

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.

In one aspect, the present disclosure provides for a system comprising: (i) a receptor polypeptide comprising a mutein of the alpha subunit of interleukin-2 receptor (IL2R), wherein the alpha subunit of IL2R has the amino acid sequence according to SEQ ID NO: 2 or 4, or of a functional variant of the alpha subunit of IL2R capable of binding to and being activated by IL2, (ii) a ligand polypeptide comprising a mutein of IL2, wherein the IL2 has the amino acid sequence according to SEQ ID NO: 1, or of a functional variant of IL2 capable of binding to and activating IL2R, wherein the ligand polypeptide of (ii) is capable of binding to and activating the receptor polypeptide of (i), and wherein the mutein of the human alpha subunit of IL2R or the functional variant thereof and the mutein of human IL2 or the functional variant thereof are substituted at at least the following positions relative to the alpha subunit of IL2R and numbered in accordance to SEQ ID NO: 2, and relative to the IL2 and numbered in accordance to SEQ ID NO: 1:

- (I) (i) in the alpha subunit of IL2R or the functional variant thereof, glutamic acid is substituted at position 1 by lysine, and
(ii) in the IL2 or the functional variant thereof, lysine is substituted at position 35 by glutamic acid; and/or
- (II) (i) in the alpha subunit of IL2R or the functional variant thereof, glutamic acid is substituted at position 29 by lysine, and
(ii) in the IL2 or the functional variant thereof, lysine is substituted at position 43 by glutamic acid; and/or
- (III) (i) in the alpha subunit of IL2R or the functional variant thereof, lysine is substituted at position 38 by glutamic acid, and
(ii) in the IL2 or the functional variant thereof, glutamic acid is substituted at position 61 by lysine,
- (IV) (i) in the alpha subunit of IL2R or the functional variant thereof, glutamic acid is substituted at position 1 by lysine, glutamic acid is substituted at position 29 by lysine, and lysine is substituted at position 38 by glutamic acid, and
(ii) in the IL2 or the functional variant thereof, lysine is substituted at position 35 by glutamic acid, lysine is substituted at position 43 by glutamic acid, and glutamic acid is substituted at position 61 by lysine; or

- (V) (i) in the alpha subunit of IL2R or the functional variant thereof, glutamic acid is substituted at position 29 by lysine, and lysine is substituted at position 38 by glutamic acid, and
(ii) in the IL2 or the functional variant thereof, lysine is substituted at position 43 by glutamic acid, and glutamic acid is substituted at position 61 by lysine; or
- 5 (VI) (i) in the alpha subunit of IL2R or the functional variant thereof, lysine is substituted at position 38 by glutamic acid, and
(ii) in the IL2 or the functional variant thereof, glutamic acid is substituted position 61 by lysine; or
- (VII) (i) in the alpha subunit of IL2R or the functional variant thereof, glutamic acid is substituted at position 29 by lysine, and
10 (ii) in the IL2 or the functional variant thereof, lysine is substituted at position 43 by glutamic acid;
or
- (VIII) (i) in the alpha subunit of IL2R or the functional variant thereof, glutamic acid is substituted at position 29 by lysine, and lysine is substituted at position 38 by glutamic acid, and
(ii) in the IL2 or the functional variant thereof, lysine is substituted at position 35 by glutamic acid,
15 lysine is substituted at position 43 by glutamic acid, and glutamic acid is substituted at position 61 by lysine; or
- (IX) (i) in the alpha subunit of IL2R or the functional variant thereof, glutamic acid is substituted at position 29 by lysine, and
20 (ii) in the IL2 or the functional variant thereof, lysine is substituted at position 43 by glutamic acid,
and glutamic acid is substituted at position 61 by lysine.

In one example, the system of the disclosure comprises

- (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,
- 25
30

(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.

In one example of the system of the disclosure the alpha subunit of IL2R is the human alpha subunit of IL2R. In one example of the system of the disclosure the IL2 is human IL2.

In different examples, the human alpha subunit of IL2R or the functional variant thereof and the human IL2 or the functional variant thereof are substituted at at least the following positions (relative to wild type human alpha subunit of IL2R and numbered in accordance with wild type human alpha subunit of IL2R, and relative to wild type human IL2 and numbered in accordance with wild type human IL2):

(i) IL2R or functional variant thereof: position 1 (glutamic acid), 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.

5 A further example of the disclosure relates to 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

10 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.

15 In one example, position 1 is substituted with lysine. In one example, position 35 is substituted with glutamic acid.

A further example of the disclosure relates to 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.

In one example, position 29 is substituted with lysine. In one example, position 43 is substituted with glutamic acid.

A further example of the disclosure relates to 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.

In one example, position 38 is substituted with glutamic acid. In one example, position 61 is substituted with lysine.

A further example of the disclosure relates to 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.

A further example of the disclosure relates to 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.

A further example of the disclosure relates to a system comprising:

- 5 (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
- 10 (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.

A further example of the disclosure relates to a system comprising:

- 15 (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
- 20 (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.

A further example of the disclosure relates to a system comprising:

- 25 (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
- 30 (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.

A further example of the disclosure relates to 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 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.

A further example of the disclosure relates to 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.

A further example of the disclosure relates to 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 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.

extended-PK polypeptide comprises a fusion protein. In one example, the fusion protein comprises a moiety of the mutein under (ii) and a moiety which is heterologous to IL2 or the functional variant thereof. In one example, the fusion protein comprises 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. In one example, the serum albumin comprises mouse serum albumin or human serum albumin. In one example, the immunoglobulin fragment comprises an immunoglobulin Fc domain.

The above described receptor polypeptides are also termed "IL2R α variant polypeptide", "IL2R variant polypeptide" or simply "IL2R variant" herein. The above described ligand polypeptides are also termed "IL2 variant polypeptide" or simply "IL2 variant" herein.

In different examples, a system described herein comprises combinations of receptor polypeptides and ligand polypeptides comprising IL2R receptor polypeptides and IL2 ligand polypeptides, respectively, selected from the following:

IL2R receptor polypeptide	IL2 ligand polypeptide
SEQ ID NO: 17 (optionally without N-terminal 21 aa signal peptide)	SEQ ID NO: 5 or SEQ ID NO: 10
SEQ ID NO: 14 (optionally without N-terminal 21 aa signal peptide)	SEQ ID NO: 6 or SEQ ID NO: 11
SEQ ID NO: 15 (optionally without N-terminal 21 aa signal peptide)	SEQ ID NO: 7 or SEQ ID NO: 12
SEQ ID NO: 16 (optionally without N-terminal 21 aa signal peptide)	SEQ ID NO: 8 or SEQ ID NO: 13
SEQ ID NO: 14 (optionally without N-terminal 21 aa signal peptide)	SEQ ID NO: 5 or SEQ ID NO: 10
SEQ ID NO: 16 (optionally without N-terminal 21 aa signal peptide)	SEQ ID NO: 6 or SEQ ID NO: 11
SEQ ID NO: 16 (optionally without N-terminal 21 aa signal peptide)	SEQ ID NO: 5 or SEQ ID NO: 10
SEQ ID NO: 17 (optionally without N-terminal 21 aa signal peptide)	SEQ ID NO: 6 or SEQ ID NO: 11

A further aspect of the disclosure relates to a receptor polypeptide of any of the systems described herein.

In another aspect, the present disclosure relates to a polynucleotide encoding the receptor polypeptide described herein, wherein the polynucleotide is DNA, preferably comprised in a transposon-based system for transfection. A further example of the disclosure relates to a polynucleotide encoding the receptor polypeptide described herein. In one example, the polynucleotide is RNA.

In another aspect, the present disclosure relates to a host cell comprising the polynucleotide described herein, preferably wherein the host cell is a T cell, more preferably wherein the T cell is a CAR T cell. A further example of the disclosure relates to a host cell comprising the polynucleotide described herein. In another aspect, the present disclosure relates to a host cell genetically modified to express a receptor polypeptide of the system described herein, preferably wherein the cell is a T cell, more preferably wherein the T cell is a CAR T cell. A further example of the disclosure relates to a host cell genetically modified to express a receptor polypeptide of any of the systems described herein. In one example, the host cell is an immune effector cell. In one example, the immune effector cell is a T cell.

A further aspect of the disclosure relates to a pharmaceutical composition comprising the polynucleotide or the host cell described herein, wherein the host cell is a T cell. A further example 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.

In another aspect, the present disclosure relates to the polynucleotide described herein, the host cell described herein, wherein the host cell is a T cell, or the pharmaceutical composition described herein, wherein the polynucleotide or the pharmaceutical composition comprising the polynucleotide is to be transfected into the T cell, 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, wherein the host cell is a T cell, or the pharmaceutical composition described herein in the manufacture of a medicament for treating cancer in a subject, wherein the use of the polynucleotide or of the pharmaceutical composition comprising the polynucleotide comprises that a T cell of the subject is to be transfected with the polynucleotide.

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.

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

(i) a polynucleotide, preferably DNA, encoding a receptor polypeptide of the system described herein, wherein the polynucleotide is suitable for transfecting a T cell in vivo, or a T cell genetically modified to express a receptor polypeptide of the system described herein, preferably a T cell genetically modified to

5 stably express a CAR and the receptor polypeptide, and

(ii) the corresponding ligand polypeptide of the system described herein, a polynucleotide, preferably RNA, 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 cancer.

10

A further example of the 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.

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.

In yet another aspect, the present disclosure relates to a polynucleotide encoding a receptor polypeptide of the system as described herein, or a T 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, wherein the use of the polynucleotide encoding the receptor polypeptide comprises that a T cell is to be transfected with the polynucleotide. A further example of the disclosure relates to the medical preparation described herein for pharmaceutical use. In one example, the pharmaceutical use comprises a therapeutic or prophylactic treatment of a disease or disorder.

In yet another aspect, the present disclosure relates to a use of (i) a polynucleotide encoding a receptor polypeptide of the system as described herein or a T cell genetically modified to express a receptor polypeptide of the system as described herein, and (ii) 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 in the manufacture of a medicament for a combination therapy for treating cancer in a subject, wherein the combination therapy using the polynucleotide encoding the receptor polypeptide comprises that a T cell is to be transfected with the polynucleotide. A further example of the disclosure relates to the medical preparation described herein for use in a method for treating or preventing cancer in a subject.

In yet another aspect, the present disclosure provides a use of a polynucleotide encoding a receptor polypeptide of the system as described herein, or a T 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 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, wherein the combination therapy using the polynucleotide encoding the receptor polypeptide comprises that a T cell is to be transfected with the polynucleotide.

In yet another aspect, the present disclosure relates to a use of T 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, wherein cells of the cancer overexpress a tumor-associated antigen, comprising that:

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

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

wherein treating the cancer with the polynucleotide encoding the receptor polypeptide comprises that a T cell is to be transfected with the polynucleotide.

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

(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.

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.

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

(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.

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

Claims

1. A system comprising:

- (i) a receptor polypeptide comprising a mutein of the human alpha subunit of interleukin-2 receptor (IL2R), wherein the alpha subunit of IL2R has the amino acid sequence according to SEQ ID NO: 2 or 4, or of a functional variant of the alpha subunit of IL2R capable of binding to and being activated by IL2,
- (ii) a ligand polypeptide comprising a mutein of human IL2, wherein the IL2 has the amino acid sequence according to SEQ ID NO: 1, or of a functional variant of IL2 capable of binding to and activating IL2R,

wherein the ligand polypeptide of (ii) is capable of binding to and activating the receptor polypeptide of (i), wherein the mutein of the human alpha subunit of IL2R or the functional variant thereof and the mutein of human IL2 or the functional variant thereof are substituted at least at the following positions relative to the alpha subunit of IL2R and numbered in accordance to SEQ ID NO: 2, and relative to the IL2 and numbered in accordance to SEQ ID NO: 1:

- (I) (i) in the alpha subunit of IL2R or the functional variant thereof, glutamic acid is substituted at position 1 by lysine, and
(ii) in the IL2 or the functional variant thereof, lysine is substituted at position 35 by glutamic acid; and/or
- (II) (i) in the alpha subunit of IL2R or the functional variant thereof, glutamic acid is substituted at position 29 by lysine, and
(ii) in the IL2 or the functional variant thereof, lysine is substituted at position 43 by glutamic acid; and/or
- (III) (i) in the alpha subunit of IL2R or the functional variant thereof, lysine is substituted at position 38 by glutamic acid, and
(ii) in the IL2 or the functional variant thereof, glutamic acid is substituted at position 61 by lysine,
- (IV) (i) in the alpha subunit of IL2R or the functional variant thereof, glutamic acid is substituted at position 1 by lysine, glutamic acid is substituted at position 29 by lysine, and lysine is substituted at position 38 by glutamic acid, and
(ii) in the IL2 or the functional variant thereof, lysine is substituted at position 35 by glutamic acid, lysine is substituted at position 43 by glutamic acid, and glutamic acid is substituted at position 61 by lysine; or
- (V) (i) in the alpha subunit of IL2R or the functional variant thereof, glutamic acid is substituted at position 29 by lysine, and lysine is substituted at position 38 by glutamic acid, and

- (ii) in the IL2 or the functional variant thereof, lysine is substituted at position 43 by glutamic acid, and glutamic acid is substituted at position 61 by lysine; or
- (VI) (i) in the alpha subunit of IL2R or the functional variant thereof, lysine is substituted at position 38 by glutamic acid, and
 - (ii) in the IL2 or the functional variant thereof, glutamic acid is substituted position 61 by lysine; or
- (VII) (i) in the alpha subunit of IL2R or the functional variant thereof, glutamic acid is substituted at position 29 by lysine, and
 - (ii) in the IL2 or the functional variant thereof, lysine is substituted at position 43 by glutamic acid; or
- (VIII) (i) in the alpha subunit of IL2R or the functional variant thereof, glutamic acid is substituted at position 29 by lysine, and lysine is substituted at position 38 by glutamic acid, and
 - (ii) in the IL2 or the functional variant thereof, lysine is substituted at position 35 by glutamic acid, lysine is substituted at position 43 by glutamic acid, and glutamic acid is substituted at position 61 by lysine; or
- (IX) (i) in the alpha subunit of IL2R or the functional variant thereof, glutamic acid is substituted at position 29 by lysine, and
 - (ii) in the IL2 or the functional variant thereof, lysine is substituted at position 43 by glutamic acid, and glutamic acid is substituted at position 61 by lysine.

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 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.

3. The system of claim 1 or 2, 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.

4. The system of any one of claims 1 to 3, wherein the ligand polypeptide is an extended pharmacokinetic (PK) polypeptide, wherein the extended-PK polypeptide comprises a fusion protein comprising a moiety of the mutein under (ii) and a moiety selected from the group consisting of serum albumin, an immunoglobulin Fc domain, transferrin, and Fn3.

5. The system of claim 4, wherein the serum albumin comprises mouse serum albumin or human serum albumin.

6. A receptor polypeptide of the system of any one of claims 1 to 5.

7. A polynucleotide encoding the receptor polypeptide of claim 6, wherein the polynucleotide is DNA, preferably comprised in a transposon-based system for transfection.

8. The polynucleotide of claim 7, further comprising nucleic acid encoding an antigen receptor, preferably a CAR.

9. A host cell comprising the polynucleotide of claim 7 or 8, preferably wherein the host cell is a T cell, more preferably wherein the T cell is a CAR T cell.

10. The host cell of claim 9, wherein the host cell is a T cell genetically modified to stably express a CAR and the receptor polypeptide.

11. A host cell genetically modified to express a receptor polypeptide of the system of any one of claims 1 to 5, preferably wherein the cell is a T cell, more preferably wherein the T cell is a CAR T cell.

12. A pharmaceutical composition comprising the polynucleotide of claim 7 or the host cell of claim 11, wherein the host cell is a T cell.

13. The polynucleotide of claim 7, the host cell of claim 11, wherein the host cell is a T cell, or the pharmaceutical composition of claim 12, wherein the polynucleotide or the pharmaceutical composition comprising the polynucleotide is to be transfected into the T cell, for use in therapy.

14. Use of the polynucleotide of claim 7, the host cell of claim 11, wherein the host cell is a T cell, or the pharmaceutical composition of claim 12 in the manufacture of a medicament for treating cancer in a subject, wherein the use of the polynucleotide or of the pharmaceutical composition comprising the polynucleotide comprises that a T cell of the subject is to be transfected with the polynucleotide.

15. A medical preparation comprising:

- (i) a polynucleotide, preferably DNA, encoding a receptor polypeptide of the system of any one of claims 1 to 5, wherein the polynucleotide is suitable for transfecting a T cell in vivo, or a T cell genetically modified to express a receptor polypeptide of the system of any one of claims 1 to 5, preferably a T cell genetically modified to stably express a CAR and the receptor polypeptide, and
- (ii) the corresponding ligand polypeptide of the system of any one of claims 1 to 5, a polynucleotide, preferably RNA, 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 cancer.

16. The medical preparation of claim 15, wherein the polynucleotide encoding a receptor polypeptide is comprised in a transposon-based system for transfection, preferably further comprising nucleic acid encoding an antigen receptor, wherein the antigen receptor preferably is a CAR.

17. The medical preparation of claim 15, which comprises each component (i) and (ii) in separate containers.

18. A polynucleotide encoding a receptor polypeptide of the system of any one of claims 1 to 5, or a T cell genetically modified to express a receptor polypeptide of the system of any one of claims 1 to 5, and the corresponding ligand polypeptide of the system of any one of claims 1 to 5, a polynucleotide encoding the ligand polypeptide, or a host cell genetically modified to express the ligand polypeptide for use in a combination therapy, wherein the use of the polynucleotide encoding the receptor polypeptide comprises that a T cell is to be transfected with the polynucleotide.

19. Use of (i) a polynucleotide encoding a receptor polypeptide of the system of any one of claims 1 to 5 or a T cell genetically modified to express a receptor polypeptide of the system of any one of claims 1 to 5, and

(ii) the corresponding ligand polypeptide of the system of any one of claims 1 to 5, 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 cancer in a subject, wherein the combination therapy using the polynucleotide encoding the receptor polypeptide comprises that a T cell is to be transfected with the polynucleotide.

20. Use of a polynucleotide encoding a receptor polypeptide of the system of any one of claims 1 to 5, or a T cell genetically modified to express a receptor polypeptide of the system of any one of claims 1 to 5 in the manufacture of a medicament for use in a combination therapy for treating 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 5, a polynucleotide encoding the ligand polypeptide, or a host cell genetically modified to express the ligand polypeptide, wherein the combination therapy using the polynucleotide encoding the receptor polypeptide comprises that a T cell is to be transfected with the polynucleotide.

21. Use of T cells genetically modified to express a receptor polypeptide of the system of any one of claims 1 to 5 in the manufacture of a medicament for treating cancer in a subject, wherein cells of the cancer overexpress a tumor-associated antigen, comprising that:

(i) the T cells genetically modified to express a receptor polypeptide of the system of any one of claims 1 to 5 are to be provided to the subject, the T cells being targeted to the antigen or cells expressing the antigen and

(ii) the corresponding ligand polypeptide of the system of any one of claims 1 to 5, a polynucleotide encoding the ligand polypeptide, or a host cell genetically modified to express the ligand polypeptide is to be administered to the subject,

wherein treating the cancer with the polynucleotide encoding the receptor polypeptide comprises that a T cell is to be transfected with the polynucleotide.

22. The use of claim 21, wherein the T cells genetically modified to express a receptor polypeptide are to be provided to the subject by administration of the T cells genetically modified to express a receptor polypeptide or by generation of the T cells genetically modified to express a receptor polypeptide in the subject.

23. The medical preparation of claim 15, 16 or 17, or the use of claim 19, wherein the polynucleotide encoding the receptor polypeptide and/or the polynucleotide encoding the ligand polypeptide is RNA, or wherein the T 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.

24. The medical preparation or the use of claim 23, wherein the polynucleotide encoding the receptor polypeptide is DNA and the polynucleotide encoding the ligand polypeptide is RNA.

25. The polynucleotide for use claim 13 or 18 or the use of the polynucleotide of any one of claims 14 and 18 to 22, wherein the polynucleotide encoding a receptor polypeptide is comprised in a transposon-based system for transfection, preferably further comprising nucleic acid encoding an antigen receptor, wherein the antigen receptor preferably is a CAR.