

most responsive indications the response rate is limited to about 30% of patients. Accordingly, there is a need for improved T cell modulating therapeutics.

SUMMARY

[0006] Provided herein are polypeptides comprising a modified IL-2 comprising at least one substitution at at least one amino acid position. In some embodiment examples, the modified IL-2 has reduced binding affinity for CD25, CD122, and/or an IL-2R relative to wild type IL-2. In some embodiment examples, the modified IL-2 has reduced activity on resting or activated T cells relative to wild type IL-2.

[0006a] In one aspect, the present disclosure refers to a polypeptide comprising a modified IL-2, wherein the modified IL-2 comprises a D84Y substitution, wherein the amino acid positions correspond to the amino acid positions in SEQ ID NO: 1.

[0006b] In one aspect, the present disclosure refers to a modified polypeptide comprising a modified IL-2, wherein the modified IL-2 comprises a set of substitutions selected from [T3A, H16A, E61R, P65R, D84Y, C125S], [T3A, H16A, M23T, E61R, P65R, D84Y, E95Q, C125S], [T3A, H16A, L19N, E61R, P65R, D84Y, C125S], [T3A, H16A, L19N, M23T, E61R, P65R, D84Y, E95Q, C125S], [T3A, H16A, E61R, P65R, D84Y, C125S, S127D], [T3A, H16A, M23T, E61R, P65R, D84Y, E95Q, C125S, S127D], [T3A, H16A, L19N, E61R, P65R, D84Y, C125S, S127D], and [T3A, H16A, L19N, M23T, E61R, P65R, D84Y, E95Q, C125S, S127D].

[0006c] In one aspect, the present disclosure refers to a complex comprising a first polypeptide and a second polypeptide, wherein the first polypeptide is any one of the polypeptides as disclosed herein.

[0006d] In one aspect, the present disclosure refers to a pharmaceutical composition comprising any one of the polypeptides as disclosed herein or any one of the complexed as disclosed herein and a pharmaceutically acceptable carrier.

[0006e] In one aspect, the present disclosure refers to an isolated nucleic acid that encodes any one of polypeptides as disclosed herein or any one of the complexes as disclosed herein.

[0006f] In one aspect, the present disclosure refers to an expression vector comprising the nucleic acid as disclosed herein.

[0006g] In one aspect, the present disclosure refers to an isolated host cell comprising the nucleic acid as disclosed herein or the expression vector as disclosed herein.

[0006h] In one aspect, the present disclosure refers to an isolated host cell that expresses any one of the polypeptides as disclosed herein or any one of the complexes as disclosed herein.

[0006i] In one aspect, the present disclosure refers to a method of producing any one of the polypeptides as disclosed herein or any one of the complexes as disclosed herein comprising incubating any one of the host cells as disclosed herein under conditions suitable to express the polypeptide or complex, and optionally isolating the polypeptide of complex.

[0006j] In one aspect, the present disclosure refers to a method of increasing CD4+ and/or CD8+ T cell proliferation comprising contacting T cells with any one of the polypeptides as disclosed herein or any one of the complexes as disclosed herein, wherein the CD4+ and/or CD8+ T cells are in vitro or in vivo.

[0006k] In one aspect, the present disclosure refers to a method of increasing NK cell proliferation comprising contacting NK cells with any one of the polypeptides as disclosed herein or any one of the complexes as disclosed herein.

[0006l] In one aspect, the present disclosure refers to use of any one of the polypeptides as disclosed herein or any one of the complexes as disclosed herein, or the pharmaceutical composition as disclosed herein, in the manufacture of a medicament for treating cancer in a subject with cancer.

[0007] The following embodiments are provided herein:

Embodiment 1. A polypeptide comprising a modified IL-2, wherein the modified IL-2 comprises a D84Y substitution.

Embodiment 2. The polypeptide of embodiment 1, wherein the modified IL-2 has reduced affinity for CD122 compared to wild-type IL-2.

Embodiment 3. The polypeptide of any one of embodiments 1-2, wherein the modified IL-2 comprises at least one substitution at at least one amino acid position selected from H16, L19, M23, N88, and E95.

Embodiment 4. The polypeptide of embodiment 3, wherein the modified IL-2 comprises a substitution at amino acid position H16.

Embodiment 5. The polypeptide of embodiment 4, wherein the substitution is selected from H16A H16N, H16V, and H16T.

Embodiment 6. The polypeptide of any one of embodiments 1-5, wherein the modified IL-2 comprises a substitution at amino acid position L19.

Embodiment 7. The polypeptide of embodiment 6, wherein the substitution is selected from L19A, L19P, L19Q, L19Y, L19N, L19S, L19T, L19V.

Embodiment 8. The polypeptide of any one of embodiments 1-7, wherein the modified IL-2 comprises a substitution at amino acid position M23.

Embodiment 9. The polypeptide of embodiment 8, wherein the substitution is selected from M23A, M23G, M23S, M23T, M23V, M23D, M23E, M23I, M23K, M23L, M23N, M23Q, M23R, and M23Y.

Embodiment 10. The polypeptide of any one of embodiments 1-9, wherein the modified IL-2 comprises a substitution at amino acid position N88.

Embodiment 11. The polypeptide of embodiment 10, wherein the substitution is selected from N88T, N88A, and N88S.