

treatment provides for the selective eradication of cells that express an antigen, thereby minimizing adverse effects to normal cells not expressing the antigen. In one example, vaccine antigen or polynucleotide coding therefor is administered to provide (optionally following expression of the polynucleotide by appropriate target cells) antigen for stimulation, priming and/or expansion of the immune effector cells, wherein the immune effector cells (optionally genetically modified to express an antigen receptor) are targeted to the antigen or a procession product thereof and the immune response is an immune response to a target cell population or target tissue expressing the antigen. In one example, the polynucleotide encoding the vaccine antigen is RNA. Immune effector cells such as T cells stimulated, primed and/or expanded in the patient are able to recognize cells expressing an antigen resulting in the eradication of diseased cells. The methods and agents described herein are particularly effective if RNA encoding IL2 variants is targeted to the liver for systemic availability. Liver cells can be efficiently transfected and are able to produce large amounts of protein. Antigen-encoding RNA is preferably targeted to secondary lymphoid organs.

Accordingly, one example relates to systems of alpha subunit of interleukin-2 receptor (IL2R α) and interleukin-2 (IL2) variants for specific activation of immune effector cells in the treatment of diseases where such immune effector cells can be effective such as cancer including but not limited to solid tumors. In one example, the present disclosure relates to a strategy of adoptive cell transfer of cells such as T cells transduced to express a CAR. CARs are molecules that combine specificity for a desired antigen (e.g., tumor antigen) which preferably is antibody-based with a T cell receptor-activating intracellular domain to generate a chimeric protein that exhibits a specific cellular immune activity (e.g., a specific anti-tumor cellular immune activity). Preferably, a cell can be genetically modified to stably express a CAR (and an IL2 receptor polypeptide described herein) on its surface, conferring novel antigen specificity that is MHC independent. T cells expressing a CAR are referred to herein as CAR T cells or CAR-modified T cells.

One aspect example of the disclosure relates to a system comprising:

- (i) a receptor polypeptide comprising a mutein of the alpha subunit of interleukin-2 receptor (IL2R) or of a functional variant of the alpha subunit of IL2R, wherein the alpha subunit of IL2R or the functional variant thereof is substituted at at least one position,
 - (ii) a ligand polypeptide comprising a mutein of IL2 or of a functional variant of IL2, wherein the IL2 or the functional variant thereof is substituted at at least one position,
- wherein the substitutions are such that

A further aspect of the disclosure relates to a pharmaceutical composition comprising the polynucleotide described herein or the host cell described herein. In one example, the pharmaceutical composition further comprises one or more pharmaceutically acceptable carriers, diluents and/or excipients.

5 In another aspect, the present disclosure relates to the polynucleotide described herein, the host cell described herein, or the pharmaceutical composition described herein for use in therapy. In yet another aspect, the present disclosure relates to a use of the polynucleotide described herein, the host cell described herein, or the pharmaceutical composition described herein in the manufacture of a medicament for treating or preventing cancer in a subject.

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A further example of the disclosure relates to a method of treating a subject comprising administering to the subject the polynucleotide described herein, the host cell described herein, or the pharmaceutical composition described herein. In one example, the method is a method for treating or preventing cancer in a subject.

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In another aspect, the present disclosure relates to a medical preparation comprising:

(i) a polynucleotide encoding a receptor polypeptide of the system described herein or an immune effector cell genetically modified to express a receptor polypeptide of the system described herein, and

(ii) the corresponding ligand polypeptide of the system under (i), a polynucleotide encoding the ligand polypeptide, or a host cell genetically modified to express the ligand polypeptide, optionally wherein the medical preparation is a kit comprising instructions for use of the medical preparation for treating or preventing cancer.

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A further example of the disclosure relates to a medical preparation comprising:

25 (i) a polynucleotide encoding a receptor polypeptide of the system described herein or an immune effector cell genetically modified to express a receptor polypeptide of the system described herein, and

(ii) the corresponding ligand polypeptide of the system under (i), a polynucleotide encoding the ligand polypeptide, or a host cell genetically modified to express the ligand polypeptide.

30 In one example, the medical preparation is a kit. In one example, the medical preparation comprises each component (i) and (ii) in separate containers. In one example, the components are present in a pharmaceutical composition. In one example, the pharmaceutical composition further comprises one or more pharmaceutically acceptable carriers, diluents and/or excipients. In one example, the medical

preparation further comprises instructions for use of the medical preparation for treating or preventing cancer.

5 In yet another aspect, the present disclosure relates to ~~the medical preparation described herein for use in therapy~~a polynucleotide encoding a receptor polypeptide of the system as described herein, or an immune effector cell genetically modified to express a receptor polypeptide of the system as described herein, and the corresponding ligand polypeptide of the system as described herein, a polynucleotide encoding the ligand polypeptide, or a host cell genetically modified to express the ligand polypeptide for use in a combination therapy. A further example of the disclosure relates to the medical preparation
10 described herein for pharmaceutical use. In one example, the pharmaceutical use comprises a therapeutic or prophylactic treatment of a disease or disorder.

15 In yet another aspect, the present disclosure relates to a use (i) a polynucleotide encoding a receptor polypeptide of the system as described herein or an immune effector cell genetically modified to express a receptor polypeptide of the system as described herein, and (ii) the corresponding ligand polypeptide of the system under (i), a polynucleotide encoding the ligand polypeptide, or a host cell genetically modified to express the ligand polypeptide~~of the medical preparation described herein~~ in the manufacture of a ~~combination therapy medicament~~ for treating or preventing cancer in a subject. A further example of the disclosure relates to the medical preparation described herein for use in a method for treating or
20 preventing cancer in a subject.

25 In yet another aspect, the present disclosure provides a use of a polynucleotide encoding a receptor polypeptide of the system as described herein, or an immune effector cell genetically modified to express a receptor polypeptide of the system as described herein in the manufacture of a medicament for use in a combination therapy for treating or preventing cancer in a subject, wherein said medicament is to be administered in combination with the corresponding ligand polypeptide of the system as described herein, a polynucleotide encoding the ligand polypeptide, or a host cell genetically modified to express the ligand polypeptide.

30 In yet another aspect, the present disclosure relates to a use of immune effector cells genetically modified to express a receptor polypeptide of the system described herein in the manufacture of a medicament for treating cancer in a subject associated with expression or elevated expression of a tumor-associated antigen, comprising that:

(i) the immune effector cells genetically modified to express a receptor polypeptide of the system as described herein are to be provided to the subject, the immune effector cells being targeted to the antigen or cells expressing the antigen and

5 (ii) the corresponding ligand polypeptide of the system under (i), a polynucleotide encoding the ligand polypeptide, or a host cell genetically modified to express the ligand polypeptide is to be administered to the subject.

A further example of the disclosure relates to a method for treating a subject comprising:

10 (i) providing to the subject immune effector cells genetically modified to express a receptor polypeptide of the system described herein, and

(ii) administering to the subject the corresponding ligand polypeptide of the system under (i), a polynucleotide encoding the ligand polypeptide, or a host cell genetically modified to express the ligand polypeptide.

15 In one example, the subject has cancer.

In one example, the method is a method of inducing an immune response in said subject. In one example, the immune response is a T cell-mediated immune response.

20 A further example of the disclosure relates to a method for treating a subject having a disease, disorder or condition associated with expression or elevated expression of an antigen comprising:

(i) providing to the subject immune effector cells genetically modified to express a receptor polypeptide of the system described herein, the immune effector cells being targeted to the antigen or cells expressing the antigen and

25 (ii) administering to the subject the corresponding ligand polypeptide of the system under (i), a polynucleotide encoding the ligand polypeptide, or a host cell genetically modified to express the ligand polypeptide.

30 In one example, the disease, disorder or condition is cancer and the antigen is a tumor-associated antigen.

In one example, the immune effector cells genetically modified to express a receptor polypeptide are provided to the subject by administering the immune effector cells genetically modified to express a

receptor polypeptide or by generating the immune effector cells genetically modified to express a receptor polypeptide in the subject.

In one example, the method described herein is a method for treating or preventing cancer in a subject.

5 In one example, the cancer is selected from the group consisting of melanoma, leukemia, lymphoma, lung cancer, breast cancer, prostate cancer, ovarian cancer, colon cancer, mesothelioma, renal cell carcinoma, and brain cancer.

10 In one example of a medical preparation or method described herein, the polynucleotide encoding the receptor polypeptide and/or the polynucleotide encoding the ligand polypeptide is RNA.

In one example of the medical preparation, the RNA is present in a form selected from a liquid form, a solid form, or a combination thereof. In one example, the solid form is a frozen form or a dehydrated form. In one example, the dehydrated form is a freeze-dried or spray-dried form.

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In one example of a medical preparation or method described herein, the immune effector cells genetically modified to express a receptor polypeptide comprise a polynucleotide encoding the receptor polypeptide.

20 In one example of a medical preparation or method described herein, the host cell genetically modified to express the ligand polypeptide comprises a polynucleotide encoding the ligand polypeptide.

In one example of a medical preparation or method described herein, the polynucleotide encoding the receptor polypeptide and/or the polynucleotide encoding the ligand polypeptide is RNA.

25 In one example of a medical preparation or method described herein, the immune effector cells are T cells.

30 In one example, the methods described herein further comprise administering to the subject an immune checkpoint inhibitor. In one example, the immune checkpoint inhibitor targets the interaction between (i) PD-1 and PD-L1, or (ii) CTLA-4 and CD80 or CD86. In one example, the immune checkpoint inhibitor is an antibody or antibody fragment. In one example, the antibody or antibody fragment targets PD-1, PD-L1, or CTLA-4.

Similarly, in one example, the medical preparation described herein further comprises an immune checkpoint inhibitor. In one example, the immune checkpoint inhibitor targets the interaction between (i) PD-1 and PD-L1, or (ii) CTLA-4 and CD80 or CD86. In one example, the immune checkpoint inhibitor is an antibody or antibody fragment. In one example, the antibody or antibody fragment targets PD-1, PD-L1, or CTLA-4.

In a further example, the disclosure relates to the agents and compositions described herein, e.g., IL2R variants, IL2 variants or IL2R/IL2 variant systems described herein, polynucleotides coding for IL2R variants, IL2 variants or IL2R/IL2 variant systems described herein, cells expressing IL2R variants described herein, for therapeutic use, in particular for use in the methods described herein.

Other features and advantages of the instant disclosure will be apparent from the following detailed description and claims.

Claims

1. A system comprising:

(i) a receptor polypeptide comprising a mutein of the alpha subunit of interleukin-2 receptor (IL2R) or of a functional variant of the alpha subunit of IL2R, wherein the alpha subunit of IL2R or the functional variant thereof is substituted at at least one position;

(ii) a ligand polypeptide comprising a mutein of IL2 or of a functional variant of IL2, wherein the IL2 or the functional variant thereof is substituted at at least one position;

wherein the substitutions are such that

(a) the mutein under (ii) binds to and activates IL2R comprising the mutein under (i) as alpha subunit, and

(b) binding to and/or activation of IL2R comprising the mutein under (i) as alpha subunit by the mutein under (ii) exceeds binding to and/or activation of IL2R comprising the alpha subunit of IL2R or the functional variant thereof as alpha subunit by the mutein under (ii).

2. The system of claim 1, wherein binding to and/or activation of IL2R comprising the mutein under (i) as alpha subunit by the mutein under (ii) exceeds binding to and/or activation of IL2R comprising the mutein under (i) as alpha subunit by IL2 or the functional variant thereof and/or,

wherein binding to and/or activation of IL2R comprising the alpha subunit of IL2R or the functional variant thereof as alpha subunit by IL2 or the functional variant thereof exceeds binding to and/or activation of IL2R comprising the alpha subunit of IL2R or the functional variant thereof as alpha subunit by the mutein under (ii), and/or

wherein binding to and/or activation of IL2R comprising the alpha subunit of IL2R or the functional variant thereof as alpha subunit by IL2 or the functional variant thereof exceeds binding to and/or activation of IL2R comprising the mutein under (i) as alpha subunit by IL2 or the functional variant thereof.

3. The system of claim 1 or 2, comprising

(i) a receptor polypeptide comprising a mutein of the alpha subunit of IL2R or of a functional variant of the alpha subunit of IL2R, wherein the alpha subunit of IL2R or the functional variant thereof is substituted at at least a position having an acidic amino acid residue in wild type alpha subunit of IL2R that contacts a basic amino acid residue in wild type IL2 and/or is substituted at at least a position having a basic amino acid residue in wild type alpha subunit of IL2R that contacts an acidic amino acid residue in wild type IL2, wherein if the amino acid residue is an acidic amino acid residue in wild type

~~alpha subunit of IL2R the substitution is by a basic amino acid residue and if the amino acid residue is a basic amino acid residue in wild type alpha subunit of IL2R the substitution is by an acidic amino acid residue,~~

~~(ii) a ligand polypeptide comprising a mutein of IL2 or of a functional variant of IL2, wherein when the alpha subunit of IL2R or the functional variant thereof is substituted at at least a position having an acidic amino acid residue in wild type alpha subunit of IL2R that contacts a basic amino acid residue in wild type IL2, the IL2 or the functional variant thereof is substituted at at least said basic amino acid residue in wild type IL2 and/or when the alpha subunit of IL2R or the functional variant thereof is substituted at at least a position having a basic amino acid residue in wild type alpha subunit of IL2R that contacts an acidic amino acid residue in wild type IL2, the IL2 or the functional variant thereof is substituted at at least said acidic amino acid residue in wild type IL2, wherein if the amino acid residue is a basic amino acid residue in wild type IL2 the substitution is by an acidic amino acid residue and if the amino acid residue is an acidic amino acid residue in wild type IL2 the substitution is by a basic amino acid residue.~~

41. A system comprising:

(i) a receptor polypeptide comprising a mutein of the alpha subunit of interleukin-2 receptor (IL2R) or of a functional variant of the alpha subunit of IL2R, wherein the alpha subunit of IL2R or the functional variant thereof is substituted at at least a position having an acidic amino acid residue in wild type alpha subunit of IL2R that contacts a basic amino acid residue in wild type IL2 and/or is substituted at at least a position having a basic amino acid residue in wild type alpha subunit of IL2R that contacts an acidic amino acid residue in wild type IL2, wherein if the amino acid residue is an acidic amino acid residue in wild type alpha subunit of IL2R the substitution is by a basic amino acid residue and if the amino acid residue is a basic amino acid residue in wild type alpha subunit of IL2R the substitution is by an acidic amino acid residue,

(ii) a ligand polypeptide comprising a mutein of IL2 or of a functional variant of IL2, wherein when the alpha subunit of IL2R or the functional variant thereof is substituted at at least a position having an acidic amino acid residue in wild type alpha subunit of IL2R that contacts a basic amino acid residue in wild type IL2, the IL2 or the functional variant thereof is substituted at at least said basic amino acid residue in wild type IL2 and/or when the alpha subunit of IL2R or the functional variant thereof is substituted at at least a position having a basic amino acid residue in wild type alpha subunit of IL2R that contacts an acidic amino acid residue in wild type IL2, the IL2 or the functional variant thereof is substituted at at least said acidic amino acid residue in wild type IL2, wherein if the amino acid residue is a basic amino acid residue in wild type IL2 the substitution is by an acidic amino acid residue and if

the amino acid residue is an acidic amino acid residue in wild type IL2 the substitution is by a basic amino acid residue.

52. The system of ~~any one of claims 1 to 4~~, wherein the alpha subunit of IL2R is the human alpha subunit of IL2R, and/or
wherein the IL2 is human IL2.

63. The system of ~~any one of claims 1 to 5 or 2~~, wherein
(i) the alpha subunit of IL2R is the human alpha subunit of IL2R and the alpha subunit of IL2R or the functional variant thereof is substituted at at least position 1 (glutamic acid) relative to wild type human alpha subunit of IL2R and numbered in accordance with wild type human alpha subunit of IL2R, and
(ii) the IL2 is human IL2 and the IL2 or the functional variant thereof is substituted at at least position 35 (lysine) relative to wild type human IL2 and numbered in accordance with wild type human IL2,
optionally wherein position 1 is substituted with lysine and/or
wherein position 35 is substituted with glutamic acid.

74. The system of any one of claims 1 to 63, wherein
(i) the alpha subunit of IL2R is the human alpha subunit of IL2R and the alpha subunit of IL2R or the functional variant thereof is substituted at at least position 29 (glutamic acid) relative to wild type human alpha subunit of IL2R and numbered in accordance with wild type human alpha subunit of IL2R, and
(ii) the IL2 is human IL2 and the IL2 or the functional variant thereof is substituted at at least position 43 (lysine) relative to wild type human IL2 and numbered in accordance with wild type human IL2,
optionally wherein position 29 is substituted with lysine and/or
wherein position 43 is substituted with glutamic acid.

85. The system of any one of claims 1 to 74, wherein
(i) the alpha subunit of IL2R is the human alpha subunit of IL2R and the alpha subunit of IL2R or the functional variant thereof is substituted at at least position 38 (lysine) relative to wild type human alpha subunit of IL2R and numbered in accordance with wild type human alpha subunit of IL2R, and
(ii) the IL2 is human IL2 and the IL2 or the functional variant thereof is substituted at at least position 61 (glutamic acid) relative to wild type human IL2 and numbered in accordance with wild type human IL2,
optionally wherein position 38 is substituted with glutamic acid and/or
wherein position 61 is substituted with lysine.

96. The system of any one of claims 1 to 85,

wherein (i) the alpha subunit of IL2R is the human alpha subunit of IL2R and the alpha subunit of IL2R or the functional variant thereof is substituted at at least position 1 (glutamic acid) by lysine, position 29 (glutamic acid) by lysine and position 38 (lysine) by glutamic acid relative to wild type human alpha subunit of IL2R and numbered in accordance with wild type human alpha subunit of IL2R, and

(ii) the IL2 is human IL2 and the IL2 or the functional variant thereof is substituted at at least position 35 (lysine) by glutamic acid, position 43 (lysine) by glutamic acid and position 61 (glutamic acid) by lysine relative to wild type human IL2 and numbered in accordance with wild type human IL2, or

wherein (i) the alpha subunit of IL2R is the human alpha subunit of IL2R and the alpha subunit of IL2R or the functional variant thereof is substituted at at least position 29 (glutamic acid) by lysine and position 38 (lysine) by glutamic acid relative to wild type human alpha subunit of IL2R and numbered in accordance with wild type human alpha subunit of IL2R, and

(ii) the IL2 is human IL2 and the IL2 or the functional variant thereof is substituted at at least position 43 (lysine) by glutamic acid and position 61 (glutamic acid) by lysine relative to wild type human IL2 and numbered in accordance with wild type human IL2, or

wherein (i) the alpha subunit of IL2R is the human alpha subunit of IL2R and the alpha subunit of IL2R or the functional variant thereof is substituted at at least position 38 (lysine) by glutamic acid relative to wild type human alpha subunit of IL2R and numbered in accordance with wild type human alpha subunit of IL2R, and

(ii) the IL2 is human IL2 and the IL2 or the functional variant thereof is substituted at at least position 61 (glutamic acid) by lysine relative to wild type human IL2 and numbered in accordance with wild type human IL2, or

wherein (i) the alpha subunit of IL2R is the human alpha subunit of IL2R and the alpha subunit of IL2R or the functional variant thereof is substituted at at least position 29 (glutamic acid) by lysine relative to wild type human alpha subunit of IL2R and numbered in accordance with wild type human alpha subunit of IL2R, and

(ii) the IL2 is human IL2 and the IL2 or the functional variant thereof is substituted at at least position 43 (lysine) by glutamic acid relative to wild type human IL2 and numbered in accordance with wild type human IL2, or

wherein (i) the alpha subunit of IL2R is the human alpha subunit of IL2R and the alpha subunit of IL2R or the functional variant thereof is substituted at at least position 29 (glutamic acid) by lysine and position 38 (lysine) by glutamic acid relative to wild type human alpha subunit of IL2R and numbered in accordance with wild type human alpha subunit of IL2R, and

(ii) the IL2 is human IL2 and the IL2 or the functional variant thereof is substituted at at least position 35 (lysine) by glutamic acid, position 43 (lysine) by glutamic acid and position 61 (glutamic acid) by lysine relative to wild type human IL2 and numbered in accordance with wild type human IL2, or wherein (i) the alpha subunit of IL2R is the human alpha subunit of IL2R and the alpha subunit of IL2R or the functional variant thereof is substituted at at least position 29 (glutamic acid) by lysine relative to wild type human alpha subunit of IL2R and numbered in accordance with wild type human alpha subunit of IL2R, and

(ii) the IL2 is human IL2 and the IL2 or the functional variant thereof is substituted at at least position 43 (lysine) by glutamic acid and position 61 (glutamic acid) by lysine relative to wild type human IL2 and numbered in accordance with wild type human IL2.

107. A system comprising:

(i) a receptor polypeptide comprising a mutein of the human alpha subunit of interleukin-2 receptor (IL2R) or of a functional variant of the human alpha subunit of IL2R, wherein the alpha subunit of IL2R or the functional variant thereof is substituted at at least position 1 (glutamic acid) by a basic amino acid residue relative to wild type human alpha subunit of IL2R and numbered in accordance with wild type human alpha subunit of IL2R, and

(ii) a ligand polypeptide comprising a mutein of human IL2 or of a functional variant of human IL2, wherein the IL2 or the functional variant thereof is substituted at at least position 35 (lysine) by an acidic amino acid residue relative to wild type human IL2 and numbered in accordance with wild type human IL2, optionally wherein position 1 is substituted with lysine and/or wherein position 35 is substituted with glutamic acid.

118. A system comprising:

(i) a receptor polypeptide comprising a mutein of the human alpha subunit of interleukin-2 receptor (IL2R) or of a functional variant of the human alpha subunit of IL2R, wherein the alpha subunit of IL2R or the functional variant thereof is substituted at at least position 29 (glutamic acid) by a basic amino acid residue relative to wild type human alpha subunit of IL2R and numbered in accordance with wild type human alpha subunit of IL2R, and

(ii) a ligand polypeptide comprising a mutein of human IL2 or of a functional variant of human IL2, wherein the IL2 or the functional variant thereof is substituted at at least position 43 (lysine) by an acidic amino acid residue relative to wild type human IL2 and numbered in accordance with wild type human IL2, optionally wherein position 29 is substituted with lysine and/or wherein position 43 is substituted with glutamic acid.

429. A system comprising:

- (i) a receptor polypeptide comprising a mutein of the human alpha subunit of interleukin-2 receptor (IL2R) or of a functional variant of the human alpha subunit of IL2R, wherein the alpha subunit of IL2R or the functional variant thereof is substituted at at least position 38 (lysine) by an acidic amino acid residue relative to wild type human alpha subunit of IL2R and numbered in accordance with wild type human alpha subunit of IL2R, and
- (ii) a ligand polypeptide comprising a mutein of human IL2 or of a functional variant of human IL2, wherein the IL2 or the functional variant thereof is substituted at at least position 61 (glutamic acid) by a basic amino acid residue relative to wild type human IL2 and numbered in accordance with wild type human IL2, optionally wherein position 38 is substituted with glutamic acid and/or wherein position 61 is substituted with lysine.

4310. A system comprising:

- (i) a receptor polypeptide comprising a mutein of the human alpha subunit of interleukin-2 receptor (IL2R) or of a functional variant of the human alpha subunit of IL2R, wherein the alpha subunit of IL2R or the functional variant thereof is substituted at at least position 1 (glutamic acid) by lysine, position 29 (glutamic acid) by lysine and position 38 (lysine) by glutamic acid relative to wild type human alpha subunit of IL2R and numbered in accordance with wild type human alpha subunit of IL2R, and
- (ii) a ligand polypeptide comprising a mutein of human IL2 or of a functional variant of human IL2, wherein the IL2 or the functional variant thereof is substituted at at least position 35 (lysine) by glutamic acid, position 43 (lysine) by glutamic acid and position 61 (glutamic acid) by lysine relative to wild type human IL2 and numbered in accordance with wild type human IL2.

4411. A system comprising:

- (i) a receptor polypeptide comprising a mutein of the human alpha subunit of interleukin-2 receptor (IL2R) or of a functional variant of the human alpha subunit of IL2R, wherein the alpha subunit of IL2R or the functional variant thereof is substituted at at least position 29 (glutamic acid) by lysine and position 38 (lysine) by glutamic acid relative to wild type human alpha subunit of IL2R and numbered in accordance with wild type human alpha subunit of IL2R, and
- (ii) a ligand polypeptide comprising a mutein of human IL2 or of a functional variant of human IL2, wherein the IL2 or the functional variant thereof is substituted at at least position 43 (lysine) by glutamic acid and position 61 (glutamic acid) by lysine relative to wild type human IL2 and numbered in accordance with wild type human IL2.

4512. A system comprising:

- (i) a receptor polypeptide comprising a mutein of the human alpha subunit of interleukin-2 receptor (IL2R) or of a functional variant of the human alpha subunit of IL2R, wherein the alpha subunit of IL2R or the functional variant thereof is substituted at at least position 38 (lysine) by glutamic acid relative to wild type human alpha subunit of IL2R and numbered in accordance with wild type human alpha subunit of IL2R, and
- (ii) a ligand polypeptide comprising a mutein of human IL2 or of a functional variant of human IL2, wherein the IL2 or the functional variant thereof is substituted at at least position 61 (glutamic acid) by lysine relative to wild type human IL2 and numbered in accordance with wild type human IL2.

4613. A system comprising:

- (i) a receptor polypeptide comprising a mutein of the human alpha subunit of interleukin-2 receptor (IL2R) or of a functional variant of the human alpha subunit of IL2R, wherein the alpha subunit of IL2R or the functional variant thereof is substituted at at least position 29 (glutamic acid) by lysine relative to wild type human alpha subunit of IL2R and numbered in accordance with wild type human alpha subunit of IL2R, and
- (ii) a ligand polypeptide comprising a mutein of human IL2 or of a functional variant of human IL2, wherein the IL2 or the functional variant thereof is substituted at at least position 43 (lysine) by glutamic acid relative to wild type human IL2 and numbered in accordance with wild type human IL2.

4714. A system comprising:

- (i) a receptor polypeptide comprising a mutein of the human alpha subunit of interleukin-2 receptor (IL2R) or of a functional variant of the human alpha subunit of IL2R, wherein the alpha subunit of IL2R or the functional variant thereof is substituted at at least position 29 (glutamic acid) by lysine and position 38 (lysine) by glutamic acid relative to wild type human alpha subunit of IL2R and numbered in accordance with wild type human alpha subunit of IL2R, and
- (ii) a ligand polypeptide comprising a mutein of human IL2 or of a functional variant of human IL2, wherein the IL2 or the functional variant thereof is substituted at at least position 35 (lysine) by glutamic acid, position 43 (lysine) by glutamic acid and position 61 (glutamic acid) by lysine relative to wild type human IL2 and numbered in accordance with wild type human IL2.

4815. A system comprising:

- (i) a receptor polypeptide comprising a mutein of the human alpha subunit of interleukin-2 receptor (IL2R) or of a functional variant of the human alpha subunit of IL2R, wherein the alpha subunit of IL2R or the functional variant thereof is substituted at at least position 29 (glutamic acid) by lysine relative to wild type human alpha subunit of IL2R and numbered in accordance with wild type human alpha subunit of IL2R, and
- (ii) a ligand polypeptide comprising a mutein of human IL2 or of a functional variant of human IL2, wherein the IL2 or the functional variant thereof is substituted at at least position 43 (lysine) by glutamic acid and position 61 (glutamic acid) by lysine relative to wild type human IL2 and numbered in accordance with wild type human IL2.

~~19~~16. The system of any one of claims 1 to ~~18~~15, wherein the alpha subunit of IL2R has the amino acid sequence according to SEQ ID NO: 2 and/or wherein the IL2 has the amino acid sequence according to SEQ ID NO: 1.

~~20~~17. The system of any one of claims ~~41~~ to ~~19~~16, wherein the mutein under (ii) binds to and activates IL2R comprising the mutein under (i) as alpha subunit.

~~24~~18. The system of claim ~~20~~17, wherein binding to and/or activation of IL2R comprising the mutein under (i) as alpha subunit by the mutein under (ii) exceeds binding to and/or activation of IL2R comprising the alpha subunit of IL2R or the functional variant thereof as alpha subunit by the mutein under (ii), and/or wherein binding to and/or activation of IL2R comprising the mutein under (i) as alpha subunit by the mutein under (ii) exceeds binding to and/or activation of IL2R comprising the mutein under (i) as alpha subunit by IL2 or the functional variant thereof, and/or wherein binding to and/or activation of IL2R comprising the alpha subunit of IL2R or the functional variant thereof as alpha subunit by IL2 or the functional variant thereof exceeds binding to and/or activation of IL2R comprising the alpha subunit of IL2R or the functional variant thereof as alpha subunit by the mutein under (ii), and/or wherein binding to and/or activation of IL2R comprising the alpha subunit of IL2R or the functional variant thereof as alpha subunit by IL2 or the functional variant thereof exceeds binding to and/or activation of IL2R comprising the mutein under (i) as alpha subunit by IL2 or the functional variant thereof, and/or wherein the substitution in IL2 or the functional variant thereof reduces the affinity for IL2R comprising the wild type alpha subunit of IL2R as alpha subunit (IL2R $\alpha\beta\gamma$), and/or

wherein the substitution in IL2 or the functional variant thereof reduces the affinity for IL2R comprising the wild type alpha subunit of IL2R as alpha subunit (IL2R $\alpha\beta\gamma$) to a greater extent than for the $\beta\gamma$ IL2 receptor complex (IL2R $\beta\gamma$), and/or

wherein the mutein under (ii) has a decreased ability to stimulate regulatory T cells compared to wild type IL2.

~~22~~19. The system of any one of claims 1 to ~~24~~18, wherein the mutein under (ii) further comprises one or more amino acid substitutions which enhance the affinity for IL2R $\beta\gamma$, optionally wherein the one or more amino acid substitutions which enhance the affinity for IL2R $\beta\gamma$ comprise the following set of substitutions: 80F, 81D, 85V, 86V, 92F.

~~23~~20. The system of any one of claims 1 to ~~22~~19, wherein the ligand polypeptide is an extended pharmacokinetic (PK) polypeptide-

~~24. The system of claim 23, wherein the extended-PK polypeptide comprises a fusion protein, optionally wherein the fusion protein comprises~~ing:

(i) a moiety of the mutein under (ii) and a moiety which is heterologous to IL2 or the functional variant thereof and/or

~~wherein the fusion protein comprises~~(ii) a moiety of the mutein under (ii) and a moiety selected from the group consisting of serum albumin, an immunoglobulin fragment, transferrin, Fn3, and variants thereof.

~~25~~21. The system of claim ~~24~~20, wherein the serum albumin comprises mouse serum albumin or human serum albumin and/or wherein the immunoglobulin fragment comprises an immunoglobulin Fc domain.

~~26~~22. A receptor polypeptide of the system of any one of claims 1 to ~~25~~21.

~~27~~23. A polynucleotide encoding the receptor polypeptide of claim ~~26~~22, optionally wherein the polynucleotide is RNA.

~~28~~24. A host cell comprising the polynucleotide of claim ~~27~~23.

~~29~~25. A host cell genetically modified to express a receptor polypeptide of the system of any one of claims 1 to ~~25~~21, optionally wherein the cell is an immune effector cell, for example, a T cell.

~~3026~~. A pharmaceutical composition comprising the polynucleotide of claim ~~2723~~ or the host cell of claim ~~2925~~.

~~3427~~. The polynucleotide of claim ~~2723~~, the host cell of claim ~~2925~~, or the pharmaceutical composition of claim ~~3026~~ for use in therapy.

~~3228~~. Use of the polynucleotide of claim ~~2723~~, the host cell of claim ~~2925~~, or the pharmaceutical composition of claim ~~3026~~ in the manufacture of a medicament for treating or preventing cancer in a subject.

~~3329~~. A medical preparation comprising:

(i) a polynucleotide encoding a receptor polypeptide of the system of any one of claims 1 to ~~2521~~ or an immune effector cell genetically modified to express a receptor polypeptide of the system of any one of claims 1 to ~~2521~~, and

(ii) the corresponding ligand polypeptide of the system under (i), a polynucleotide encoding the ligand polypeptide, or a host cell genetically modified to express the ligand polypeptide, optionally wherein the medical preparation is a kit comprising instructions for use of the medical preparation for treating or preventing cancer.

~~3430~~. The medical preparation of claim ~~3329~~, which comprises each component (i) and (ii) in separate containers.

~~35. The medical preparation of claim 33 or 34, further comprising instructions for use of the medical preparation for treating or preventing cancer.~~

~~3631. The medical preparation of claim 33 or~~ A polynucleotide encoding a receptor polypeptide of the system of any one of claims 1 to 21, or an immune effector cell genetically modified to express a receptor polypeptide of the system of any one of claims 1 to 21, and the corresponding ligand polypeptide of the system of any one of claims 1 to 21, a polynucleotide encoding the ligand polypeptide, or a host cell genetically modified to express the ligand polypeptide for use in a combination therapy.

3732. Use of ~~the medical preparation of any one of claims 33 to 36~~(i) a polynucleotide encoding a receptor polypeptide of the system of any one of claims 1 to 21 or an immune effector cell genetically modified to express a receptor polypeptide of the system of any one of claims 1 to 21, and
(ii) the corresponding ligand polypeptide of the system under (i), a polynucleotide encoding the ligand polypeptide, or a host cell genetically modified to express the ligand polypeptide in the manufacture of a medicament for a combination therapy for treating or preventing cancer in a subject.

33. Use of a polynucleotide encoding a receptor polypeptide of the system of any one of claims 1 to 21, or an immune effector cell genetically modified to express a receptor polypeptide of the system of any one of claims 1 to 21 in the manufacture of a medicament for use in a combination therapy for treating or preventing cancer in a subject,
wherein said medicament is to be administered in combination with the corresponding ligand polypeptide of the system of any one of claims 1 to 21, a polynucleotide encoding the ligand polypeptide, or a host cell genetically modified to express the ligand polypeptide.

3834. Use of immune effector cells genetically modified to express a receptor polypeptide of the system of any one of claims 1 to 2521 in the manufacture of a medicament for treating cancer in a subject associated with expression or elevated expression of a tumor-associated antigen, comprising that:
(i) the immune effector cells genetically modified to express a receptor polypeptide of the system of any one of claims 1 to 2521 are to be provided to the subject, the immune effector cells being targeted to the antigen or cells expressing the antigen and
(ii) the corresponding ligand polypeptide of the system under (i), a polynucleotide encoding the ligand polypeptide, or a host cell genetically modified to express the ligand polypeptide is to be administered to the subject.

3935. The use of claim 3834, wherein the immune effector cells genetically modified to express a receptor polypeptide are to be provided to the subject by administration of the immune effector cells genetically modified to express a receptor polypeptide or by generation of the immune effector cells genetically modified to express a receptor polypeptide in the subject.

4036. The medical preparation of ~~any one of claims 3329 to 35 or 30~~, or the use of claim 3732 or 3834, wherein the polynucleotide encoding the receptor polypeptide and/or the polynucleotide encoding the ligand polypeptide is RNA, or

wherein the immune effector cells genetically modified to express a receptor polypeptide comprise a polynucleotide encoding the receptor polypeptide, or
wherein the host cell genetically modified to express the ligand polypeptide comprises a polynucleotide encoding the ligand polypeptide.

| 4137. The medical preparation or the use of claim 4036, wherein the polynucleotide encoding the receptor polypeptide and/or the polynucleotide encoding the ligand polypeptide is RNA.

| 4238. The medical preparation or the use of any one of claims 3329 to 4137, wherein the immune effector cells are T cells.