated disease or disorder is MAGE-A4-associated cancer.

[0036] In one [embodimentexample](#), the MAGE-A4-associated cancer is a liposarcoma, a neuroblastoma, a myeloma, a melanoma, a metastatic melanoma, a synovial sarcoma, a bladder cancer, an esophageal cancer, an esophageal squamous cell carcinoma, a hepatocellular cancer, a head and neck cancer, a non-small cell lung cancer, an ovarian cancer, an ovarian epithelial cancer, a prostate cancer, a breast cancer, an astrocytic tumor, a glioblastoma multiforme, an anaplastic astrocytoma, a brain tumor, a fallopian tube cancer, primary peritoneal cavity cancer, advanced solid tumors, soft tissue sarcoma, a sarcoma, a myelodysplastic syndrome, an acute myeloid leukemia, a Hodgkin lymphoma, a non-Hodgkin lymphoma, a Hodgkin disease, a multiple myeloma, a metastatic solid tumors, a colorectal carcinoma, a stomach cancer, a gastric cancer, a rhabdomyosarcoma, a myxoid round cell liposarcoma, or a recurrent non-small cell lung cancer.

[0037] In some [embodimentexamples](#) of the [inventiondisclosure](#), 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 [inventiondisclosure](#) is administered to the subject in combination with a second therapeutic agent.

[0038] The TCR, the pharmaceutical composition, or the plurality of cells may be administered subcutaneously, intravenously, intradermally, intraperitoneally, orally, intramuscularly or intracranially to the subject.

[0039] In one [aspectexample](#), the present [inventiondisclosure](#) 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 melanoma-associated antigen 4 (MAGE-A4) peptide comprising the amino acid sequence of KVLEHVVRV (SEQ ID NO:609) (MAGE-A4 286-294), wherein the TCR has a property selected from the group consisting of: (a) does not bind to cells expressing predicted off-target peptides as determined by luminescence assay; (b) activates a T cell response about two times greater than a patient-derived MAGE-A4-specific TCR as determined by a TCR-mediated T cell signaling luminescent bioassay; and (c) activates a T cell response about two times greater than an affinity-matured (e.g., by

phage display) MAGE-A4-specific TCR as determined by a TCR-mediated T cell signaling luminescent bioassay.

[0040] In one [embodimentexample](#), the isolated nucleic acid molecule encodes at least one TCR alpha chain variable domain and/or at least one beta chain variable domain.

[0041] In one [embodimentexample](#), 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 4; and beta chain variable domain CDR1, CDR2 and CDR3 contained within any one of the beta chain variable domain sequences listed in Table 4.

[0042] In another [embodimentexample](#), 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 4.

[0043] In yet another [embodimentexample](#), 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 4.

[0044] In one [embodimentexample](#), 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 4; 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 4.

[0045] In one [embodimentexample](#), 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, 17, 33, 49, 65, 81, 97, 113, 129, 145, 161, 177, 193, 209, 225, 241, 257, 273, 289, 305, 321, 337, 353, 369, 385, 401, 417, 433, 449, 465, 481, 497, 513, 529, 545, 561, 577, and 593; (b) an alpha chain variable domain CDR2 domain having an amino acid sequence selected from the group consisting of SEQ ID NOs: 2, 18, 34, 50, 66, 82, 98, 114, 130, 146, 162, 178, 194, 210, 226, 242, 258, 274, 290, 306, 322, 338, 354, 370, 386, 402, 418, 434, 450, 466, 482, 498 514, 530, 546, 562, 578, and 594; (c) an alpha chain variable domain CDR3 domain having an amino acid sequence selected from the group consisting of SEQ ID NOs: 3, 19, 35, 51, 67, 83, 99, 115, 131, 147, 163, 179, 195,

211, 227, 243, 259, 275, 291, 307, 323, 339, 355, 371, 387, 403, 419, 435, 451, 467, 483, 499, 515, 531, 547, 563, 579, and 595; (d) a beta chain variable domain CDR1 having an amino acid sequence selected from the group consisting of SEQ ID NOs: 9, 25, 41, 57, 73, 89, 105, 121, 137, 153, 169, 185, 201, 217, 233, 249, 265, 281, 297, 313, 329, 345, 361, 377, 393, 409, 425, 441, 457, 473, 489, 505, 521, 537, 553, 569, 585, and 601; (e) a beta chain variable domain CDR2 having an amino acid sequence selected from the group consisting of SEQ ID NOs: 10, 26, 42, 58, 74, 90, 106, 122, 138, 154, 170, 186, 202, 218, 234, 250, 266, 282, 298, 314, 330, 346, 362, 378, 394, 410, 426, 442, 458, 474, 490, 506, 522, 538, 554, 570, 586, and 602; and (f) a beta chain variable domain CDR3 having an amino acid sequence selected from the group consisting of SEQ ID NOs: 11, 27, 43, 59, 75, 91, 107, 123, 139, 155, 171, 187, 203, 219, 235, 251, 267, 283, 299, 315, 331, 347, 363, 379, 395, 411, 427, 443, 459, 475, 491, 507, 523, 539, 555, 571, 587, and 603.

[0046] In one [embodiment example](#), 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: 7/15, 23/31, 39/47, 55/63, 71/79, 87/95, 103/111, 119/127, 135/143, 151/159, 167/175, 183/191, 199/207, 215/223, 231/239, 247/255, 263/271, 279/287, 295/303, 311/319, 327/335, 343/351, 359/367, 375/383, 391/399, 407/415, 423/431, 439/447, 455/463, 471/479, 487/495, 503/511, 519/527, 535/543, 551/559, 567/575, 583/591, and 599/607.

[0047] In another [embodiment example](#), 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: 87/31, 23/95, 231/607, 231/223, 231/591, 231/255, 231/271, 231/79, 231/47, 231/399, 599/239, 599/223, 599/591, 599/255, 599/271, 599/79, 599/47, 599/399, 215/239, 215/607, 215/591, 215/255, 215/271, 215/79, 215/47, 215/399, 583/239, 583/607, 583/223, 583/255, 583/271, 583/79, 583/47, 583/399, 247/239, 247/607, 247/223, 247/591, 247/271, 247/79, 247/47, 247/399, 263/239, 263/607, 263/223, 263/591, 263/255, 263/79, 263/47, 263/399, 71/239, 71/607, 71/223, 71/591, 71/255, 71/271, 71/47, 71/399, 39/239, 39/607, 39/223, 39/591, 39/255, 39/271, 39/79, 39/399, 391/239, 391/607, 391/223, 391/591, 391/255, 391/271, 391/79, 391/47, 439/127, 439/319, 439/287, 439/15, 439/111, 439/383, 439/191, 439/511, 439/527, 439/559, 439/207, 119/447, 119/319, 119/287, 119/15, 119/111, 119/383, 119/191, 119/511, 119/527, 119/559, 119/207, 311/447, 311/127, 311/287, 311/15, 311/111, 311/383, 311/191, 311/511, 311/527, 311/559, 311/207, 279/447, 279/127, 279/319, 279/15, 279/111, 279/383, 279/191, 279/511, 279/527, 279/559, 279/207, 7/447, 7/127, 7/319, 7/287, 7/111, 7/383, 7/191, 7/511, 7/527, 7/559, 7/207, 103/447,

103/127, 103/319, 103/287, 103/15, 103/383, 103/191, 103/511, 103/527, 103/559, 103/207, 375/447, 375/127, 375/319, 375/287, 375/15, 375/111, 375/191, 375/511, 375/527, 375/559, 375/207, 183/447, 183/127, 183/319, 183/287, 183/15, 183/111, 183/383, 183/511, 183/527, 183/559, 183/207, 503/447, 503/127, 503/319, 503/287, 503/15, 503/111, 503/383, 503/191, 503/527, 503/559, 503/207, 519/447, 519/127, 519/319, 519/287, 519/15, 519/111, 519/383, 519/191, 519/511, 510/559, 519/207, 551/447, 551/127, 551/319, 551/287, 551/15, 551/111, 551/383, 551/191, 551/511, 551/527, 551/207, 199/447, 199/127, 199/319, 199/287, 199/15, 199/111, 199/383, 199/191, 199/511, 199/527, and 199/559.

[0048] In one [embodimentexample](#), 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: 4, 20, 36, 52, 68, 84, 100, 116, 132, 148, 164, 180, 196, 212, 228, 244, 260, 276, 292, 308, 324, 340, 356, 372, 388, 404, 420, 436, 452, 468, 484, 500, 516, 532, 548, 564, 580, and 596; (b) an alpha chain variable domain CDR2 encoded by a nucleic acid sequence selected from the group consisting of SEQ ID NOs: 5, 21, 37, 53, 69, 85, 101, 117, 133, 149, 165, 181, 197, 213, 229, 245, 261, 277, 293, 309, 325, 341, 357, 373, 389, 405, 421, 437, 453, 469, 485, 501, 517, 533, 549, 565, 581, and 597; (c) an alpha chain variable domain CDR3 encoded by a nucleic acid sequence selected from the group consisting of SEQ ID NOs: 6, 22, 38, 54, 70, 86, 102, 118, 134, 150, 166, 182, 198, 214, 230, 246, 262, 278, 294, 310, 326, 342, 358, 374, 390, 406, 422, 438, 454, 470, 486, 502, 518, 534, 550, 566, 582, and 598; (d) a beta chain variable domain CDR1 encoded by a nucleic acid sequence selected from the group consisting of SEQ ID NOs: 12, 28, 44, 60, 76, 92, 108, 124, 140, 156, 172, 188, 204, 220, 236, 252, 268, 284, 300, 316, 332, 348, 364, 380, 396, 412, 428, 444, 460, 476, 492, 508, 524, 540, 556, 572, 588, and 604; (e) a beta chain variable domain CDR2 encoded by a nucleic acid sequence selected from the group consisting of SEQ ID NOs: 13, 29, 45, 61, 77, 93, 109, 125, 141, 157, 173, 189, 205, 221, 237, 253, 269, 285, 301, 317, 333, 349, 365, 381, 397, 413, 429, 445, 461, 477, 493, 509, 525, 541, 557, 573, 589, and 605; and (f) a beta chain variable domain CDR3 encoded by a nucleic acid sequence selected from the group consisting of SEQ ID NOs: 14, 30, 46, 62, 78, 94, 110, 126, 142, 158, 174, 190, 206, 222, 238, 254, 270, 286, 302, 318, 334, 350, 366, 382, 398, 414, 430, 446, 462, 478, 494, 510, 526, 542, 558, 574, 590, and 606.

[0049] In one [embodimentexample](#), 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: 8/16, 24/32, 40/48, 56/64, 72/80, 88/96, 104/112, 120/128, 136/144, 152/160, 168/176, 184/192, 200/208, 216/224, 232/240, 248/256, 264/272, 280/288, 296/304,

312/320, 328/336, 344/352, 360/368, 376/384, 392/400, 408/416, 424/432, 440/448, 456/464, 472/480, 488/496, 504/512, 520/528, 536/544, 552/560, 568/576, 584/592, 600/608.

[0050] The present [inventiondisclosure](#) also provides vectors comprising an isolated nucleic acid molecule of the [inventiondisclosure](#) and isolated cells comprising a vector of the [inventiondisclosure](#).

[0051] In one [aspectexample](#), the present [inventiondisclosure](#) provides a method of treating a subject having a MAGE-A4-associated disease or disorder, comprising administering to the subject a plurality of the cells of claim 42, thereby treating the subject.

[0052] In one [embodimentexample](#), the MAGE-A4-associated disease or disorder is MAGE-A4-associated cancer.

[0053] In one [embodimentexample](#), the MAGE-A4-associated cancer is a liposarcoma, a neuroblastoma, a myeloma, a melanoma, a metastatic melanoma, a synovial sarcoma, a bladder cancer, an esophageal cancer, an esophageal squamous cell carcinoma, a hepatocellular cancer, a head and neck cancer, a non-small cell lung cancer, an ovarian cancer, an ovarian epithelial cancer, a prostate cancer, a breast cancer, an astrocytic tumor, a glioblastoma multiforme, an anaplastic astrocytoma, a brain tumor, a fallopian tube cancer, primary peritoneal cavity cancer, advanced solid tumors, soft tissue sarcoma, a sarcoma, a myelodysplastic syndrome, an acute myeloid leukemia, a Hodgkin lymphoma, a non-Hodgkin lymphoma, a Hodgkin disease, a multiple myeloma, a metastatic solid tumors, a colorectal carcinoma, a stomach cancer, a gastric cancer, a rhabdomyosarcoma, a myxoid round cell liposarcoma, or a recurrent non-small cell lung cancer.

[0054] In one [embodimentexample](#), a plurality of cells is administered to the subject in combination with a second therapeutic agent.

[0055] In one [aspectexample](#), the present [inventiondisclosure](#) 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 melanoma-associated antigen 4 (MAGE-A4) peptide comprising the amino acid sequence of KVLEHVVRV (SEQ ID NO:609) (MAGE-A4 286-294), wherein the TCR has a property selected from the group consisting of (a) does not bind to cells expressing predicted off-target peptides as determined by luminescence assay; (b) activates a T cell response having a signal to noise ratio greater than or equal to a patient-derived MAGE-A4-specific TCR as determined by a TCR-mediated T cell signaling luminescent bioassay; and (c) activates a T cell response about two times greater than an affinity-matured (e.g., by phage display) MAGE-A4-specific TCR as determined by a TCR-mediated T cell signaling luminescent bioassay.

[0056] In some [embodimentexamples](#), the TCR activates a T cell response about two times greater, or about three times greater, or about four times greater than a patient-derived MAGE-A4-specific TCR as determined by a TCR-mediated T cell signaling luminescent bioassay. In some [embodimentexamples](#), the TCR activates a T cell response about two times greater, or about three times greater, or about four times greater than an affinity-matured (e.g., by phage display) MAGE-A4-specific TCR as determined by a TCR-mediated T cell signaling luminescent bioassay

[0057] In one [aspectexample](#), 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 melanoma-associated antigen 4 (MAGE-A4) peptide comprising the amino acid sequence of GGYDGREHTV (SEQ ID NO:612) (MAGE-A4 230-239), wherein the TCR comprises a complementary determining region 3 (CDR3) contained with an alpha chain variable domain of any one of SEQ ID NOs: 620, 636, 652, 668, 684, 700, 716, 732, 748, 764, 780, 796, 812, 828, 844, and 860.

[0058] In one [aspectexample](#), 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 melanoma-associated antigen 4 (MAGE-A4) peptide comprising the amino acid sequence of GGYDGREHTV (SEQ ID NO:612) (MAGE-A4 230-239), wherein the TCR comprises a complementary determining region 3 (CDR3) contained within a beta chain variable domain of any one of SEQ ID NOs: 628, 644, 660, 676, 692, 708, 724, 740, 756, 772, 788, 804, 820, 836, 852, and 868.

[0059] In some [embodimentexamples](#), 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. In some [embodimentexamples](#), 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. In some [embodimentexamples](#), the TCR comprises at least one TCR alpha chain variable domain and/or at least one beta chain variable domain. In some [embodimentexamples](#), the TCR comprises a TCR alpha chain variable domain and a TCR beta chain variable domain.

[0060] In some [embodimentexamples](#), 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 variable domain CDR1, CDR2 and CDR3 contained within any one of the beta chain variable domain sequences listed in Table 8. In some [embodimentexamples](#), 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. In some [embodimentexamples](#), 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. In some [embodimentexamples](#), 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.

[0061] In some [embodimentexamples](#), 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: 614, 630, 646, 662, 678, 694, 710, 726, 742, 758, 774, 790, 806, 822, 838, and 854; (b) an alpha chain variable domain CDR2 domain having an amino acid sequence selected from the group consisting of SEQ ID NOs: 615, 631, 647, 663, 679, 695, 711, 727, 743, 759, 775, 791, 807, 823, 839, and 855; (c) an alpha chain variable domain CDR3 domain having an amino acid sequence selected from the group consisting of SEQ ID NOs: 616, 632, 648, 664, 680, 696, 712, 728, 744, 760, 776, 792, 808, 824, 840, and 856; (d) a beta chain variable domain CDR1 having an amino acid sequence selected from the group consisting of SEQ ID NOs: 622, 638, 654, 670, 686, 702, 718, 734, 750, 766, 782, 798, 814, 830, 846, and 862; (e) a beta chain variable domain CDR2 having an amino acid sequence selected from the group consisting of SEQ ID NOs: 623, 639, 655, 671, 687, 703, 719, 735, 751, 767, 783, 799, 815, 831, 847, and 863; and (f) a beta chain variable domain CDR3 having an amino acid sequence selected from the group consisting of SEQ ID NOs: 624, 640, 656, 672, 688, 704, 720, 736, 752, 768, 784, 800, 816, 832, 848, and 864.

[0062] In some [embodimentexamples](#), 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: 620/628, 636/644, 652/660, 668/676, 684/692, 700/708, 716/724, 732/740, 748/756, 764/772, 780/788, 796/804, 812/820, 828/836, 844/852, and

860/868. In some [embodimentexamples](#), 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: 620/628, 620/644, 620/660, 620/676, 620/692, 620/708, 620/724, 620/740, 620/756, 620/772, 620/788, 620/804, 620/820, 620/836, 620/852, 620/868, 636/628, 636/644, 636/660, 636/676, 636/692, 636/708, 636/724, 636/740, 636/756, 636/772, 636/788, 636/804, 636/820, 636/836, 636/852, 636/868, 652/628, 652/644, 652/660, 652/676, 652/692, 652/708, 652/724, 652/740, 652/756, 652/772, 652/788, 652/804, 652/820, 652/836, 652/852, 652/868, 668/628, 668/644, 668/660, 668/676, 668/692, 668/708, 668/724, 668/740, 668/756, 668/772, 668/788, 668/804, 668/820, 668/836, 668/852, 668/868, 684/628, 684/644, 684/660, 684/676, 684/692, 684/708, 684/724, 684/740, 684/756, 684/772, 684/788, 684/804, 684/820, 684/836, 684/852, 684/868, 700/628, 700/644, 700/660, 700/676, 700/692, 700/708, 700/724, 700/740, 700/756, 700/772, 700/788, 700/804, 700/820, 700/836, 700/852, 700/868, 716/628, 716/644, 716/660, 716/676, 716/692, 716/708, 716/724, 716/740, 716/756, 716/772, 716/788, 716/804, 716/820, 716/836, 716/852, 716/868, 732/628, 732/644, 732/660, 732/676, 732/692, 732/708, 732/724, 732/740, 732/756, 732/772, 732/788, 732/804, 732/820, 732/836, 732/852, 732/868, 748/628, 748/644, 748/660, 748/676, 748/692, 748/708, 748/724, 748/740, 748/756, 748/772, 748/788, 748/804, 748/820, 748/836, 748/852, 748/868, 764/628, 764/644, 764/660, 764/676, 764/692, 764/708, 764/724, 764/740, 764/756, 764/772, 764/788, 764/804, 764/820, 764/836, 764/852, 764/868, 780/628, 780/644, 780/660, 780/676, 780/692, 780/708, 780/724, 780/740, 780/756, 780/772, 780/788, 780/804, 780/820, 780/836, 780/852, 780/868, 796/628, 796/644, 796/660, 796/676, 796/692, 796/708, 796/724, 796/740, 796/756, 796/772, 796/788, 796/804, 796/820, 796/836, 796/852, 796/868, 812/628, 812/644, 812/660, 812/676, 812/692, 812/708, 812/724, 812/740, 812/756, 812/772, 812/788, 812/804, 812/820, 812/836, 812/852, 812/868, 828/628, 828/644, 828/660, 828/676, 828/692, 828/708, 828/724, 828/740, 828/756, 828/772, 828/788, 828/804, 828/820, 828/836, 828/852, 828/868, 844/628, 844/644, 844/660, 844/676, 844/692, 844/708, 844/724, 844/740, 844/756, 844/772, 844/788, 844/804, 844/820, 844/836, 844/852, 844/868, 860/628, 860/644, 860/660, 860/676, 860/692, 860/708, 860/724, 860/740, 860/756, 860/772, 860/788, 860/804, 860/820, 860/836, 860/852, and 860/868.

[0063] In some [embodimentexamples](#), the TCR comprises a detectable moiety. In some [embodimentexamples](#), the TCR has an on-target binding/off-target binding value of greater than 2.5, greater than 3, greater than 3.5, greater than 4, greater than 4.5, greater than 5, greater than

10, greater than 15, greater than 20, greater than 50, greater than 100, greater than 200, greater than 300, greater than 400, greater than 500, greater than 600, greater than 700, greater than 800, greater than 900, or greater than 1000. In some [embodimentexamples](#), the TCR has an on-target binding/off-target binding value of greater than 10. In some [embodimentexamples](#), the TCR has an on-target binding/off-target binding value of greater than 500. In some [embodimentexamples](#), the TCR competes for binding to a TCR (e.g., an isolated TCR or a TCR expressed on an isolated cell) as described herein.

[0064] In one [aspectexample](#), the present disclosure provides a pharmaceutical composition comprising a TCR (e.g., an isolated TCR or a TCR expressed on an isolated cell) as described herein and a pharmaceutically acceptable carrier or diluent. In one [aspectexample](#), the present disclosure provides an isolated cell presenting a TCR as described herein. In one [aspectexample](#), the present disclosure provides an isolated polynucleic acid comprising a polynucleotide sequence that encodes an alpha chain variable domain of a TCR (e.g., an isolated TCR or a TCR expressed on an isolated cell) as described herein. In one [aspectexample](#), the present disclosure provides an isolated polynucleic acid comprising a polynucleotide sequence that encodes a beta chain variable domain of a TCR (e.g., an isolated TCR or a TCR expressed on an isolated cell) as described herein. In one [aspectexample](#), the present disclosure provides a vector comprising a polynucleotide sequence as described herein. In one [aspectexample](#), the present disclosure provides an isolated cell expressing that vector.

[0065] In one [aspectexample](#), the present disclosure provides a method of treating a subject having a MAGE-A4-associated disease or disorder, comprising administering to the subject a therapeutically effective amount of a TCR (e.g., an isolated TCR or a TCR expressed on an isolated cell) as described herein, a pharmaceutical composition as described herein, or an isolated cell as described herein, thereby treating the subject. In some [embodimentexamples](#), the MAGE-A4-associated disease or disorder is MAGE-A4-associated cancer. In some [embodimentexamples](#), the MAGE-A4-associated cancer is a liposarcoma, a neuroblastoma, a myeloma, a melanoma, a metastatic melanoma, a synovial sarcoma, a bladder cancer, an esophageal cancer, an esophageal squamous cell carcinoma, a hepatocellular cancer, a head and neck cancer, a non-small cell lung cancer, an ovarian cancer, an ovarian epithelial cancer, a prostate cancer, a breast cancer, an astrocytic tumor, a glioblastoma multiforme, an anaplastic astrocytoma, a brain tumor, a fallopian tube cancer, primary peritoneal cavity cancer, advanced solid tumors, soft tissue sarcoma, a sarcoma, a myelodysplastic syndrome, an acute myeloid leukemia, a Hodgkin lymphoma, a non-Hodgkin lymphoma, a Hodgkin disease, a multiple myeloma, a metastatic solid tumors, a colorectal carcinoma, a stomach

cancer, a gastric cancer, a rhabdomyosarcoma, a myxoid round cell liposarcoma, or a recurrent non-small cell lung cancer. In some [embodimentexamples](#), the TCR, the pharmaceutical composition, or the cell is administered to the subject in combination with a second therapeutic agent. In some [embodimentexamples](#), the administering is parenteral.

[0066] In one [aspectexample](#), 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 melanoma-associated antigen 4 (MAGE-A4) peptide comprising the amino acid sequence of GVDYDGREHTV (SEQ ID NO:612) (MAGE-A4 230-239), wherein the TCR has a property selected from the group consisting of: (a) does not bind to cells expressing predicted off-target peptides as determined by a luminescence assay; (b) does not bind to cells expressing predicted off-target peptides as determined by a flow cytometry assay; (c) activates a T cell response about two times greater than a patient-derived MAGE-A4-specific TCR as determined by a TCR-mediated T cell signaling luminescent bioassay; and (d) activates a T cell response about two times greater than an affinity-matured (e.g., by phage display) MAGE-A4-specific TCR as determined by a TCR-mediated T cell signaling luminescent bioassay. In some [embodimentexamples](#), the isolated nucleic acid molecule encodes at least one TCR alpha chain variable domain and/or at least one beta chain variable domain.

[0067] In some [embodimentexamples](#), 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. In some [embodimentexamples](#), 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. In some [embodimentexamples](#), 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.

[0068] In some [embodimentexamples](#), 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. In some [embodimentexamples](#), 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: 614, 630, 646, 662, 678, 694, 710, 726, 742, 758, 774, 790, 806, 822, 838, and 854; (b) an alpha chain variable domain CDR2 domain having an amino acid sequence selected from the group consisting of SEQ ID NOs: 615, 631, 647, 663, 679, 695, 711, 727, 743, 759, 775, 791, 807, 823, 839, and 855; (c) an alpha chain variable domain CDR3 domain having an amino acid sequence selected from the group consisting of SEQ ID NOs: 616, 632, 648, 664, 680, 696, 712, 728, 744, 760, 776, 792, 808, 824, 840, and 856; (d) a beta chain variable domain CDR1 having an amino acid sequence selected from the group consisting of SEQ ID NOs: 622, 638, 654, 670, 686, 702, 718, 734, 750, 766, 782, 798, 814, 830, 846, and 862; (e) a beta chain variable domain CDR2 having an amino acid sequence selected from the group consisting of SEQ ID NOs: 623, 639, 655, 671, 687, 703, 719, 735, 751, 767, 783, 799, 815, 831, 847, and 863; and (f) a beta chain variable domain CDR3 having an amino acid sequence selected from the group consisting of SEQ ID NOs: 624, 640, 656, 672, 688, 704, 720, 736, 752, 768, 784, 800, 816, 832, 848, and 864.

[0069] In some [embodimentexamples](#), 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: 620/628, 636/644, 652/660, 668/676, 684/692, 700/708, 716/724, 732/740, 748/756, 764/772, 780/788, 796/804, 812/820, 828/836, 844/852, and 860/868. In some [embodimentexamples](#), 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: 620/628, 620/644, 620/660, 620/676, 620/692, 620/708, 620/724, 620/740, 620/756, 620/772, 620/788, 620/804, 620/820, 620/836, 620/852, 620/868, 636/628, 636/644, 636/660, 636/676, 636/692, 636/708, 636/724, 636/740, 636/756, 636/772, 636/788, 636/804, 636/820, 636/836, 636/852, 636/868, 652/628, 652/644, 652/660, 652/676, 652/692, 652/708, 652/724, 652/740, 652/756, 652/772, 652/788, 652/804, 652/820, 652/836, 652/852, 652/868, 668/628, 668/644, 668/660, 668/676, 668/692, 668/708, 668/724, 668/740, 668/756, 668/772, 668/788, 668/804, 668/820, 668/836, 668/852, 668/868, 684/628, 684/644, 684/660, 684/676, 684/692, 684/708, 684/724, 684/740, 684/756, 684/772, 684/788, 684/804, 684/820, 684/836, 684/852, 684/868, 700/628, 700/644, 700/660, 700/676, 700/692, 700/708, 700/724, 700/740, 700/756, 700/772, 700/788, 700/804, 700/820, 700/836, 700/852, 700/868, 716/628, 716/644, 716/660, 716/676, 716/692, 716/708, 716/724, 716/740, 716/756, 716/772, 716/788,

716/804, 716/820, 716/836, 716/852, 716/868, 732/628, 732/644, 732/660, 732/676, 732/692, 732/708, 732/724, 732/740, 732/756, 732/772, 732/788, 732/804, 732/820, 732/836, 732/852, 732/868, 748/628, 748/644, 748/660, 748/676, 748/692, 748/708, 748/724, 748/740, 748/756, 748/772, 748/788, 748/804, 748/820, 748/836, 748/852, 748/868, 764/628, 764/644, 764/660, 764/676, 764/692, 764/708, 764/724, 764/740, 764/756, 764/772, 764/788, 764/804, 764/820, 764/836, 764/852, 764/868, 780/628, 780/644, 780/660, 780/676, 780/692, 780/708, 780/724, 780/740, 780/756, 780/772, 780/788, 780/804, 780/820, 780/836, 780/852, 780/868, 796/628, 796/644, 796/660, 796/676, 796/692, 796/708, 796/724, 796/740, 796/756, 796/772, 796/788, 796/804, 796/820, 796/836, 796/852, 796/868, 812/628, 812/644, 812/660, 812/676, 812/692, 812/708, 812/724, 812/740, 812/756, 812/772, 812/788, 812/804, 812/820, 812/836, 812/852, 812/868, 828/628, 828/644, 828/660, 828/676, 828/692, 828/708, 828/724, 828/740, 828/756, 828/772, 828/788, 828/804, 828/820, 828/836, 828/852, 828/868, 844/628, 844/644, 844/660, 844/676, 844/692, 844/708, 844/724, 844/740, 844/756, 844/772, 844/788, 844/804, 844/820, 844/836, 844/852, 844/868, 860/628, 860/644, 860/660, 860/676, 860/692, 860/708, 860/724, 860/740, 860/756, 860/772, 860/788, 860/804, 860/820, 860/836, 860/852, and 860/868.

[0070] In some [embodimentexamples](#), 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: 617, 633, 649, 665, 681, 697, 713, 729, 745, 761, 777, 793, 809, 825, 841, and 857; (b) an alpha chain variable domain CDR2 encoded by a nucleic acid sequence selected from the group consisting of SEQ ID NOs: 618, 634, 650, 666, 682, 698, 714, 730, 746, 762, 778, 794, 810, 826, 842, and 858; (c) an alpha chain variable domain CDR3 encoded by a nucleic acid sequence selected from the group consisting of SEQ ID NOs: 619, 635, 651, 667, 683, 699, 715, 731, 747, 763, 779, 795, 811, 827, 843, and 859; (d) a beta chain variable domain CDR1 encoded by a nucleic acid sequence selected from the group consisting of SEQ ID NOs: 625, 641, 657, 673, 689, 705, 721, 737, 753, 769, 785, 801, 817, 833, 849, and 865; (e) a beta chain variable domain CDR2 encoded by a nucleic acid sequence selected from the group consisting of SEQ ID NOs: 626, 642, 658, 674, 690, 706, 722, 738, 754, 770, 786, 802, 818, 834, 850, and 866; and (f) a beta chain variable domain CDR3 encoded by a nucleic acid sequence selected from the group consisting of SEQ ID NOs: 627, 643, 659, 675, 691, 707, 723, 739, 755, 771, 787, 803, 819, 835, 851, and 867. In some [embodimentexamples](#), 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: 621/629, 637/645,

653/661, 669/677, 685/693, 701/709, 717/725, 733/741, 749/757, 765/773, 781/789, 797/805, 813/821, 829/837, 845/853, and 861/869.

[0071] In one [aspectexample](#), the present disclosure provides a vector comprising the polynucleotide sequence of an isolated nucleic acid molecule as described herein. In one [aspectexample](#), the present disclosure provides an isolated cell comprising that vector. In one [aspectexample](#), the present disclosure provides a method of treating a subject having a MAGE-A4-associated disease or disorder, comprising administering to the subject that cell, thereby treating the subject. In some [embodimentexamples](#), the MAGE-A4-associated disease or disorder is MAGE-A4-associated cancer. In some [embodimentexamples](#), the MAGE-A4-associated cancer is a liposarcoma, a neuroblastoma, a myeloma, a melanoma, a metastatic melanoma, a synovial sarcoma, a bladder cancer, an esophageal cancer, an esophageal squamous cell carcinoma, a hepatocellular cancer, a head and neck cancer, a non-small cell lung cancer, an ovarian cancer, an ovarian epithelial cancer, a prostate cancer, a breast cancer, an astrocytic tumor, a glioblastoma multiforme, an anaplastic astrocytoma, a brain tumor, a fallopian tube cancer, primary peritoneal cavity cancer, advanced solid tumors, soft tissue sarcoma, a sarcoma, a myelodysplastic syndrome, an acute myeloid leukemia, a Hodgkin lymphoma, a non-Hodgkin lymphoma, a Hodgkin disease, a multiple myeloma, a metastatic solid tumors, a colorectal carcinoma, a stomach cancer, a gastric cancer, a rhabdomyosarcoma, a myxoid round cell liposarcoma, or a recurrent non-small cell lung cancer. In some [embodimentexamples](#), the cell is administered to the subject in combination with a second therapeutic agent.

[0072] The present [inventiondisclosure](#) is further illustrated by the following detailed description and drawings.

BRIEF DESCRIPTION OF THE DRAWINGS

[0073] **FIG. 1** depict FACS analysis showing the expression of TRACtargeted MAGE-A4 TCRs in primary human T cells, quantified by pMHC tetramer, analysis Day 14 post-activation. MAGE-A4 targets for these TCRs were either the MAGE-A4 (286-294) peptide (KVLEHVVRV, SEQ ID NO: 609; “KVLE”) or the MAGE-A4 (230-239) peptide (GVYDGREHTV, SEQ ID NO: 612; “GVY”) Transgenic TCR sequences were introduced to primary human T cells by site-directed targeting of adeno-associated virus (AAV) vector insertion at the human TRAC locus. Cells were stained with the indicated peptide MHC

CLAIMS

We claim:

1. A T cell receptor (TCR) that binds specifically to an HLA-A2 presented cancer testis antigen melanoma-associated antigen 4 (MAGE-A4) peptide comprising the amino acid sequence of KVLEHVVRV (SEQ ID NO:609) (MAGE-A4 286-294), 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 Formula I:

N₁-N₂-N₃-N₄-N₅-N₆-N₇-N₈-N₉-N₁₀-N₁₁-N₁₂-N₁₃-N₁₄-N₁₅ (Formula I), wherein

N₁ is a non-polar amino acid;

N₂, which may or may not be present, is Val;

N₃ is Tyr, Gly, Leu, Val, Glu, Met, Ala, or Phe;

N₄, which may or may not be present, is Arg, Glu, Ser, Asn, Gln, Lys, Asp, Gly, or Met;

N₅, which may or may not be present, is Ser, Arg, Glu, Leu, Ala, Asp, Pro, Met, Gly or Lys;

N₆, which may or may not be present, is Ala, Asp, Gly, Ser, Val, Pro, Leu, Tyr, or Thr;

N₇ is Thr, Pro, Ser, Glu, Asp, Trp, Arg, Asn, Ile, Gln, or Leu;

N₈ is His, Trp, Thr, Lys, Tyr, or Ala;

N₉ is Asn, Gly, Lys, Ile, Ser, or Arg;

N₁₀, which may or may not be present, is Gln, Lys, Gly, Thr, Leu, Asp, or Ser;

N₁₁, which may or may not be present, is Phe, Asn, Thr, Tyr, Ala, Leu, Met or Glu;

N₁₂, which may or may not be present, is Lys, Phe, Tyr, or Asp;

N₁₃, which may or may not be present, is Lys or Gly;

N₁₄, which may or may not be present, is Thr, Leu, or Tyr; and

N₁₅ is Tyr, Gln, Ile, Thr, Val, or Arg.

2. The TCR of claim 1, wherein N₁ is Ala, Ile, or Gly.

3. A T cell receptor (TCR) that binds specifically to an HLA-A2 presented cancer testis antigen melanoma-associated antigen 4 (MAGE-A4) peptide comprising the amino acid sequence of KVLEHVVRV (SEQ ID NO:609) (MAGE-A4 286-294), wherein

the TCR comprises a beta chain variable domain comprising complementary determining region (CDR)3, wherein the CDR3 comprises the amino acid sequence of Formula II:

$N_1-N_2-N_3-N_4-N_5-N_6-N_7-N_8-N_9-N_{10}-N_{11}-N_{12}-N_{13}-N_{14}-N_{15}-N_{16}-N_{17}-N_{18}$ (Formula II),

wherein

N_1 is Ala or Ser;

N_2 is Ala, Ser, or Thr;

N_3 is Ser, Gly, or Trp;

N_4 is Leu, Tyr, Trp, Asp, Phe, Gly, Pro, or His;

N_5 , which may or may not be present, is Gly or Asp;

N_6 , which may or may not be present, is Phe or Arg;

N_7 , which may or may not be present, is Trp, Phe, Asp, Pro, Tyr, Gly, Thr, Ser, or Val;

N_8 , which may or may not be present, is Pro, Arg, Asp, Tyr, Gln, Asn, or Gly;

N_9 , which may or may not be present, is Asp;

N_{10} , which may or may not be present, is Arg;

N_{11} , which may or may not be present, is Gly, Ala, or Thr;

N_{12} is Ser, Trp, Thr, Gly, Val, Leu, Arg, Met, Tyr, or Gln;

N_{13} , which may or may not be present, is Gly;

N_{14} , which may or may not be present, is Asn, Asp, Gly, Thr, Pro, Gln, or His;

N_{15} , which may or may not be present, is Thr, Ser, Glu, Asn, Tyr, Gln, Asp, or Pro;

N_{16} , which may or may not be present, is Glu, Pro, Lys, Thr, Ala, Gly, or Gln;

N_{17} , which may or may not be present, is Ala, Leu, Ile, Tyr, or Gln; and

N_{18} is Phe, His, Tyr, or Thr.

4. The TCR of claim 1 or 2, 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 2 and the CDR2 independently comprises any one of the alpha chain variable domain CDR2 amino acid sequences set forth in Table 2.

5. The TCR of claim 3, 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 2 and the CDR2 independently comprises any one of the beta chain variable domain CDR2 amino acid sequences set forth in Table 2.

6. The TCR of any one of claims 1-5, wherein the TCR comprises at least one TCR alpha chain variable domain and/or at least one beta chain variable domain.

7. The TCR of claim 6, wherein the TCR comprises a TCR alpha chain variable domain and a TCR beta chain variable domain.

8. The TCR of any one of claims 3-7, comprising alpha chain variable domain CDR1, CDR2 and CDR3 contained within any one of the alpha chain variable domain sequences listed in Table 4; and beta chain variable domain CDR1, CDR2 and CDR3 contained within any one of the beta chain variable domain sequences listed in Table 4.

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 4.

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 4.

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 4; 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 4.

12. The TCR of any one of claims 3-11, comprising:

(a) an alpha chain variable domain CDR1 domain having an amino acid sequence selected from the group consisting of SEQ ID NOs: 1, 17, 33, 49, 65, 81, 97, 113, 129, 145,

161, 177, 193, 209, 225, 241, 257, 273, 289, 305, 321, 337, 353, 369, 385, 401, 417, 433, 449, 465, 481, 497, 513, 529, 545, 561, 577, and 593;

(b) an alpha chain variable domain CDR2 domain having an amino acid sequence selected from the group consisting of SEQ ID NOs: 2, 18, 34, 50, 66, 82, 98, 114, 130, 146, 162, 178, 194, 210, 226, 242, 258, 274, 290, 306, 322, 338, 354, 370, 386, 402, 418, 434, 450, 466, 482, 498, 514, 530, 546, 562, 578, and 594;

(c) an alpha chain variable domain CDR3 domain having an amino acid sequence selected from the group consisting of SEQ ID NOs: 3, 19, 35, 51, 67, 83, 99, 115, 131, 147, 163, 179, 195, 211, 227, 243, 259, 275, 291, 307, 323, 339, 355, 371, 387, 403, 419, 435, 451, 467, 483, 499, 515, 531, 547, 563, 579, and 595;

(d) a beta chain variable domain CDR1 having an amino acid sequence selected from the group consisting of SEQ ID NOs: 9, 25, 41, 57, 73, 89, 105, 121, 137, 153, 169, 185, 201, 217, 233, 249, 265, 281, 297, 313, 329, 345, 361, 377, 393, 409, 425, 441, 457, 473, 489, 505, 521, 537, 553, 569, 585, and 601;

(e) a beta chain variable domain CDR2 having an amino acid sequence selected from the group consisting of SEQ ID NOs: 10, 26, 42, 58, 74, 90, 106, 122, 138, 154, 170, 186, 202, 218, 234, 250, 266, 282, 298, 314, 330, 346, 362, 378, 394, 410, 426, 442, 458, 474, 490, 506, 522, 538, 554, 570, 586, and 602; and

(f) a beta chain variable domain CDR3 having an amino acid sequence selected from the group consisting of SEQ ID NOs: 11, 27, 43, 59, 75, 91, 107, 123, 139, 155, 171, 187, 203, 219, 235, 251, 267, 283, 299, 315, 331, 347, 363, 379, 395, 411, 427, 443, 459, 475, 491, 507, 523, 539, 555, 571, 587, and 603.

13. The TCR of claim 12, comprising an alpha chain variable domain/beta chain variable domain amino acid sequence pair selected from the group consisting of SEQ ID NOs: 7/15, 23/31, 39/47, 55/63, 71/79, 87/95, 103/111, 119/127, 135/143, 151/159, 167/175, 183/191, 199/207, 215/223, 231/239, 247/255, 263/271, 279/287, 295/303, 311/319, 327/335, 343/351, 359/367, 375/383, 391/399, 407/415, 423/431, 439/447, 455/463, 471/479, 487/495, 503/511, 519/527, 535/543, 551/559, 567/575, 583/591, and 599/607.

14. The TCR of claim 12, comprising an alpha chain variable domain/beta chain variable domain amino acid sequence pair selected from the group consisting of SEQ ID NOs: 87/31, 23/95, 231/607, 231/223, 231/591, 231/255, 231/271, 231/79, 231/47, 231/399,

599/239, 599/223, 599/591, 599/255, 599/271, 599/79, 599/47, 599/399, 215/239, 215/607, 215/591, 215/255, 215/271, 215/79, 215/47, 215/399, 583/239, 583/607, 583/223, 583/255, 583/271, 583/79, 583/47, 583/399, 247/239, 247/607, 247/223, 247/591, 247/271, 247/79, 247/47, 247/399, 263/239, 263/607, 263/223, 263/591, 263/255, 263/79, 263/47, 263/399, 71/239, 71/607, 71/223, 71/591, 71/255, 71/271, 71/47, 71/399, 39/239, 39/607, 39/223, 39/591, 39/255, 39/271, 39/79, 39/399, 391/239, 391/607, 391/223, 391/591, 391/255, 391/271, 391/79, 391/47, 439/127, 439/319, 439/287, 439/15, 439/111, 439/383, 439/191, 439/511, 439/527, 439/559, 439/207, 119/447, 119/319, 119/287, 119/15, 119/111, 119/383, 119/191, 119/511, 119/527, 119/559, 119/207, 311/447, 311/127, 311/287, 311/15, 311/111, 311/383, 311/191, 311/511, 311/527, 311/559, 311/207, 279/447, 279/127, 279/319, 279/15, 279/111, 279/383, 279/191, 279/511, 279/527, 279/559, 279/207, 7/447, 7/127, 7/319, 7/287, 7/111, 7/383, 7/191, 7/511, 7/527, 7/559, 7/207, 103/447, 103/127, 103/319, 103/287, 103/15, 103/383, 103/191, 103/511, 103/527, 103/559, 103/207, 375/447, 375/127, 375/319, 375/287, 375/15, 375/111, 375/191, 375/511, 375/527, 375/559, 375/207, 183/447, 183/127, 183/319, 183/287, 183/15, 183/111, 183/383, 183/511, 183/527, 183/559, 183/207, 503/447, 503/127, 503/319, 503/287, 503/15, 503/111, 503/383, 503/191, 503/527, 503/559, 503/207, 519/447, 519/127, 519/319, 519/287, 519/15, 519/111, 519/383, 519/191, 519/511, 519/559, 519/207, 551/447, 551/127, 551/319, 551/287, 551/15, 551/111, 551/383, 551/191, 551/511, 551/527, 551/207, 199/447, 199/127, 199/319, 199/287, 199/15, 199/111, 199/383, 199/191, 199/511, 199/527, and 199/559.

15. An TCR that competes for binding to the TCR of any one of claims 1-14.
16. The TCR of any one of claims 1-15, further comprising a detectable moiety.
17. A pharmaceutical composition comprising the TCR of any one of claims 1-16 and a pharmaceutically acceptable carrier or diluent.
18. An isolated cell presenting the TCR of any one of claims 1-16.
19. 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 1-16.

20. 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 1-16.

21. A vector comprising the polynucleotide molecule of claim 19 or 20.

22. An isolated cell expressing the vector of claim 21.

23. Use of the TCR as set forth in any one of claims 1-16, the pharmaceutical composition of claim 17, or a plurality of the isolated cells of claim 18 in the manufacture of a medicament for ~~A method of~~ treating a subject having a MAGE-A4-associated disease or disorder, ~~comprising administering to the subject a therapeutically effective amount of the TCR as set forth in any one of claims 1-16, the pharmaceutical composition of claim 17, or a plurality of the isolated cells of claim 18, thereby treating the subject.~~

24. The ~~method-use~~ use of claim 23, wherein the MAGE-A4-associated disease or disorder is MAGE-A4-associated cancer.

25. The ~~method-use~~ use of claim 24, wherein the MAGE-A4-associated cancer is a liposarcoma, a neuroblastoma, a myeloma, a melanoma, a metastatic melanoma, a synovial sarcoma, a bladder cancer, an esophageal cancer, an esophageal squamous cell carcinoma, a hepatocellular cancer, a head and neck cancer, a non-small cell lung cancer, an ovarian cancer, an ovarian epithelial cancer, a prostate cancer, a breast cancer, an astrocytic tumor, a glioblastoma multiforme, an anaplastic astrocytoma, a brain tumor, a fallopian tube cancer, primary peritoneal cavity cancer, advanced solid tumors, soft tissue sarcoma, a sarcoma, a myelodysplastic syndrome, an acute myeloid leukemia, a Hodgkin lymphoma, a non-Hodgkin lymphoma, a Hodgkin disease, a multiple myeloma, a metastatic solid tumors, a colorectal carcinoma, a stomach cancer, a gastric cancer, a rhabdomyosarcoma, a myxoid round cell liposarcoma, or a recurrent non-small cell lung cancer.

26. The ~~method~~ use of any one of claims 23-25, 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.

27. The ~~method-use~~ of any one of claims 23-26, 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.

28. A polynucleotide molecule encoding a T cell receptor (TCR), wherein the TCR binds specifically to an HLA-A2 presented cancer testis antigen melanoma-associated antigen 4 (MAGE-A4) peptide comprising the amino acid sequence of KVLEHVVRV (SEQ ID NO:609) (MAGE-A4 286-294), wherein the TCR has a property selected from the group consisting of: (a) does not bind to cells expressing predicted off-target peptides as determined by luminescence assay; (b) activates a T cell response about two times greater than a patient-derived MAGE-A4-specific TCR as determined by a TCR-mediated T cell signaling luminescent bioassay; and (c) activates a T cell response about two times greater than an affinity-matured (e.g., by phage display) MAGE-A4-specific TCR as determined by a TCR-mediated T cell signaling luminescent bioassay.

29. The polynucleotide molecule of claim 28, encoding at least one TCR alpha chain variable domain and/or at least one beta chain variable domain.

30. The polynucleotide molecule of claim 28, 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 4; and beta chain variable domain CDR1, CDR2 and CDR3 contained within any one of the beta chain variable domain sequences listed in Table 4.

31. The polynucleotide molecule of claim 29 or 30, 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 4.

32. The polynucleotide molecule of any one of claims 28-31, 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 4.

33. The polynucleotide molecule of any one of claims 28-32, 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 4; 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 4.

34. The polynucleotide molecule of any one of claims 28-33, 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, 17, 33, 49, 65, 81, 97, 113, 129, 145, 161, 177, 193, 209, 225, 241, 257, 273, 289, 305, 321, 337, 353, 369, 385, 401, 417, 433, 449, 465, 481, 497, 513, 529, 545, 561, 577, and 593;

(b) an alpha chain variable domain CDR2 domain having an amino acid sequence selected from the group consisting of SEQ ID NOs: 2, 18, 34, 50, 66, 82, 98, 114, 130, 146, 162, 178, 194, 210, 226, 242, 258, 274, 290, 306, 322, 338, 354, 370, 386, 402, 418, 434, 450, 466, 482, 498, 514, 530, 546, 562, 578, and 594;

(c) an alpha chain variable domain CDR3 domain having an amino acid sequence selected from the group consisting of SEQ ID NOs: 3, 19, 35, 51, 67, 83, 99, 115, 131, 147, 163, 179, 195, 211, 227, 243, 259, 275, 291, 307, 323, 339, 355, 371, 387, 403, 419, 435, 451, 467, 483, 499, 515, 531, 547, 563, 579, and 595;

(d) a beta chain variable domain CDR1 having an amino acid sequence selected from the group consisting of SEQ ID NOs: 9, 25, 41, 57, 73, 89, 105, 121, 137, 153, 169, 185, 201, 217, 233, 249, 265, 281, 297, 313, 329, 345, 361, 377, 393, 409, 425, 441, 457, 473, 489, 505, 521, 537, 553, 569, 585, and 601;

(e) a beta chain variable domain CDR2 having an amino acid sequence selected from the group consisting of SEQ ID NOs: 10, 26, 42, 58, 74, 90, 106, 122, 138, 154, 170, 186, 202, 218, 234, 250, 266, 282, 298, 314, 330, 346, 362, 378, 394, 410, 426, 442, 458, 474, 490, 506, 522, 538, 554, 570, 586, and 602; and

(f) a beta chain variable domain CDR3 having an amino acid sequence selected from the group consisting of SEQ ID NOs: 11, 27, 43, 59, 75, 91, 107, 123, 139, 155, 171, 187, 203, 219, 235, 251, 267, 283, 299, 315, 331, 347, 363, 379, 395, 411, 427, 443, 459, 475, 491, 507, 523, 539, 555, 571, 587, and 603.

35. The polynucleotide molecule of claim 34, 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: 7/15, 23/31, 39/47, 55/63, 71/79, 87/95, 103/111, 119/127, 135/143, 151/159, 167/175, 183/191, 199/207, 215/223, 231/239, 247/255, 263/271, 279/287, 295/303, 311/319, 327/335, 343/351, 359/367, 375/383, 391/399, 407/415, 423/431, 439/447, 455/463, 471/479, 487/495, 503/511, 519/527, 535/543, 551/559, 567/575, 583/591, and 599/607.

36. The polynucleotide molecule of claim 34, 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: 87/31, 23/95, 231/607, 231/223, 231/591, 231/255, 231/271, 231/79, 231/47, 231/399, 599/239, 599/223, 599/591, 599/255, 599/271, 599/79, 599/47, 599/399, 215/239, 215/607, 215/591, 215/255, 215/271, 215/79, 215/47, 215/399, 583/239, 583/607, 583/223, 583/255, 583/271, 583/79, 583/47, 583/399, 247/239, 247/607, 247/223, 247/591, 247/271, 247/79, 247/47, 247/399, 263/239, 263/607, 263/223, 263/591, 263/255, 263/79, 263/47, 263/399, 71/239, 71/607, 71/223, 71/591, 71/255, 71/271, 71/47, 71/399, 39/239, 39/607, 39/223, 39/591, 39/255, 39/271, 39/79, 39/399, 391/239, 391/607, 391/223, 391/591, 391/255, 391/271, 391/79, 391/47, 439/127, 439/319, 439/287, 439/15, 439/111, 439/383, 439/191, 439/511, 439/527, 439/559, 439/207, 119/447, 119/319, 119/287, 119/15, 119/111, 119/383, 119/191, 119/511, 119/527, 119/559, 119/207, 311/447, 311/127, 311/287, 311/15, 311/111, 311/383, 311/191, 311/511, 311/527, 311/559, 311/207, 279/447, 279/127, 279/319, 279/15, 279/111, 279/383, 279/191, 279/511, 279/527, 279/559, 279/207, 7/447, 7/127, 7/319, 7/287, 7/111, 7/383, 7/191, 7/511, 7/527, 7/559, 7/207, 103/447, 103/127, 103/319, 103/287, 103/15, 103/383, 103/191, 103/511, 103/527, 103/559, 103/207, 375/447, 375/127, 375/319, 375/287, 375/15, 375/111, 375/191, 375/511, 375/527, 375/559, 375/207, 183/447, 183/127, 183/319, 183/287, 183/15, 183/111, 183/383, 183/511, 183/527, 183/559, 183/207, 503/447, 503/127, 503/319, 503/287, 503/15, 503/111, 503/383, 503/191, 503/527, 503/559, 503/207, 519/447, 519/127, 519/319, 519/287, 519/15, 519/111,

519/383, 519/191, 519/511, 510/559, 519/207, 551/447, 551/127, 551/319, 551/287, 551/15, 551/111, 551/383, 551/191, 551/511, 551/527, 551/207, 199/447, 199/127, 199/319, 199/287, 199/15, 199/111, 199/383, 199/191, 199/511, 199/527, and 199/559.

37. The polynucleotide molecule of claim 33, 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: 4, 20, 36, 52, 68, 84, 100, 116, 132, 148, 164, 180, 196, 212, 228, 244, 260, 276, 292, 308, 324, 340, 356, 372, 388, 404, 420, 436, 452, 468, 484, 500, 516, 532, 548, 564, 580, and 596;

(b) an alpha chain variable domain CDR2 encoded by a nucleic acid sequence selected from the group consisting of SEQ ID NOs: 5, 21, 37, 53, 69, 85, 101, 117, 133, 149, 165, 181, 197, 213, 229, 245, 261, 277, 293, 309, 325, 341, 357, 373, 389, 405, 421, 437, 453, 469, 485, 501, 517, 533, 549, 565, 581, and 597;

(c) an alpha chain variable domain CDR3 encoded by a nucleic acid sequence selected from the group consisting of SEQ ID NOs: 6, 22, 38, 54, 70, 86, 102, 118, 134, 150, 166, 182, 198, 214, 230, 246, 262, 278, 294, 310, 326, 342, 358, 374, 390, 406, 422, 438, 454, 470, 486, 502, 518, 534, 550, 566, 582, and 598;

(d) a beta chain variable domain CDR1 encoded by a nucleic acid sequence selected from the group consisting of SEQ ID NOs: 12, 28, 44, 60, 76, 92, 108, 124, 140, 156, 172, 188, 204, 220, 236, 252, 268, 284, 300, 316, 332, 348, 364, 380, 396, 412, 428, 444, 460, 476, 492, 508, 524, 540, 556, 572, 588, and 604;

(e) a beta chain variable domain CDR2 encoded by a nucleic acid sequence selected from the group consisting of SEQ ID NOs: 13, 29, 45, 61, 77, 93, 109, 125, 141, 157, 173, 189, 205, 221, 237, 253, 269, 285, 301, 317, 333, 349, 365, 381, 397, 413, 429, 445, 461, 477, 493, 509, 525, 541, 557, 573, 589, and 605; and

(f) a beta chain variable domain CDR3 encoded by a nucleic acid sequence selected from the group consisting of SEQ ID NOs: 14, 30, 46, 62, 78, 94, 110, 126, 142, 158, 174, 190, 206, 222, 238, 254, 270, 286, 302, 318, 334, 350, 366, 382, 398, 414, 430, 446, 462, 478, 494, 510, 526, 542, 558, 574, 590, and 606.

38. The polynucleotide molecule of claim 37, 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: 8/16, 24/32, 40/48, 56/64, 72/80, 88/96, 104/112,

120/128, 136/144, 152/160, 168/176, 184/192, 200/208, 216/224, 232/240, 248/256, 264/272, 280/288, 296/304, 312/320, 328/336, 344/352, 360/368, 376/384, 392/400, 408/416, 424/432, 440/448, 456/464, 472/480, 488/496, 504/512, 520/528, 536/544, 552/560, 568/576, 584/592, 600/608.

39. A vector comprising the polynucleotide molecule of any one of claims 28-38.

40. An isolated cell comprising the vector of claim 39.

41. Use of a plurality of the cells of claim 40 in the manufacture of a medicament for ~~A method of~~ treating a subject having a MAGE-A4-associated disease or disorder, ~~comprising administering to the subject a plurality of the cells of claim 40, thereby treating the subject.~~

42. The method-use of claim 41, wherein the MAGE-A4-associated disease or disorder is MAGE-A4-associated cancer.

43. The method-use of claim 43, wherein the MAGE-A4-associated cancer is a liposarcoma, a neuroblastoma, a myeloma, a melanoma, a metastatic melanoma, a synovial sarcoma, a bladder cancer, an esophageal cancer, an esophageal squamous cell carcinoma, a hepatocellular cancer, a head and neck cancer, a non-small cell lung cancer, an ovarian cancer, an ovarian epithelial cancer, a prostate cancer, a breast cancer, an astrocytic tumor, a glioblastoma multiforme, an anaplastic astrocytoma, a brain tumor, a fallopian tube cancer, primary peritoneal cavity cancer, advanced solid tumors, soft tissue sarcoma, a sarcoma, a myelodysplastic syndrome, an acute myeloid leukemia, a Hodgkin lymphoma, a non-Hodgkin lymphoma, a Hodgkin disease, a multiple myeloma, a metastatic solid tumors, a colorectal carcinoma, a stomach cancer, a gastric cancer, a rhabdomyosarcoma, a myxoid round cell liposarcoma, or a recurrent non-small cell lung cancer.

44. The method-use of any one of claims 41-43, wherein the plurality of cells is to be administered to the subject in combination with a second therapeutic agent.

45. A T cell receptor (TCR) that binds specifically to an HLA-A2 presented cancer testis antigen melanoma-associated antigen 4 (MAGE-A4) peptide comprising the amino acid sequence of GGYDGREHTV (SEQ ID NO:612) (MAGE-A4 230-239), wherein the TCR comprises a complementary determining region 3 (CDR3) contained with an alpha chain variable domain of any one of SEQ ID NOs: 620, 636, 652, 668, 684, 700, 716, 732, 748, 764, 780, 796, 812, 828, 844, and 860.

46. A T cell receptor (TCR) that binds specifically to an HLA-A2 presented cancer testis antigen melanoma-associated antigen 4 (MAGE-A4) peptide comprising the amino acid sequence of GGYDGREHTV (SEQ ID NO:612) (MAGE-A4 230-239), wherein the TCR comprises a complementary determining region 3 (CDR3) contained within a beta chain variable domain of any one of SEQ ID NOs: 628, 644, 660, 676, 692, 708, 724, 740, 756, 772, 788, 804, 820, 836, 852, and 868.

47. The TCR of claim 45, 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 6 and the CDR2 independently comprises any one of the alpha chain variable domain CDR2 amino acid sequences set forth in Table 6.

48. The TCR of claim 46, 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.

49. The TCR of any one of claims 45-48, wherein the TCR comprises at least one TCR alpha chain variable domain and/or at least one beta chain variable domain.

50. The TCR of claim 49, wherein the TCR comprises a TCR alpha chain variable domain and a TCR beta chain variable domain.

51. The TCR of any one of claims 46-50, 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.

52. The TCR of any one of claims 45-51, 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.

53. The TCR of any one of claims 45-52, 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.

54. The TCR of any one of claims 45-53, 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.

55. The TCR of any one of claims 46-54, comprising:

(a) an alpha chain variable domain CDR1 domain having an amino acid sequence selected from the group consisting of SEQ ID NOs: 614, 630, 646, 662, 678, 694, 710, 726, 742, 758, 774, 790, 806, 822, 838, and 854;

(b) an alpha chain variable domain CDR2 domain having an amino acid sequence selected from the group consisting of SEQ ID NOs: 615, 631, 647, 663, 679, 695, 711, 727, 743, 759, 775, 791, 807, 823, 839, and 855;

(c) an alpha chain variable domain CDR3 domain having an amino acid sequence selected from the group consisting of SEQ ID NOs: 616, 632, 648, 664, 680, 696, 712, 728, 744, 760, 776, 792, 808, 824, 840, and 856;

(d) a beta chain variable domain CDR1 having an amino acid sequence selected from the group consisting of SEQ ID NOs: 622, 638, 654, 670, 686, 702, 718, 734, 750, 766, 782, 798, 814, 830, 846, and 862;

(e) a beta chain variable domain CDR2 having an amino acid sequence selected from the group consisting of SEQ ID NOs: 623, 639, 655, 671, 687, 703, 719, 735, 751, 767, 783, 799, 815, 831, 847, and 863; and

(f) a beta chain variable domain CDR3 having an amino acid sequence selected from the group consisting of SEQ ID NOs: 624, 640, 656, 672, 688, 704, 720, 736, 752, 768, 784, 800, 816, 832, 848, and 864.

56. The TCR of claim 55, comprising an alpha chain variable domain/beta chain variable domain amino acid sequence pair selected from the group consisting of SEQ ID NOs: 620/628, 636/644, 652/660, 668/676, 684/692, 700/708, 716/724, 732/740, 748/756, 764/772, 780/788, 796/804, 812/820, 828/836, 844/852, and 860/868.

57. The TCR of claim 55, comprising an alpha chain variable domain/beta chain variable domain amino acid sequence pair selected from the group consisting of SEQ ID NOs: 620/628, 620/644, 620/660, 620/676, 620/692, 620/708, 620/724, 620/740, 620/756, 620/772, 620/788, 620/804, 620/820, 620/836, 620/852, 620/868, 636/628, 636/644, 636/660, 636/676, 636/692, 636/708, 636/724, 636/740, 636/756, 636/772, 636/788, 636/804, 636/820, 636/836, 636/852, 636/868, 652/628, 652/644, 652/660, 652/676, 652/692, 652/708, 652/724, 652/740, 652/756, 652/772, 652/788, 652/804, 652/820, 652/836, 652/852, 652/868, 668/628, 668/644, 668/660, 668/676, 668/692, 668/708, 668/724, 668/740, 668/756, 668/772, 668/788, 668/804, 668/820, 668/836, 668/852, 668/868, 684/628, 684/644, 684/660, 684/676, 684/692, 684/708, 684/724, 684/740, 684/756, 684/772, 684/788, 684/804, 684/820, 684/836, 684/852, 684/868, 700/628, 700/644, 700/660, 700/676, 700/692, 700/708, 700/724, 700/740, 700/756, 700/772, 700/788, 700/804, 700/820, 700/836, 700/852, 700/868, 716/628, 716/644, 716/660, 716/676, 716/692, 716/708, 716/724, 716/740, 716/756, 716/772, 716/788, 716/804, 716/820, 716/836, 716/852, 716/868, 732/628, 732/644, 732/660, 732/676, 732/692, 732/708, 732/724, 732/740, 732/756, 732/772, 732/788, 732/804, 732/820, 732/836, 732/852, 732/868, 748/628, 748/644, 748/660, 748/676, 748/692, 748/708, 748/724, 748/740, 748/756, 748/772, 748/788, 748/804, 748/820, 748/836, 748/852, 748/868, 764/628, 764/644, 764/660, 764/676, 764/692, 764/708, 764/724, 764/740, 764/756, 764/772, 764/788, 764/804, 764/820, 764/836,

764/852, 764/868, 780/628, 780/644, 780/660, 780/676, 780/692, 780/708, 780/724, 780/740, 780/756, 780/772, 780/788, 780/804, 780/820, 780/836, 780/852, 780/868, 796/628, 796/644, 796/660, 796/676, 796/692, 796/708, 796/724, 796/740, 796/756, 796/772, 796/788, 796/804, 796/820, 796/836, 796/852, 796/868, 812/628, 812/644, 812/660, 812/676, 812/692, 812/708, 812/724, 812/740, 812/756, 812/772, 812/788, 812/804, 812/820, 812/836, 812/852, 812/868, 828/628, 828/644, 828/660, 828/676, 828/692, 828/708, 828/724, 828/740, 828/756, 828/772, 828/788, 828/804, 828/820, 828/836, 828/852, 828/868, 844/628, 844/644, 844/660, 844/676, 844/692, 844/708, 844/724, 844/740, 844/756, 844/772, 844/788, 844/804, 844/820, 844/836, 844/852, 844/868, 860/628, 860/644, 860/660, 860/676, 860/692, 860/708, 860/724, 860/740, 860/756, 860/772, 860/788, 860/804, 860/820, 860/836, 860/852, and 860/868.

58. The TCR of any one of claims 45-57, further comprising a detectable moiety.

59. The TCR of any one of claims 45-57, wherein said isolated TCR has an on-target binding/off-target binding value of greater than 5, greater than 10, greater than 15, greater than 20, greater than 50, greater than 100, greater than 200, greater than 300, greater than 400, greater than 500, greater than 600, greater than 700, greater than 800, greater than 900, or greater than 1000.

60. The TCR of claim 61, wherein said isolated TCR has an on-target binding/off-target binding value of greater than 10.

61. The TCR of claim 61, wherein said isolated TCR has an on-target binding/off-target binding value of greater than 500.

62. A TCR that competes for binding to the isolated TCR of any one of claims 45-61.

63. A pharmaceutical composition comprising the TCR of any one of claims 45-61 and a pharmaceutically acceptable carrier or diluent.

64. An isolated cell presenting the TCR of any one of claims 45-61.

65. A polynucleotide molecule comprising a polynucleotide sequence that encodes an alpha chain variable domain of the TCR as set forth in any one of claims 45, 47, and 49-61.

66. 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 46, 48, and 49-61.

67. A vector comprising the polynucleotide sequence of claim 65 or 66.

68. An isolated cell expressing the vector of claim 67.

69. Use of the TCR of any one of claims 45-61, the pharmaceutical composition of claim 63, or the isolated cell of claim 64 in the manufacture of a medicament for ~~A method of treating a subject having a MAGE-A4-associated disease or disorder, comprising administering to the subject a therapeutically effective amount of the TCR of any one of claims 45-61, the pharmaceutical composition of claim 63, or the isolated cell of claim 64, thereby treating the subject.~~

70. The method-use of claim 69, wherein the MAGE-A4-associated disease or disorder is MAGE-A4-associated cancer.

71. The method-use of claim 70, wherein the MAGE-A4-associated cancer is a liposarcoma, a neuroblastoma, a myeloma, a melanoma, a metastatic melanoma, a synovial sarcoma, a bladder cancer, an esophageal cancer, an esophageal squamous cell carcinoma, a hepatocellular cancer, a head and neck cancer, a non-small cell lung cancer, an ovarian cancer, an ovarian epithelial cancer, a prostate cancer, a breast cancer, an astrocytic tumor, a glioblastoma multiforme, an anaplastic astrocytoma, a brain tumor, a fallopian tube cancer, primary peritoneal cavity cancer, advanced solid tumors, soft tissue sarcoma, a sarcoma, a myelodysplastic syndrome, an acute myeloid leukemia, a Hodgkin lymphoma, a non-Hodgkin lymphoma, a Hodgkin disease, a multiple myeloma, a metastatic solid tumors, a colorectal carcinoma, a stomach cancer, a gastric cancer, a rhabdomyosarcoma, a myxoid round cell liposarcoma, or a recurrent non-small cell lung cancer.

72. The ~~method-use~~ of any one of claims 69-71, wherein the TCR, the pharmaceutical composition, or the cell is to be administered to the subject in combination with a second therapeutic agent.

73. The ~~method-use~~ of any one of claims 69-71, wherein said ~~administering TCR, said pharmaceutical composition, or said cell is to be administered~~ is parenterally.

74. A polynucleotide molecule encoding a T cell receptor (TCR), wherein the TCR binds specifically to an HLA-A2 presented cancer testis antigen melanoma-associated antigen 4 (MAGE-A4) peptide comprising the amino acid sequence of GGYDGREHTV (SEQ ID NO:612) (MAGE-A4 230-239), wherein the TCR has a property selected from the group consisting of: (a) does not bind to cells expressing predicted off-target peptides as determined by a luminescence assay; (b) does not bind to cells expressing predicted off-target peptides as determined by a flow cytometry assay; (c) activates a T cell response about two times greater than a patient-derived MAGE-A4-specific TCR as determined by a TCR-mediated T cell signaling luminescent bioassay; and (d) activates a T cell response about two times greater than an affinity-matured (e.g., by phage display) MAGE-A4-specific TCR as determined by a TCR-mediated T cell signaling luminescent bioassay.

75. The polynucleotide molecule of claim 74, encoding at least one TCR alpha chain variable domain and/or at least one beta chain variable domain.

76. The polynucleotide molecule of claim 74, 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.

77. The polynucleotide molecule of claim 75 or 76, 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.

78. The polynucleotide molecule of any one of claims 74-77, wherein 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.

79. The polynucleotide molecule of any one of claims 74-78, 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.

80. The polynucleotide molecule of any one of claims 74-79, 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: 614, 630, 646, 662, 678, 694, 710, 726, 742, 758, 774, 790, 806, 822, 838, and 854;

(b) an alpha chain variable domain CDR2 domain having an amino acid sequence selected from the group consisting of SEQ ID NOs: 615, 631, 647, 663, 679, 695, 711, 727, 743, 759, 775, 791, 807, 823, 839, and 855;

(c) an alpha chain variable domain CDR3 domain having an amino acid sequence selected from the group consisting of SEQ ID NOs: 616, 632, 648, 664, 680, 696, 712, 728, 744, 760, 776, 792, 808, 824, 840, and 856;

(d) a beta chain variable domain CDR1 having an amino acid sequence selected from the group consisting of SEQ ID NOs: 622, 638, 654, 670, 686, 702, 718, 734, 750, 766, 782, 798, 814, 830, 846, and 862;

(e) a beta chain variable domain CDR2 having an amino acid sequence selected from the group consisting of SEQ ID NOs: 623, 639, 655, 671, 687, 703, 719, 735, 751, 767, 783, 799, 815, 831, 847, and 863; and

(f) a beta chain variable domain CDR3 having an amino acid sequence selected from the group consisting of SEQ ID NOs: 624, 640, 656, 672, 688, 704, 720, 736, 752, 768, 784, 800, 816, 832, 848, and 864.

81. The polynucleotide molecule of claim 80, 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: 620/628, 636/644, 652/660, 668/676, 684/692, 700/708, 716/724, 732/740, 748/756, 764/772, 780/788, 796/804, 812/820, 828/836, 844/852, and 860/868.

82. The polynucleotide molecule of claim 80, 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: 620/628, 620/644, 620/660, 620/676, 620/692, 620/708, 620/724, 620/740, 620/756, 620/772, 620/788, 620/804, 620/820, 620/836, 620/852, 620/868, 636/628, 636/644, 636/660, 636/676, 636/692, 636/708, 636/724, 636/740, 636/756, 636/772, 636/788, 636/804, 636/820, 636/836, 636/852, 636/868, 652/628, 652/644, 652/660, 652/676, 652/692, 652/708, 652/724, 652/740, 652/756, 652/772, 652/788, 652/804, 652/820, 652/836, 652/852, 652/868, 668/628, 668/644, 668/660, 668/676, 668/692, 668/708, 668/724, 668/740, 668/756, 668/772, 668/788, 668/804, 668/820, 668/836, 668/852, 668/868, 684/628, 684/644, 684/660, 684/676, 684/692, 684/708, 684/724, 684/740, 684/756, 684/772, 684/788, 684/804, 684/820, 684/836, 684/852, 684/868, 700/628, 700/644, 700/660, 700/676, 700/692, 700/708, 700/724, 700/740, 700/756, 700/772, 700/788, 700/804, 700/820, 700/836, 700/852, 700/868, 716/628, 716/644, 716/660, 716/676, 716/692, 716/708, 716/724, 716/740, 716/756, 716/772, 716/788, 716/804, 716/820, 716/836, 716/852, 716/868, 732/628, 732/644, 732/660, 732/676, 732/692, 732/708, 732/724, 732/740, 732/756, 732/772, 732/788, 732/804, 732/820, 732/836, 732/852, 732/868, 748/628, 748/644, 748/660, 748/676, 748/692, 748/708, 748/724, 748/740, 748/756, 748/772, 748/788, 748/804, 748/820, 748/836, 748/852, 748/868, 764/628, 764/644, 764/660, 764/676, 764/692, 764/708, 764/724, 764/740, 764/756, 764/772, 764/788, 764/804, 764/820, 764/836, 764/852, 764/868, 780/628, 780/644, 780/660, 780/676, 780/692, 780/708, 780/724, 780/740, 780/756, 780/772, 780/788, 780/804, 780/820, 780/836, 780/852, 780/868, 796/628, 796/644, 796/660, 796/676, 796/692, 796/708, 796/724, 796/740, 796/756, 796/772, 796/788, 796/804, 796/820, 796/836, 796/852, 796/868, 812/628, 812/644, 812/660, 812/676, 812/692, 812/708, 812/724, 812/740, 812/756, 812/772, 812/788, 812/804,

812/820, 812/836, 812/852, 812/868, 828/628, 828/644, 828/660, 828/676, 828/692, 828/708, 828/724, 828/740, 828/756, 828/772, 828/788, 828/804, 828/820, 828/836, 828/852, 828/868, 844/628, 844/644, 844/660, 844/676, 844/692, 844/708, 844/724, 844/740, 844/756, 844/772, 844/788, 844/804, 844/820, 844/836, 844/852, 844/868, 860/628, 860/644, 860/660, 860/676, 860/692, 860/708, 860/724, 860/740, 860/756, 860/772, 860/788, 860/804, 860/820, 860/836, 860/852, and 860/868.

83. The polynucleotide molecule of claim 33, 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: 617, 633, 649, 665, 681, 697, 713, 729, 745, 761, 777, 793, 809, 825, 841, and 857;

(b) an alpha chain variable domain CDR2 encoded by a nucleic acid sequence selected from the group consisting of SEQ ID NOs: 618, 634, 650, 666, 682, 698, 714, 730, 746, 762, 778, 794, 810, 826, 842, and 858;

(c) an alpha chain variable domain CDR3 encoded by a nucleic acid sequence selected from the group consisting of SEQ ID NOs: 619, 635, 651, 667, 683, 699, 715, 731, 747, 763, 779, 795, 811, 827, 843, and 859;

(d) a beta chain variable domain CDR1 encoded by a nucleic acid sequence selected from the group consisting of SEQ ID NOs: 625, 641, 657, 673, 689, 705, 721, 737, 753, 769, 785, 801, 817, 833, 849, and 865;

(e) a beta chain variable domain CDR2 encoded by a nucleic acid sequence selected from the group consisting of SEQ ID NOs: 626, 642, 658, 674, 690, 706, 722, 738, 754, 770, 786, 802, 818, 834, 850, and 866; and

(f) a beta chain variable domain CDR3 encoded by a nucleic acid sequence selected from the group consisting of SEQ ID NOs: 627, 643, 659, 675, 691, 707, 723, 739, 755, 771, 787, 803, 819, 835, 851, and 867.

84. The isolated nucleic acid molecule of claim 83, 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: 621/629, 637/645, 653/661, 669/677, 685/693, 701/709, 717/725, 733/741, 749/757, 765/773, 781/789, 797/805, 813/821, 829/837, 845/853, and 861/869.

85. A vector comprising the polynucleotide sequence of the isolated nucleic acid molecule of any one of claims 74-84.

86. An isolated cell comprising the vector of claim 85.

87. Use of the cell of claim 86 in the manufacture of a medicament for ~~A method of treating a subject having a MAGE-A4-associated disease or disorder, comprising administering to the subject the cell of claim 86, thereby treating the subject.~~

88. The method-use of claim 87, wherein the MAGE-A4-associated disease or disorder is MAGE-A4-associated cancer.

89. The method-use of claim 88, wherein the MAGE-A4-associated cancer is a liposarcoma, a neuroblastoma, a myeloma, a melanoma, a metastatic melanoma, a synovial sarcoma, a bladder cancer, an esophageal cancer, an esophageal squamous cell carcinoma, a hepatocellular cancer, a head and neck cancer, a non-small cell lung cancer, an ovarian cancer, an ovarian epithelial cancer, a prostate cancer, a breast cancer, an astrocytic tumor, a glioblastoma multiforme, an anaplastic astrocytoma, a brain tumor, a fallopian tube cancer, primary peritoneal cavity cancer, advanced solid tumors, soft tissue sarcoma, a sarcoma, a myelodysplastic syndrome, an acute myeloid leukemia, a Hodgkin lymphoma, a non-Hodgkin lymphoma, a Hodgkin disease, a multiple myeloma, a metastatic solid tumors, a colorectal carcinoma, a stomach cancer, a gastric cancer, a rhabdomyosarcoma, a myxoid round cell liposarcoma, or a recurrent non-small cell lung cancer.

90. The method-use of any one of claims 87-89, wherein the cell is to be administered to the subject in combination with a second therapeutic agent.