

CLAIMS

1. An antibody cytokine engrafted protein comprising:
 - (a) a heavy chain variable region (VH), comprising Complementarity Determining Regions (CDRs) HCDR1, HCDR2, HCDR3; and
 - (b) a light chain variable region (VL), comprising LCDR1, LCDR2, LCDR3; and
 - (c) a mutated Interleukin 2 (IL2) molecule ~~or a fragment thereof~~ engrafted into the HCDR1, ~~HCDR2, or HCDR3 of the VH or engrafted into the LCDR1, LCDR2, or LCDR3 of the VL~~ wherein the HCDR1 engrafted with the mutated IL2 molecule comprises SEQ ID NO: 7, SEQ ID NO: 10, SEQ ID NO: 13, SEQ ID NO: 16, SEQ ID NO: 39, SEQ ID NO: 42, SEQ ID NO: 45, or SEQ ID NO: 48, and wherein the mutated IL2 molecule contains a mutation that reduces the affinity of the mutated IL2 molecule to a high affinity IL2 receptor.

2. An antibody cytokine engrafted protein comprising:
 - (a) a heavy chain variable region (VH), comprising Complementarity Determining Regions (CDRs) HCDR1, HCDR2, HCDR3; and
 - (b) a light chain variable region (VL), comprising LCDR1, LCDR2, LCDR3; and
 - (c) ~~an~~ mutated Interleukin 2 (IL2) molecule ~~or a fragment thereof~~ engrafted into the HCDR1, ~~HCDR2, or HCDR3 of the VH or engrafted into the LCDR1, LCDR2, or LCDR3 of the VL~~ wherein the HCDR1 engrafted with the mutated IL2 molecule comprises SEQ ID NO: 7, SEQ ID NO: 10, SEQ ID NO: 13, SEQ ID NO: 16, SEQ ID NO: 39, SEQ ID NO: 42, SEQ ID NO: 45, or SEQ ID NO: 48,
 wherein the antibody cytokine engrafted protein preferentially expands T effector cells over regulatory T cells.

3. An antibody cytokine engrafted protein comprising:
 - (a) a heavy chain variable region (VH), comprising Complementarity Determining Regions (CDRs) HCDR1, HCDR2, HCDR3; and
 - (b) a light chain variable region (VL), comprising LCDR1, LCDR2, LCDR3;
 - (c) ~~an~~ mutated Interleukin 2 (IL2) molecule ~~or a fragment thereof~~ engrafted into the HCDR1, ~~HCDR2, or HCDR3 of the VH or engrafted into the LCDR1, LCDR2, or LCDR3 of the VL~~ wherein the HCDR1 engrafted with the mutated IL2 molecule

comprises SEQ ID NO: 7, SEQ ID NO: 10, SEQ ID NO: 13, SEQ ID NO: 16, SEQ ID NO: 39, SEQ ID NO: 42, SEQ ID NO: 45, or SEQ ID NO: 48,

wherein the antibody cytokine engrafted protein stimulates one or more of CD8 T effector cell, NK cell proliferation, or combination thereof, greater than recombinant IL2 or a modified aglycosylated IL2 lacking an N-terminal alanine and having a S125C mutation.

4. The antibody cytokine engrafted protein of any one of claims 1 to 3, wherein the mutated IL2 molecule ~~or a fragment thereof~~ comprises SEQ ID NO: 4.

5. The antibody cytokine engrafted protein of any one of claims 1 to 3, wherein the mutated IL2 molecule ~~or a fragment thereof~~ comprises SEQ ID NO: 6.

~~6. The antibody cytokine engrafted protein of claim 1, wherein the CDR of the VH is HCDR1, wherein HCDR1 comprises SEQ ID NO: 7, SEQ ID NO: 10, SEQ ID NO: 13, SEQ ID NO: 16, SEQ ID NO: 39, SEQ ID NO: 42, SEQ ID NO: 45, or SEQ ID NO: 48.~~

~~76. The antibody cytokine engrafted protein of ~~claim 6~~ any one of claims 1 to 3, wherein the CDR of the VH is HCDR1, and wherein the VH comprises SEQ ID NO: 19 or SEQ ID NO: 51.~~

~~87. The antibody cytokine engrafted protein of any one of claims 1 to ~~76~~, further comprising an IgG class antibody heavy chain.~~

~~98. The antibody cytokine engrafted protein of claim ~~87~~, wherein the IgG class heavy chain is selected from IgG1, IgG2, and IgG4.~~

~~109. The antibody cytokine engrafted protein of claim ~~87~~, wherein the IgG class heavy chain comprises SEQ ID NO: 21 or SEQ ID NO: 53.~~

~~140. The antibody cytokine engrafted protein of any one of claims 1 to 3, wherein the IgG class light chain comprises SEQ ID NO: 69 and the IgG class heavy chain comprises SEQ ID NO: 53.~~

121. The antibody cytokine engrafted protein of any one of claims 1 to 3, wherein the IgG class light chain comprises SEQ ID NO:37 and the IgG class heavy chain comprises SEQ ID NO:21.

132. The antibody cytokine engrafted protein of any one of claims 1 to 3, wherein the IgG class light chain comprises SEQ ID NO:69 and the IgG class heavy chain comprises SEQ ID NO:21.

143. The antibody cytokine engrafted protein of any one of claims 1 to 3, wherein the IgG class light chain comprises SEQ ID NO:37 and the IgG class heavy chain comprises SEQ ID NO:53.

154. A pharmaceutical composition comprising the antibody cytokine engrafted protein of any one of claims 1 to 143 and a pharmaceutically acceptable carrier.

165. Use of the antibody cytokine engrafted protein of any one of claims 1 to 143 or the pharmaceutical composition of claim 154 in the manufacture of a medicament for the treatment of cancer.

176. The use of claim 165, wherein the cancer is selected from the group consisting of melanoma, lung cancer, colorectal cancer, prostate cancer, breast cancer, and lymphoma.

187. The use of claim 165 or 176 for combination therapy of cancer, wherein the antibody cytokine engrafted protein or pharmaceutical composition is to be administered in combination with a therapeutic agent.

198. The use of claim 187, wherein the therapeutic agent is a second antibody cytokine engrafted protein.

2019. The use of claim 187, wherein the therapeutic agent is an immune checkpoint inhibitor.

240. The use of claim ~~20~~19, wherein the immune checkpoint inhibitor is selected from the group consisting of: PD-1, PD-L1, PD-L2, TIM3, CTLA-4, LAG-3, CEACAM-1, CEACAM-5, VISTA, BTLA, TIGIT, LAIR1, CD160, 2B4 and TGFR.

221. The use of claim ~~18~~7, wherein the therapeutic agent is a tyrosine kinase inhibitor.

232. A method of preferentially expanding T effector cells over regulatory T cells in a patient in need thereof, wherein a therapeutically effective amount of the antibody cytokine engrafted protein of any one of claims 1 to ~~14~~3 or the pharmaceutical composition of claim ~~15~~4 is to be administered to the patient.

243. The method of claim ~~23~~2, wherein the T effector cells are expanded and Treg cells are not expanded.

254. The method of any one of claims ~~23~~2 to ~~24~~3, wherein an immune checkpoint inhibitor is to be administered.

265. The method of claim ~~25~~4, wherein the immune checkpoint inhibitor is selected from the group consisting of: PD-1, PD-L1, PD-L2, TIM3, CTLA-4, LAG-3, CEACAM-1, CEACAM-5, VISTA, BTLA, TIGIT, LAIR1, CD160, 2B4 and TGFR.

276. The antibody cytokine engrafted protein of any one of claims 1 to ~~14~~3 or the pharmaceutical composition of claim 14 for use in ~~a method for~~ the treatment of cancer.

~~28. The antibody cytokine engrafted protein of claim 27 for use in combination therapy of cancer, wherein the antibody cytokine engrafted protein is to be administered in combination with a therapeutic agent.~~

~~29. The antibody cytokine engrafted protein of claim 28, wherein the therapeutic agent is an immune checkpoint inhibitor.~~

~~30. The antibody cytokine engrafted protein of claim 29, wherein the immune checkpoint is selected from the group consisting of: PD-1, PD-L1, PD-L2, TIM3,~~

~~CTLA-4, LAG-3, CEACAM-1, CEACAM-5, VISTA, BTLA, TIGIT, LAIR1, CD160, 2B4 and TGFR.~~

~~3127.~~ An isolated nucleic acid encoding an antibody cytokine engrafted protein comprising: (i) a heavy chain of SEQ ID NO:22 and a light chain of SEQ ID NO:38; or (ii) a heavy chain of SEQ ID NO:54 and a light chain of SEQ ID NO:70.

~~328.~~ A recombinant host cell suitable for the production of an antibody cytokine engrafted protein, comprising the nucleic acid of claim ~~3127~~ encoding the heavy and light chain polypeptides of the antibody cytokine engrafted protein, and optionally, a secretion signal.

~~329.~~ The recombinant host cell of claim ~~328~~, which is a mammalian cell line.

~~340.~~ The recombinant host cell of claim ~~329~~, wherein the mammalian cell line is a CHO cell line, Cos cell line, HeLa cell line, myeloma cell line, transformed B-cell line, or a hybridoma.