

CLAIMS

1. An antibody cytokine engrafted protein comprising:
 - (a) a heavy chain variable region (VH), comprising Complementarity Determining Regions (CDR) HCDR1, HCDR2, HCDR3; and
 - (b) a light chain variable region (VL), comprising LCDR1, LCDR2, LCDR3; and
 - (c) an Interleukin 2 (IL2) molecule or a fragment thereof engrafted into a CDR of the VH or the VL,
wherein the IL2 molecule or the fragment thereof comprises a R38A mutation according to the numbering of SEQ ID NO: 4 or comprises a F42A mutation according to the numbering of SEQ ID NO:6.
2. An antibody cytokine engrafted protein comprising:
 - (a) a heavy chain variable region (VH), comprising Complementarity Determining Regions (CDR) HCDR1, HCDR2, HCDR3; and
 - (b) a light chain variable region (VL), comprising LCDR1, LCDR2, LCDR3; and
 - (c) an Interleukin 2 (IL2) molecule or a fragment thereof engrafted into a CDR of the VH or the VL,
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 (CDR) HCDR1, HCDR2, HCDR3; and
 - (b) a light chain variable region (VL), comprising LCDR1, LCDR2, LCDR3;
 - (c) an Interleukin 2 (IL2) molecule or a fragment thereof engrafted into a CDR of the VH or the VL,
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 Proleukin®.
4. The antibody cytokine engrafted protein of any one of claims 1 to 3, wherein the 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 IL2 molecule or a fragment thereof comprises SEQ ID NO: 6.
6. The antibody cytokine engrafted protein of any one of claims 1 to 5, wherein the IL2 molecule is engrafted into a CDR of the VH.
7. The antibody cytokine engrafted protein of claim 6, wherein the CDR of the VH is HCDR1, HCDR2, or HCDR3.
8. The antibody cytokine engrafted protein of claim 7, wherein the CDR of the VH is HCDR1, and wherein the IL2 molecule engrafted into 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.
9. The antibody cytokine engrafted protein of claim 7, wherein the CDR of the VH is HCDR1, and wherein the VH comprises SEQ ID NO: 19 or SEQ ID NO: 51.
10. The antibody cytokine engrafted protein of any one of claims 1 to 5, wherein the IL2 molecule is engrafted into a CDR of the VL.
11. The antibody cytokine engrafted protein of claim 10, wherein the CDR of the VL is LCDR1, LCDR2, or LCDR3.
12. The antibody cytokine engrafted protein of any one of claims 1 to 11, further comprising an IgG class antibody heavy chain.
13. The antibody cytokine engrafted protein of claim 12, wherein the IgG class heavy chain is selected from IgG1, IgG2, and IgG4.
14. The antibody cytokine engrafted protein of claim 12, wherein the IgG class heavy chain comprises SEQ ID NO: 21 or SEQ ID NO: 53.

15. 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.
16. 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.
17. 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.
18. 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.
19. A pharmaceutical composition comprising the antibody cytokine engrafted protein of any one of claims 1 to 18 and a pharmaceutically acceptable carrier.
20. Use of the antibody cytokine engrafted protein of any one of claims 1 to 18 or the pharmaceutical composition of claim 19 in the manufacture of a medicament for the treatment of cancer.
21. The use of claim 20, wherein the cancer is selected from the group consisting of melanoma, lung cancer, colorectal cancer, prostate cancer, breast cancer, and lymphoma.
22. The use of claim 20 or 21, wherein the antibody cytokine engrafted protein or pharmaceutical composition is to be administered in combination with a therapeutic agent.
23. The use of claim 22, wherein the therapeutic agent is a second antibody cytokine engrafted protein.
24. The use of claim 22, wherein the therapeutic agent is an immune checkpoint inhibitor.

25. The use of claim 24, 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.
26. The use of claim 22, wherein the therapeutic agent is a tyrosine kinase inhibitor.
27. 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 18 or the pharmaceutical composition of claim 19 is to be administered to the patient.
28. The method of claim 27, wherein the T effector cells are expanded and Treg cells are not expanded.
29. The method of any one of claims 27 to 28, wherein an immune checkpoint inhibitor is to be administered.
30. The method 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.
31. The antibody cytokine engrafted protein of any one of claims 1 to 18 for use in a method for the treatment of cancer.
32. The antibody cytokine engrafted protein of claim 31, wherein the antibody cytokine engrafted protein is to be administered in combination with a therapeutic agent.
33. The antibody cytokine engrafted protein of claim 32, wherein the therapeutic agent is an immune checkpoint inhibitor.
34. The antibody cytokine engrafted protein of claim 33, 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.

35. 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.

36. A recombinant host cell suitable for the production of an antibody cytokine engrafted protein, comprising the nucleic acid of claim 35 encoding the heavy and light chain polypeptides of the antibody cytokine engrafted protein, and optionally, a secretion signal.

37. The recombinant host cell of claim 36, which is a mammalian cell line.

38. The recombinant host cell of claim 37, 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.