

the treatment of cancer (as a direct and/or adjunct therapy). In particular, administration of IL2 variant RNA is a promising approach to boost the therapeutic efficacy of multiple T and NK cell-based (cancer) immunotherapies.

5 The present disclosure provides novel IL2 variants. Specifically, variants of IL2 are described that contain mutations enhancing IL2R $\beta\gamma$ binding, in particular CD122 binding ("mut $\beta\gamma$ ") and optionally further contain mutations affecting IL2R $\alpha\beta\gamma$ binding, in particular CD25 binding ("mut α "). In particular, variants of IL2 are described herein reducing expansion of T_{reg} cells and increasing effector T-cell and NK-cell stimulation, preferably IL2R $\beta\gamma$ ⁺ effector T-cell and NK-cell stimulation. The IL2 variant hAlb-hIL2_A4s8 described
10 herein shows, compared to wild-type IL2, a markedly reduced capacity to activate T_{reg} cells and increased ability to stimulate effector immune cells, preferably IL2R $\beta\gamma$ ⁺ effector immune cells like CD8⁺ T cells and NK cells already at lower concentrations. *In vivo*, treatment with nanoparticulate mRNA encoding wild-type IL2 or the selected IL2 variant with mutations affecting both IL2R α binding and IL2R β binding (hAlb-hIL2_A4s8) targeted to the liver of mice for systemic availability strongly inhibited tumor growth, with
15 hIL2_A4s8 being most effective. Whereas hAlb-hIL2 increases mainly antigen-specific T cells and T_{reg} cells, hAlb-hIL2_A4s8 activates NK cells and elevates both antigen-specific and non-antigen-specific CD8⁺ T-cell numbers without expanding T_{reg} cells. Treatment with hAlb-hIL2_A4s8 strongly synergizes with RNA vaccination by expanding vaccine-induced CD8⁺ T cell responses while avoiding stimulation and expansion of T_{reg} cells, and augments the anti-tumoral efficacy of PD-L1 immune checkpoint blockade
20 by specifically expanding pre-existing antigen-specific CD8⁺ T cells.

Summary

In a first aspect, provided herein is a polypeptide comprising a mutein of human interleukin-2 (IL2) or of a
25 functional variant of human IL2, wherein the human IL2 or the functional variant thereof is substituted at at least position 80 (leucine), position 81 (arginine), position 85 (leucine) and position 92 (isoleucine) relative to wild type human IL2 and numbered in accordance with wild type human IL2, wherein the substitution enhances the affinity for the $\beta\gamma$ IL2 receptor complex (IL2R $\beta\gamma$) and wherein the human IL2 or the functional variant thereof is not substituted at position 86 (isoleucine) relative to wild type human IL2
30 and numbered in accordance with wild type human IL2.

In one embodiment example, position 80 (leucine) is substituted by phenylalanine, position 81 (arginine) is substituted by glutamic acid, position 85 (leucine) is substituted by valine and position 92 (isoleucine)

is substituted by phenylalanine relative to wild type human IL2 and numbered in accordance with wild type human IL2.

5 In one embodimentexample, the human IL2 or the functional variant thereof is further substituted at position 74 (glutamine) relative to wild type human IL2 and numbered in accordance with wild type human IL2. In one embodimentexample, position 74 (glutamine) is substituted by histidine relative to wild type human IL2 and numbered in accordance with wild type human IL2.

10 In a second aspect, provided herein is a polypeptide comprising a mutein of human IL2 or of a functional variant of human IL2, wherein the human IL2 or the functional variant thereof is substituted at at least position 80 (leucine) by phenylalanine, position 81 (arginine) by glutamic acid, position 85 (leucine) by valine and position 92 (isoleucine) by phenylalanine relative to wild type human IL2 and numbered in accordance with wild type human IL2.

15 In one embodimentexample, the human IL2 or the functional variant thereof is further substituted at position 74 (glutamine) by histidine relative to wild type human IL2 and numbered in accordance with wild type human IL2.

20 In a third aspect, provided herein is a polypeptide comprising a mutein of human IL2 or of a functional variant of human IL2, wherein the human IL2 or the functional variant thereof is substituted at at least position 74 (glutamine) by histidine, position 80 (leucine) by phenylalanine, position 81 (arginine) by glutamic acid, position 85 (leucine) by valine and position 92 (isoleucine) by phenylalanine relative to wild type human IL2 and numbered in accordance with wild type human IL2.

25 In one embodimentexample of the second and third aspectexample, the substitution enhances the affinity for IL2R $\beta\gamma$.

30 In one embodimentexample, the substituted IL2 or functional variant thereof (IL2 mutein) described above has an amino acid sequence identical to wild type IL2 at the other, non-substituted residues. In one embodimentexample, the IL2 mutein described above has amino acid modifications such as amino acid substitutions at one or more sites in or at the other residues of wild type human IL2. In one embodimentexample, such amino acid substitutions result in relatively decreased affinity for IL2R $\alpha\beta\gamma$

when compared to wild type IL2 (also termed "muta" mutations herein). In one embodimentexample, such amino acid substitutions are at amino acid residues that contact IL2R α .

Thus, in one embodimentexample, the human IL2 or the functional variant thereof further comprises one or more amino acid substitutions which reduce the affinity for the alpha subunit of the $\alpha\beta\gamma$ IL2 receptor complex (IL2R $\alpha\beta\gamma$).

In one embodimentexample, the one or more amino acid substitutions which reduce the affinity for the alpha subunit of IL2R $\alpha\beta\gamma$ reduce the affinity for IL2R $\alpha\beta\gamma$ to a greater extent than for IL2R $\beta\gamma$.

In one embodimentexample, the one or more amino acid substitutions which reduce the affinity for the alpha subunit of IL2R $\alpha\beta\gamma$ comprise substitutions of the human IL2 or the functional variant thereof at at least one of positions 35 (lysine), 43 (lysine), 61 (glutamic acid) and 62 (glutamic acid) relative to wild type human IL2 and numbered in accordance with wild type human IL2. In one embodimentexample, if the amino acid residue is an acidic amino acid residue in wild type human IL2 the substitution is by a basic amino acid residue and if the amino acid residue is a basic amino acid residue in wild type human IL2 the substitution is by an acidic amino acid residue.

In different embodimentexamples, the one or more amino acid substitutions which reduce the affinity for the alpha subunit of IL2R $\alpha\beta\gamma$ comprise substitutions of the human IL2 or the functional variant thereof at at least the following positions relative to wild type human IL2 and numbered in accordance with wild type human IL2:

- position 35,
- position 43,
- position 61,
- position 62,
- position 35 and position 43,
- position 35 and position 61,
- position 35 and position 62,
- position 43 and position 61,
- position 43 and position 62,
- position 61 and position 62,
- position 35, position 43 and position 61,

- position 35, position 43 and position 62,
- position 35, position 61 and position 62,
- position 43, position 61 and position 62, or
- position 35, position 43, position 61 and position 62.

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In one [embodimentexample](#), position 35 is substituted with glutamic acid. In one [embodimentexample](#), position 43 is substituted with glutamic acid. In one [embodimentexample](#), position 61 is substituted with lysine. In one [embodimentexample](#), position 62 is substituted with lysine.

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In one [embodimentexample](#), position 35 is substituted. In one [embodimentexample](#), position 35 is substituted with glutamic acid.

In one [embodimentexample](#), position 43 is substituted. In one [embodimentexample](#), position 43 is substituted with glutamic acid.

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In one [embodimentexample](#), position 61 is substituted. In one [embodimentexample](#), position 61 is substituted with lysine.

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In one [embodimentexample](#), position 62 is substituted. In one [embodimentexample](#), position 62 is substituted with lysine.

In one [embodimentexample](#), positions 43 and 61 are substituted. In one [embodimentexample](#), position 43 is substituted with glutamic acid and position 61 is substituted with lysine.

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In one [embodimentexample](#), positions 35, 43 and 61 are substituted. In one [embodimentexample](#), position 35 is substituted with glutamic acid, position 43 is substituted with glutamic acid and position 61 is substituted with lysine.

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In one [embodimentexample](#), positions 61 and 62 are substituted. In one [embodimentexample](#), position 61 is substituted with lysine and position 62 is substituted with lysine.

In one [embodimentexample](#), the one or more amino acid substitutions which reduce the affinity for the alpha subunit of IL2R $\alpha\beta\gamma$ comprise substitutions of the human IL2 or the functional variant thereof at

position 43 (lysine) and position 61 (glutamic acid) relative to wild type human IL2 and numbered in accordance with wild type human IL2. In one [embodimentexample](#), position 43 (lysine) is substituted by glutamic acid and position 61 (glutamic acid) is substituted by lysine.

5 In a fourth aspect, provided herein is a polypeptide comprising a mutein of human IL2 or of a functional variant of human IL2, wherein the human IL2 or the functional variant thereof is substituted at at least position 43 (lysine) by glutamic acid, position 61 (glutamic acid) by lysine, position 74 (glutamine) by histidine, position 80 (leucine) by phenylalanine, position 81 (arginine) by glutamic acid, position 85 (leucine) by valine and position 92 (isoleucine) by phenylalanine relative to wild type human IL2 and
10 numbered in accordance with wild type human IL2.

In one [embodimentexample](#) of the second to fourth [aspectexample](#)s, the human IL2 or the functional variant thereof is not substituted at position 86 (isoleucine) relative to wild type human IL2 and numbered in accordance with wild type human IL2.

15 In one [embodimentexample](#), the human IL2 has the amino acid sequence according to SEQ ID NO: 1.

In one [embodimentexample](#), the mutein of human IL2 or the functional variant thereof has a decreased ability to stimulate regulatory T cells compared to wild type human IL2.

20 In one [embodimentexample](#), the mutein of human IL2 or the functional variant thereof has an increased ability to stimulate effector T cells compared to wild type human IL2.

The IL2 mutein described herein may be attached to a pharmacokinetic modifying group and, thus, may
25 be an "extended-pharmacokinetic (PK) IL2".

In one [embodimentexample](#), the polypeptide described herein is an extended pharmacokinetic (PK) polypeptide. In one [embodimentexample](#), the extended-PK polypeptide comprises a fusion protein. In one [embodimentexample](#), the fusion protein comprises a moiety of the mutein of human IL2 or the functional variant thereof and a moiety which is heterologous to human IL2 or the functional variant thereof. In one
30 [embodimentexample](#), the fusion protein comprises a moiety of the mutein of human IL2 or the functional variant thereof and a moiety selected from the group consisting of serum albumin, an immunoglobulin fragment, transferrin, Fn3, and variants thereof. In one [embodimentexample](#), the serum albumin

comprises mouse serum albumin or human serum albumin. In one ~~embodiment~~example, the immunoglobulin fragment comprises an immunoglobulin Fc domain.

In one ~~aspect~~example, provided herein is a polypeptide comprising an amino acid sequence selected from the group consisting of SEQ ID NOs: 2, 11, 13, and 22, such as SEQ ID NO: 2, SEQ ID NO: 11, SEQ ID NO: 13 or SEQ ID NO: 22 of the sequence listing.

The above described polypeptides are also termed "IL2 variant polypeptide" or simply "IL2 variant" herein.

In one aspect, provided herein is a polynucleotide encoding the polypeptide described herein. In one ~~embodiment~~example, the polynucleotide is RNA.

In one aspect, provided herein is a host cell comprising the polynucleotide described herein.

In one ~~aspect~~example, provided herein is the polypeptide described herein, the polynucleotide described herein, or the host cell described herein for pharmaceutical use. In one ~~embodiment~~example, the pharmaceutical use comprises a therapeutic or prophylactic treatment of a disease or disorder.

In one ~~aspect~~example, provided herein is the polypeptide described herein, the polynucleotide described herein, or the host cell described herein for use in a method for treating or preventing cancer in a subject.

In one aspect, provided herein is a pharmaceutical composition comprising the polypeptide described herein, the polynucleotide described herein, or the host cell described herein.

In a further aspect, the present disclosure provides the polypeptide described herein, the polynucleotide described herein, the host cell described herein, or the pharmaceutical composition described herein for use in therapy. In one ~~aspect~~example, provided herein is a method of treating a subject comprising administering to the subject the polypeptide described herein, the polynucleotide described herein, the host cell described herein, or the pharmaceutical composition described herein.

In a further aspect, the present disclosure provides a use of the polypeptide described herein, the polynucleotide described herein, the host cell described herein, or the pharmaceutical composition described herein in the manufacture of a medicament for inducing an immune response in a subject. In

one aspectexample, provided herein is a method for inducing an immune response in a subject comprising administering to the subject the polypeptide described herein, the polynucleotide described herein, the host cell described herein, or the pharmaceutical composition described herein.

- 5 In one embodimentexample, the subject is further treated using one or more immunotherapies, e.g., using vaccination or adoptive transfer of T cells, such as T cell vaccines or adoptive transfer of (naïve or T cell receptor transgenic or chimeric antigen receptor transgenic) T cells or NK cells.

10 The effectiveness of vaccines, wherein the antigen is either delivered *per se* or as a polynucleotide, in particular as RNA encoding the antigen (e.g. RNA encoding a peptide or protein used for vaccination also referred to as "peptide or protein comprising an epitope for inducing an immune response against an antigen", "vaccine antigen" or simply "antigen" herein) can be increased by co-administering IL2 variant polypeptides described herein, wherein the IL2 variant polypeptide is either delivered *per se* or as a polynucleotide, in particular RNA encoding the IL2 variant polypeptide. The vaccine is particularly effective
15 if the RNA encoding the IL2 variant polypeptide 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. Furthermore, the vaccine is particularly effective if an immune checkpoint inhibitor such as an anti-PD-L1 antibody is further administered.

20 In a further aspect, the present disclosure provides a use of the polypeptide described herein, the polynucleotide described herein, the host cell described herein, or the pharmaceutical composition described herein; and a peptide or protein comprising an epitope or a polynucleotide encoding the peptide or protein in the manufacture of a medicament for inducing an immune response specific for an antigen in the subject. In one embodimentexample, the method described herein further comprises administering
25 to the subject a peptide or protein comprising an epitope for inducing an immune response specific for an antigen in the subject or a polynucleotide encoding the peptide or protein. In one embodimentexample, the polynucleotide encoding the peptide or protein is RNA.

30 In a further aspect, the present disclosure provides a use of the polypeptide described herein, the polynucleotide described herein, the host cell described herein, or the pharmaceutical composition described herein in the manufacture of a first medicament and use of a peptide or protein comprising an epitope or a polynucleotide encoding the peptide or protein in the manufacture of a second medicament,

wherein the first and second medicaments are to be used in combination therapy for inducing an immune response in a subject.

In a further aspect, the present disclosure provides a use of the polypeptide described herein, the polynucleotide described herein, the host cell described herein, or the pharmaceutical composition described herein in the manufacture of a medicament for use in combinatorial therapy for inducing an immune response in a subject, wherein said medicament is to be administered in combination with a peptide or protein comprising an epitope or a polynucleotide encoding the peptide or protein.

In one embodimentexample, the method described herein is a method for treating or preventing cancer in a subject, wherein optionally the antigen is a tumor-associated antigen.

In one aspectexample, provided herein is a method for treating or preventing cancer in a subject comprising administering to the subject the polypeptide described herein, the polynucleotide described herein, the host cell described herein, or the pharmaceutical composition described herein.

In one embodimentexample, the method further comprises administering to the subject a peptide or protein comprising an epitope for inducing an immune response specific for a tumor-associated antigen in the subject or a polynucleotide encoding the peptide or protein. In one embodimentexample, the polynucleotide encoding the peptide or protein is RNA.

In one embodimentexample, the methods described herein comprise administering to a subject:

- RNA encoding the IL2 variant polypeptide described herein; and
- RNA encoding a peptide or protein comprising an epitope for inducing an immune response specific for an antigen in the subject.

In one embodimentexample, 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.

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

the immune checkpoint inhibitor is an antibody or antibody fragment. In one [embodimentexample](#), the antibody or antibody fragment targets PD-1, PD-L1, or CTLA-4.

In one [embodimentexample](#), the RNA encoding the IL2 variant polypeptide described herein, the RNA encoding a peptide or protein comprising an epitope for inducing an immune response against an antigen in the subject, and optionally the immune checkpoint inhibitor are administered simultaneously or sequentially.

In one aspect, provided herein is a medical preparation comprising the polypeptide described herein, the polynucleotide described herein, the host cell described herein, or the pharmaceutical composition described herein.

In one [embodimentexample](#), the medical preparation further comprises a peptide or protein comprising an epitope for inducing an immune response specific for an antigen in a subject or a polynucleotide encoding the peptide or protein. In one [embodimentexample](#), the polynucleotide encoding the peptide or protein is RNA.

In one [embodimentexample](#), the medical preparation comprises the polypeptide, polynucleotide, host cell, or pharmaceutical composition and the peptide or protein comprising an epitope or polynucleotide encoding the peptide or protein, respectively, in separate containers.

In one [embodimentexample](#), the medical preparation comprises:

- a. RNA encoding the IL2 variant polypeptide described herein; and
- b. RNA encoding a peptide or protein comprising an epitope for inducing an immune response specific for an antigen in a subject.

In one [embodimentexample](#) 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 [embodimentexample](#), the solid form is a frozen form or a dehydrated form. In one [embodimentexample](#), the dehydrated form is a freeze-dried or spray-dried form.

In one [embodimentexample](#), the medical preparation further comprises an immune checkpoint inhibitor. In one [embodimentexample](#), the immune checkpoint inhibitor targets the interaction between (i) PD-1 and

PD-L1, or (ii) CTLA-4 and CD80 or CD86. In one embodimentexample, the immune checkpoint inhibitor is an antibody or antibody fragment. In one embodimentexample, the antibody or antibody fragment targets PD-1, PD-L1, or CTLA-4.

5 In one embodimentexample, the medical preparation is a kit. In one embodimentexample, the medical preparation comprises each component a. and b. in a separate container.

In one embodimentexample, the medical preparation is a pharmaceutical composition. In one embodimentexample, the pharmaceutical composition further comprises one or more pharmaceutically acceptable carriers, diluents and/or excipients.

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In one embodimentexample, the medical preparation further comprises instructions for use of the medical preparation for treating or preventing cancer wherein optionally the antigen is a tumor-associated antigen.

15 In another aspect, the present disclosure provides the medical preparation described herein for use in therapy. In one aspectexample, provided herein is the medical preparation described herein for pharmaceutical use. In one embodimentexample, the pharmaceutical use comprises a therapeutic or prophylactic treatment of a disease or disorder.

20 In another aspect, the present disclosure provides a use of the medical preparation described herein in the manufacture of a medicament for treating or preventing cancer in a subject, wherein optionally the antigen is a tumor-associated antigen. In one aspectexample, provided herein is the medical preparation described herein for use in a method for treating or preventing cancer in a subject, wherein optionally the antigen is a tumor-associated antigen.

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In one embodimentexample, 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.

30 In a further aspectexample, the inventiondisclosure relates to the IL2 variant polypeptide described herein, the polynucleotide encoding the IL2 variant polypeptide described herein, the host cell comprising the polynucleotide encoding the IL2 variant polypeptide described herein, or the pharmaceutical composition described herein for use in a method described herein.

Claims

1. A polypeptide comprising a mutein of human interleukin-2 (IL2) or of a functional variant of human IL2, wherein the human IL2 or the functional variant thereof is substituted at at least position 80 (leucine), position 81 (arginine), position 85 (leucine) and position 92 (isoleucine) relative to wild type human IL2 and numbered in accordance with wild type human IL2, wherein the substitution enhances the affinity for the $\beta\gamma$ IL2 receptor complex (IL2R $\beta\gamma$) and wherein the human IL2 or the functional variant thereof is not substituted at position 86 (isoleucine) relative to wild type human IL2 and numbered in accordance with wild type human IL2.
2. The polypeptide of claim 1, wherein position 80 (leucine) is substituted by phenylalanine, position 81 (arginine) is substituted by glutamic acid, position 85 (leucine) is substituted by valine and position 92 (isoleucine) is substituted by phenylalanine relative to wild type human IL2 and numbered in accordance with wild type human IL2.
3. The polypeptide of claim 1 or 2, wherein the human IL2 or the functional variant thereof is further substituted at position 74 (glutamine) relative to wild type human IL2 and numbered in accordance with wild type human IL2.
4. The polypeptide of claim 3, wherein position 74 (glutamine) is substituted by histidine relative to wild type human IL2 and numbered in accordance with wild type human IL2.
5. A polypeptide comprising a mutein of human IL2 or of a functional variant of human IL2, wherein the human IL2 or the functional variant thereof is substituted at at least position 80 (leucine) by phenylalanine, position 81 (arginine) by glutamic acid, position 85 (leucine) by valine and position 92 (isoleucine) by phenylalanine relative to wild type human IL2 and numbered in accordance with wild type human IL2.
6. The polypeptide of claim 5, wherein the human IL2 or the functional variant thereof is further substituted at position 74 (glutamine) by histidine relative to wild type human IL2 and numbered in accordance with wild type human IL2.
7. A polypeptide comprising a mutein of human IL2 or of a functional variant of human IL2, wherein the human IL2 or the functional variant thereof is substituted at at least position 74 (glutamine) by histidine,

position 80 (leucine) by phenylalanine, position 81 (arginine) by glutamic acid, position 85 (leucine) by valine and position 92 (isoleucine) by phenylalanine relative to wild type human IL2 and numbered in accordance with wild type human IL2.

8. The polypeptide of any one of claims 5 to 7, wherein the substitution enhances the affinity for IL2R $\beta\gamma$.

9. The polypeptide of any one of claims 1 to 8, wherein the human IL2 or the functional variant thereof further comprises one or more amino acid substitutions which reduce the affinity for the alpha subunit of the $\alpha\beta\gamma$ IL2 receptor complex (IL2R $\alpha\beta\gamma$).

10. The polypeptide of claim 9, wherein the one or more amino acid substitutions which reduce the affinity for the alpha subunit of IL2R $\alpha\beta\gamma$ reduce the affinity for IL2R $\alpha\beta\gamma$ to a greater extent than for IL2R $\beta\gamma$.

11. The polypeptide of claim 9 or 10, wherein the one or more amino acid substitutions which reduce the affinity for the alpha subunit of IL2R $\alpha\beta\gamma$ comprise substitutions of the human IL2 or the functional variant thereof at position 43 (lysine) and position 61 (glutamic acid) relative to wild type human IL2 and numbered in accordance with wild type human IL2.

12. The polypeptide of claim 11, wherein position 43 (lysine) is substituted by glutamic acid and position 61 (glutamic acid) is substituted by lysine.

13. A polypeptide comprising a mutein of human IL2 or of a functional variant of human IL2, wherein the human IL2 or the functional variant thereof is substituted at at least position 43 (lysine) by glutamic acid, position 61 (glutamic acid) by lysine, position 74 (glutamine) by histidine, position 80 (leucine) by phenylalanine, position 81 (arginine) by glutamic acid, position 85 (leucine) by valine and position 92 (isoleucine) by phenylalanine relative to wild type human IL2 and numbered in accordance with wild type human IL2.

14. The polypeptide of any one of claims 5 to 13, wherein the human IL2 or the functional variant thereof is not substituted at position 86 (isoleucine) relative to wild type human IL2 and numbered in accordance with wild type human IL2.

15. The polypeptide of any one of claims 1 to 14, wherein the human IL2 has the amino acid sequence according to SEQ ID NO: 1.
16. The polypeptide of any one of claims 1 to 15, wherein the mutein of human IL2 or the functional variant thereof has a decreased ability to stimulate regulatory T cells compared to wild type human IL2.
17. The polypeptide of any one of claims 1 to 16, wherein the mutein of human IL2 or the functional variant thereof has an increased ability to stimulate effector T cells compared to wild type human IL2.
18. The polypeptide of any one of claims 1 to 17, which is an extended pharmacokinetic (PK) polypeptide.
19. The polypeptide of claim 18, wherein the extended-PK polypeptide comprises a fusion protein.
20. The polypeptide of claim 19, wherein the fusion protein comprises a moiety of the mutein of human IL2 or the functional variant thereof and a moiety which is heterologous to human IL2 or the functional variant thereof.
21. The polypeptide of claim 19 or 20, wherein the fusion protein comprises a moiety of the mutein of human IL2 or the functional variant thereof and a moiety selected from the group consisting of serum albumin, an immunoglobulin fragment, transferrin, Fn3, and variants thereof.
22. The polypeptide of claim 21, wherein the serum albumin comprises mouse serum albumin or human serum albumin.
23. The polypeptide of claim 21, wherein the immunoglobulin fragment comprises an immunoglobulin Fc domain.
24. A polynucleotide encoding the polypeptide of any one of claims 1 to 23.
25. The polynucleotide of claim 24, which is RNA.
26. A host cell comprising the polynucleotide of claim 24 or 25.

~~27. The polypeptide of any one of claims 1 to 23, the polynucleotide of claim 24 or 25, or the host cell of claim 26 for pharmaceutical use.~~

~~28. The polypeptide, polynucleotide or host cell of claim 27, wherein the pharmaceutical use comprises a therapeutic or prophylactic treatment of a disease or disorder.~~

~~29. The polypeptide, polynucleotide or host cell of claim 27 or 28, for use in a method for treating or preventing cancer in a subject.~~

~~30~~27. A pharmaceutical composition comprising the polypeptide of any one of claims 1 to 23, the polynucleotide of claim 24 or 25, or the host cell of claim 26.

~~31~~28. ~~A method of treating a subject comprising administering to the subject~~ The polypeptide of any one of claims 1 to 23, the polynucleotide of claim 24 or 25, the host cell of claim 26, or the pharmaceutical composition of claim ~~30~~27 for use in therapy.

~~32~~29. ~~A method for inducing an immune response in a subject comprising administering to the subject~~ Use of the polypeptide of any one of claims 1 to 23, the polynucleotide of claim 24 or 25, the host cell of claim 26, or the pharmaceutical composition of claim 30 in the manufacture of a medicament for inducing an immune response in a subject.

~~33~~30. Use of the polypeptide of any one of claims 1 to 23, the polynucleotide of claim 24 or 25, the host cell of claim 26, or the pharmaceutical composition of claim 30; The method of claim 31 or 32, which further comprises administering to the subject and a peptide or protein comprising an epitope or a polynucleotide encoding the peptide or protein in the manufacture of a medicament for inducing an immune response specific for an antigen in the subject ~~or a polynucleotide encoding the peptide or protein.~~

31. Use of the polypeptide of any one of claims 1 to 23, the polynucleotide of claim 24 or 25, the host cell of claim 26, or the pharmaceutical composition of claim 30 in the manufacture of a first medicament and use of a peptide or protein comprising an epitope or a polynucleotide encoding the peptide or protein in the manufacture of a second medicament, wherein the first and second medicaments are to be used in combination therapy for inducing an immune response in a subject.

32. Use of the polypeptide of any one of claims 1 to 23, the polynucleotide of claim 24 or 25, the host cell of claim 26, or the pharmaceutical composition of claim 30 in the manufacture of a medicament for use in combinatorial therapy for inducing an immune response in a subject, wherein said medicament is to be administered in combination with a peptide or protein comprising an epitope or a polynucleotide encoding the peptide or protein.

3433. The ~~method-use~~ of any one of claims 3330 to 32, wherein the polynucleotide encoding the peptide or protein is RNA.

3534. The ~~method-use~~ of any one of claims 31-29 to 3433, ~~which is a method~~wherein the use is for treating or preventing cancer in a subject, wherein optionally the antigen is a tumor-associated antigen.

~~36. A method for treating or preventing cancer in a subject comprising administering to the subject the polypeptide of any one of claims 1 to 23, the polynucleotide of claim 24 or 25, the host cell of claim 26, or the pharmaceutical composition of claim 30.~~

~~37. The method of claim 36, which further comprises administering to the subject a peptide or protein comprising an epitope for inducing an immune response specific for a tumor-associated antigen in the subject or a polynucleotide encoding the peptide or protein.~~

~~38. The method of claim 37, wherein the polynucleotide encoding the peptide or protein is RNA.~~

3935. A medical preparation comprising the polypeptide of any one of claims 1 to 23, the polynucleotide of claim 24 or 25, the host cell of claim 26, or the pharmaceutical composition of claim 30.

4036. The medical preparation of claim 3935, further comprising a peptide or protein comprising an epitope for inducing an immune response specific for an antigen in a subject or a polynucleotide encoding the peptide or protein.

4437. The medical preparation of claim 4036, wherein the polynucleotide encoding the peptide or protein is RNA.

~~4238~~. The medical preparation of claim ~~40-36~~ or ~~4137~~, which comprises the polypeptide, polynucleotide, host cell, or pharmaceutical composition and the peptide or protein comprising an epitope or polynucleotide encoding the peptide or protein, respectively, in separate containers.

~~4339~~. The medical preparation of any one of claims ~~39-35~~ to ~~4238~~, further comprising instructions for use of the medical preparation for treating or preventing cancer wherein optionally the antigen is a tumor-associated antigen.

~~4440~~. The medical preparation of any one of claims ~~39-35~~ to ~~43-39~~ for ~~pharmaceutical~~ use in therapy.

~~45. The medical preparation of claim 44, wherein the pharmaceutical use comprises a therapeutic or prophylactic treatment of a disease or disorder.~~

~~4641. The Use of the~~ medical preparation of any one of claims ~~39-35~~ to ~~45-40~~ for use in a method in the manufacture of a medicament for treating or preventing cancer in a subject, wherein optionally the antigen is a tumor-associated antigen.