

CLAIMS

What is claimed is:

1. An isolated T cell receptor (TCR) specific for MAGE-A4, wherein the TCR comprises:

a) a variable TCR α region comprising a CDR1 having the amino acid sequence of SEQ ID NO: 2, a CDR2 having the amino acid sequence of SEQ ID NO: 3 and a CDR3 having the amino acid sequence of SEQ ID NO: 4, and

a variable TCR β region comprising a CDR1 having the amino acid sequence of SEQ ID NO: 5, a CDR2 having the amino acid sequence of SEQ ID NO: 6 and a CDR3 having the amino acid sequence of SEQ ID NO: 7; or

b) a variable TCR α region comprising a CDR1 having the amino acid sequence of SEQ ID NO: 12, a CDR2 having the amino acid sequence of SEQ ID NO: 13 and a CDR3 having the amino acid sequence of SEQ ID NO: 14, and

a variable TCR β region comprising a CDR1 having the amino acid sequence of SEQ ID NO: 15, a CDR2 having the amino acid sequence of SEQ ID NO: 16 and a CDR3 having the amino acid sequence of SEQ ID NO: 17; or

c) a variable TCR α region comprising a CDR1 having the amino acid sequence of SEQ ID NO: 22, a CDR2 having the amino acid sequence of SEQ ID NO: 23 and a CDR3 having the amino acid sequence of SEQ ID NO: 24, and

a variable TCR β region comprising a CDR1 having the amino acid sequence of SEQ ID NO: 25, a CDR 2 having the amino acid sequence of SEQ ID NO: 26 and a CDR 3 having the amino acid sequence of SEQ ID NO: 27, wherein the TCR specifically recognizes the amino acid sequence SEQ ID NO: 1, wherein the TCR specifically recognizes the HLA-A2 bound form of the amino acid sequence of SEQ ID NO: 1.

2. The isolated TCR according to claim 1, ~~wherein the TCR specifically recognizes the amino acid sequence SEQ ID NO: 1 or a fragment thereof, preferably wherein the TCR specifically recognizes the HLA A2 bound form of the amino acid sequence of SEQ ID NO: 1, more preferably~~ wherein the TCR specifically recognizes the amino acid sequence of SEQ ID NO: 1, which is presented by the HLA-A*02:01 encoded molecule.

3. The isolated TCR according to any one of the preceding claims, wherein the TCR comprises:

- a) a variable TCR α region having the amino acid sequence of SEQ ID NO: 8 and a variable TCR β region having the amino acid sequence of SEQ ID NO: 9; or
- b) a variable TCR α region having the amino acid sequence of SEQ ID NO: 18 and a variable TCR β region having the amino acid sequence of SEQ ID NO: 19; or
- c) a variable TCR α region having the amino acid sequence of SEQ ID NO: 28 and a variable TCR β region having the amino acid sequence of SEQ ID NO: 29.

~~4. The isolated TCR of any of the preceding claims, wherein the TCR comprises a functional portion comprising at least one of the amino acid sequences of SEQ ID NOs: 4, 7, 14, 17, 24 and 27.~~

~~45.~~ The isolated TCR of any one of claims 1 to ~~34~~, wherein the TCR comprises:

- a) a TCR α chain having the amino acid sequence of SEQ ID NO: 10 and a TCR β chain having the amino acid sequence of SEQ ID NO: 11;
- b) a TCR α chain having the amino acid sequence of SEQ ID NO: 20 and a TCR β chain having the amino acid sequence of SEQ ID NO: 21; or
- c) a TCR α chain having the amino acid sequence of SEQ ID NO: 30 and a TCR β chain having the amino acid sequence of SEQ ID NO: 31.

~~56.~~ The isolated TCR of any one of claims 1 to ~~34~~, wherein the TCR comprises:

- a) a TCR α chain having the amino acid sequence of SEQ ID NO: 87 and a TCR β chain having the amino acid sequence of SEQ ID NO: 88;
- b) a TCR α chain having the amino acid sequence of SEQ ID NO: 89 and a TCR β chain having the amino acid sequence of SEQ ID NO: 90; or
- c) a TCR α chain having the amino acid sequence of SEQ ID NO: 91 and a TCR β chain having the amino acid sequence of SEQ ID NO: 92.

~~67.~~ The isolated TCR of any one of claims 1 to ~~34~~, wherein the TCR comprises:

- a) a TCR α chain having the amino acid sequence of SEQ ID NO: 102 and a TCR β chain having the amino acid sequence of SEQ ID NO: 103;
- b) a TCR α chain having the amino acid sequence of SEQ ID NO: 108 and a TCR β

chain having the amino acid sequence of SEQ ID NO: 109; or

c) a TCR α chain having the amino acid sequence of SEQ ID NO: 114 and a TCR β chain having the amino acid sequence of SEQ ID NO: 115.

78. The isolated TCR according to any one of claims 1 to ~~67~~, ~~or the multivalent TCR complex according to claim 8~~, wherein IFN- γ secretion is induced by binding to the amino acid sequence of SEQ ID NO: 1, which is presented by the HLA-A*02:01 encoded molecule.

89. The isolated TCR according to ~~any one of claims 1 to 77~~, wherein the IFN- γ secretion induced by binding of the TCR expressed on an effector cell to the amino acid sequence of SEQ ID NO: 1, which is presented by the HLA-A*02:01 encoded molecule, is ~~may be~~ more than 100 times higher, preferably 500 times higher, more preferably 2000 times higher when binding to the amino acid sequence of SEQ ID NO: 1, which is presented by the HLA-A*02:01 encoded molecule, compared to binding to an irrelevant peptide, which is presented by the HLA-A*02:01 encoded molecule.

910. A multivalent TCR complex comprising at least two TCRs as claimed in any one of claims 1 to ~~76~~.

101. A fusion protein comprising a TCR α chain and a TCR β chain, wherein the fusion protein comprises the amino acid sequence set forth in any one of SEQ ID NOs: 94, 96, 98, 104, 110, and 116.

112. A nucleic acid encoding the TCR according to any one of claims 1 to ~~67~~ or the fusion protein of claim 101.

123. The nucleic acid of claim 112, wherein the nucleic acid sequence encoding the TCR α chain is set forth in any one of SEQ ID NOs: 69, 77, 85, 99, 105, and 111.

134. The nucleic acid of claim 112, wherein the nucleic acid sequence encoding the TCR β chain is set forth in any one of SEQ ID NOs: 70, 78, 86, 100, 106, and 112.

145. The nucleic acid of claim 110, wherein the TCR comprises:

a) a TCR α chain encoded by SEQ ID NO: 69 and a TCR β chain encoded by SEQ ID NO: 70;

b) a TCR α chain encoded by SEQ ID NO: 77 and a TCR β chain encoded by SEQ ID NO: 78;

c) a TCR α chain encoded by SEQ ID NO: 85 and a TCR β chain encoded by SEQ ID NO: 86;

d) a TCR α chain encoded by SEQ ID NO: 99 and a TCR β chain encoded by SEQ ID NO: 100;

e) a TCR α chain encoded by SEQ ID NO: 105 and a TCR β chain encoded by SEQ ID NO: 106; or

f) a TCR α chain encoded by SEQ ID NO: 111 and a TCR β chain encoded by SEQ ID NO: 112.

156. The nucleic acid of claim 121, wherein the fusion protein is encoded by the nucleic acid sequence set forth in any one of SEQ ID NOs: 93, 95, 97, 101, 107, and 113.

167. A vector comprising the nucleic acid of any one of claims 112 to 156, wherein the vector is preferably an expression vector, more preferably a retroviral vector or even more preferably a lentiviral vector.

178. A vector comprising a nucleic acid encoding:

a) the polypeptide sequences set forth in SEQ ID NO: 87 and SEQ ID NO: 88;

b) the polypeptide sequences set forth in SEQ ID NO: 89 and SEQ ID NO: 90;

c) the polypeptide sequences set forth in SEQ ID NO: 91 and SEQ ID NO: 92;

d) the polypeptide sequences set forth in SEQ ID NO: 102 and SEQ ID NO: 103;

e) the polypeptide sequences set forth in SEQ ID NO: 108 and SEQ ID NO: 109; or

f) the polypeptide sequences set forth in SEQ ID NO: 114 and SEQ ID NO: 115;

wherein the vector is preferably an expression vector, more preferably a retroviral vector or even more preferably a lentiviral vector.

189. A cell expressing the TCR according to any one of claims 1 to 647.

1920. A cell comprising the vector of claim 167 or claim 178.

201. The cell of claim 189 or claim 1920, wherein the cell is an immune effector cell.

212. The cell of any one of claims 189 to 201, wherein the immune effector cell is a T cell, a natural killer (NK) cell, or a natural killer T (NKT) cell.

223. An antibody or antigen binding fragment thereof specifically binding to a portion of the TCR according to any one of claims 1 to 67 that mediates specificity for MAGE-A4, ~~preferably~~ wherein the portion of the TCR that mediates the MAGE-A4 specificity comprises the

a) CDR3 of the alpha chain of SEQ ID NO: 4 and/or the CDR3 of the beta chain of SEQ ID NO: 7 or;

b) CDR3 of the alpha chain of SEQ ID NO: 14 and/or the CDR3 of the beta chain of SEQ ID NO: 17 or;

c) CDR3 of the alpha chain of SEQ ID NO: 24 and/or the CDR3 of the beta chain of SEQ ID NO: 27.

234. A composition comprising the TCR according to any one of claims 1 to 67, the multivalent TCR complex according to claim 98, the fusion protein of claim 101, the nucleic acid according to any one of claims 112 to 156, the vector according to claim 167 or claim 178, the cell according to any one of claims 189 to 212, or the antibody according to claim 223.

245. A pharmaceutical composition comprising a pharmaceutically acceptable carrier and the TCR according to any one of claims 1 to 67, the multivalent TCR complex according to claim 98, the fusion protein of claim 101, the nucleic acid according to any one of claims 112 to 156, the vector according to claim 167 or claim 178, the cell according to any one of claims 189 to 212, or the antibody according to claim 223.

256. The TCR according to any one of claims 1 to 67, the multivalent TCR complex according to claim 98, the fusion protein of claim 101, the nucleic acid according to any one of claims 112 to 156, the vector according to claim 167 or claim 178, the cell according to any one of claims 189 to 212, the antibody according to claim 223, the composition of claim 234, or the pharmaceutical composition of claim 245 for use as a medicament.

267. The TCR according to any one of claims 1 to 67, the multivalent TCR complex according to claim 98, the fusion protein of claim 104, the nucleic acid according to any one of claims 112 to 156, the vector according to claim 167 or claim 178, the cell according to any one of claims 189 to 212, the antibody according to claim 223, the composition of claim 234, or the pharmaceutical composition of claim 245 for use in the treatment of cancer, wherein the cancer is preferably a hematological cancer or a solid tumor, more preferably wherein the cancer is selected from the group consisting of sarcoma, prostate cancer, uterine cancer, thyroid cancer, testicular cancer, renal cancer, pancreatic cancer, ovarian cancer, esophageal cancer, non-small-cell lung cancer, non-Hodgkin's lymphoma, multiple myeloma, melanoma, hepatocellular carcinoma, head and neck cancer, gastric cancer, endometrial cancer, colorectal cancer, cholangiocarcinoma, breast cancer, bladder cancer, myeloid leukemia and acute lymphoblastic leukemia, most preferably wherein the cancer is selected from the group consisting of NSCLC, SCLC, breast, ovarian or colorectal cancer, sarcoma or osteosarcoma.