

CLAIMS

1. A fusion protein, comprising a therapeutic protein connected to a mutant Interleukin-2 (IL2) polypeptide, wherein the therapeutic protein is ~~a portion of or an entire anti-PDL1 immune checkpoint antibody, or an anti-checkpoint scFv,~~ comprising a pair of heavy chains and a pair of light chains, wherein the mutant IL2 polypeptide is connected to the C-terminals of the heavy chains, wherein the mutant IL2 polypeptide ~~is less selective towards a high affinity receptor of a wild type IL2~~ comprises an amino acid sequence identical to the amino acid sequences selected from SEQ ID NO: 25 or SEQ ID NO: 27.
2. ~~The fusion protein of claim 1, wherein the portion of or the entire immune checkpoint antibody comprises a pair of heavy chains and a pair of light chains, wherein the mutant IL2 polypeptide is connected to the C-terminals of the heavy chains.~~
23. The fusion protein of claim 12, wherein the mutant IL2 polypeptide is connected to the C-terminals of the heavy chains through a linker sequence.
4. ~~The fusion protein of claim 1, wherein the fusion protein is a bispecific design antibody analog with a first arm corresponding to that of the immune checkpoint antibody and a second arm comprising a mutant IL2 polypeptide fused to the Fc-portion of the antibody analog.~~
5. ~~The fusion protein of claim 1, wherein the anti-checkpoint scFv and the mutant IL2 polypeptide are connected through a linker sequence.~~
6. ~~The fusion protein of claim 1, wherein the anti-checkpoint scFv is an anti-PDL1-scFv.~~
7. The fusion protein of any of claims 1-6, wherein the mutant IL2 polypeptide has ~~one or both of the following features in comparison to a wild type IL2: (a) it has a reduced capability for activating CTLL2 and human and mouse T_{reg} while it has retained a comparable capability for activating effector T cells or NK cells; and (b) it exhibits a significantly more selective capability for activating T_{eff} over T_{reg}.~~

~~8. The fusion protein of any of claims 1-7, wherein the mutant IL-2 polypeptide comprises an amino acid sequence substantially identical to the amino acid sequences selected from the group consisting of SEQ ID NO: 23, SEQ ID NO: 25, SEQ ID NO: 27, SEQ ID NO: 29, SEQ ID NO: 31, SEQ ID NO: 33, SEQ ID NO: 35, SEQ ID NO: 37, SEQ ID NO: 39, SEQ ID NO: 41, SEQ ID NO: 43, SEQ ID NO: 45, SEQ ID NO: 47, SEQ ID NO: 49, SEQ ID NO: 51, SEQ ID NO: 53, SEQ ID NO: 55, SEQ ID NO: 57 and combinations thereof.~~

9. The fusion protein of claim 1, wherein the immune checkpoint antibody is an anti-PDL1 antibody.

10. The fusion protein of claim 9, wherein the anti-PDL1 antibody has one or more of the following features: (a) it binds PDL1 with $K_d < 100$ nM to both purified protein as well as protein expressed on cell surface; (b) it blocks PDL1-CD1 interaction in vitro; and/or (c) it de-represses PDL1-mediated repression of effector T cells in activated PBMC cultures.

311. The fusion protein of claim 1, wherein the anti-PDL1 immune checkpoint antibody is an antibody of any available isotype or any known mutant forms of Fc region that mediates or enhances ADCC and/or CDC function.

412. The fusion protein of claim 1, wherein the anti-PDL1 immune checkpoint antibody is an antibody of IgG1 isotype.

513. The fusion protein of claim ~~16~~ or 9, wherein the anti-PDL1 antibody or anti-PDL1 scFv comprises a heavy chain variable region and a light chain variable region where their respective sequences consist essentially of the following pairings: (a) SEQ ID NO: 3 and SEQ ID NO: 6; (b) SEQ ID NO: 9 and SEQ ID NO: 12; or (c) ~~SEQ ID NO: 15 and SEQ ID NO: 18.~~

614. The fusion protein of claim ~~19~~, wherein the anti-PDL1 antibody comprises a heavy chain and a light chain where their respective sequences consist essentially of the following pairings: (a) SEQ ID NO: 2 and SEQ ID NO: 5; (b) SEQ ID NO: 8 and SEQ ID NO: 11; or (c) ~~SEQ ID NO: 14 and SEQ ID NO: 17.~~

715. The fusion protein of claim ~~23~~ or 5, wherein the linker sequence is a serine-glycine linker.

~~816.~~ The fusion protein of claim ~~715~~, wherein the linker sequence is SEQ ID NO: 19.

~~17.~~ The fusion protein of any of claims 1-16, wherein mutation has been introduced at one or more amino acid positions in the fusion protein to disrupt at least one proteolytic site.

~~18.~~ The fusion protein of any of claims 1-16, wherein mutation has been introduced at one or more amino acid positions in the fusion protein to disrupt at least one glycosylation site.

~~19.~~ The fusion protein of any of claims 1-16, wherein an alternate secretory sequence has been introduced into the fusion protein to replace an innate secretory sequence.

~~920.~~ A pharmaceutical composition comprising the fusion protein of any of claims 1-~~819~~, and a pharmaceutically acceptable excipient, carrier or diluent.

~~1021.~~ A nucleic acid molecule that encodes the fusion protein of any of claims 1-~~819~~, wherein the nucleic acid molecule is a DNA molecule or RNA molecule.

~~1122.~~ Pharmaceutical composition according to claim 9 for use in therapy, said use comprising a therapeutically effective amount of the pharmaceutical composition of claim ~~920~~ is to be administered to a subject in need thereof for a condition.

~~1223.~~ Pharmaceutical composition according to claim 9 for use in therapy, said use comprising a therapeutically effective amount of the pharmaceutical composition of claim ~~920~~ in combination with (a) antibodies targeting at least another immunosuppressive pathways; (b) chemotherapy, targeted therapy or radiation therapy; (c) another mechanism of blocking an immunosuppressive pathway; or (d) another immunotherapy agent is to be administered to a subject in need thereof for a condition.

~~1324.~~ The use of any of claims ~~1122-1223~~, wherein said condition is a mammalian cancer.

~~1425.~~ The use of any of claims ~~1322-23~~, wherein said cancer is selected from the group consisting of melanoma, lung cancer, renal cancer, head neck cancer, gastric cancer, lymphoma, ovarian cancer, colon cancer, breast cancer, lung cancer, myelomas, brain tumors, leukemias, lymphomas, bladder cancer, liver cancer,

urothelial carcinoma, cutaneous carcinoma, pancreatic cancer, and combinations thereof.

1526. A mammalian expression system that produces fusion protein of any of claims 1-~~819~~.

1627. A mutant IL2 polypeptide that is less selective towards a high-affinity receptor of a wild type IL2, wherein said mutant IL2 polypeptide comprises an amino acid sequence substantially identical to a sequence selected from the group consisting of ~~SEQ ID NO: 23, SEQ ID NO: 25, or SEQ ID NO: 27, SEQ ID NO: 29, SEQ ID NO: 31, SEQ ID NO: 33, SEQ ID NO: 35, SEQ ID NO: 37, SEQ ID NO: 39, SEQ ID NO: 41, SEQ ID NO: 43, SEQ ID NO: 45, SEQ ID NO: 47, SEQ ID NO: 49, SEQ ID NO: 51, SEQ ID NO: 53, SEQ ID NO: 55, SEQ ID NO: 57 and combinations thereof.~~