DE NOVO DESIGN OF POTENT AND SELECTIVE INTERLEUKIN MIMETICS

Cross Reference

This application claims priority to U.S. Provisional Patent Application Serial Nos. 62/689,769 filed June 25, 2018 and 62/768,733 filed November 16, 2018, each incorporated by reference herein in its entirety.

Background

The considerable potential of central immune cytokine interleukins such as IL-2 and IL-4 for cancer treatment has sparked numerous efforts to improve their therapeutic properties by mutation and/or chemical modification. However, because these approaches are closely tied to native IL-2 or IL-4, they cannot eliminate undesirable properties such as low stability and binding to the IL-2 receptor α subunit (IL-2Rα), to IL-4 receptor $\alpha\gamma_c$heterodimer (IL-4R$\alpha\gamma_c$), or to IL-13 receptor α subunit (IL-13Rα).

Summary

In one ~~aspect~~example, a method is provided. A computing device determines a structure for a plurality of residues of a protein where the structure of the plurality of residues provides a particular receptor binding interface. The computing device determines a plurality of designed residues using a mimetic design protocol provided by the computing device, wherein the plurality of designed residues provide the particular receptor binding interface, and wherein the plurality of designed residues differ from the plurality of residues.

The computing device determines one or more connecting helix structures that connect the plurality of designed residues. The computing device determines a first protein backbone for the protein by assembling the one or more connecting helix structures and the plurality of designed residues over a plurality of combinations. The computing device designs a second protein backbone for the protein for flexibility and low energy structures based on the first protein backbone. The computing device generates an output related to at least the second protein backbone.

Also included are non-naturally occurring proteins prepared by the methods described herein. The non-naturally occurring proteins can be cytokines, for example, non-naturally occurring IL-2 or IL-4 (also referred to herein as IL-2, IL-2/15 mimetics or IL-4 mimetics).

In another ~~aspect~~example, a computing device is provided. The computing device includes one or more processors; and data storage that is configured to store at least computer-readable instructions that, when executed by the one or more processors, cause the computing device to perform functions. The functions include: determining a structure for a plurality of residues of a protein that provides a particular receptor binding interface; determining a plurality of designed residues using a mimetic design protocol, wherein the plurality of designed residues provide the particular receptor binding interface, and wherein the plurality of designed residues differ from the plurality of residues; determining one or more connecting helix structures that connect the plurality of designed residues; determining a first protein backbone for the protein by assembling the one or more connecting helix structures and the plurality of designed residues over a plurality of combinations; designing a second protein backbone for the protein for flexibility and low energy structures based on the first protein backbone; and generating an output related to at least the second protein backbone for the protein.

In another ~~aspect~~example, a non-transitory computer-readable medium is provided. The non-transitory computer-readable medium is configured to store at least computer-readable instructions that, when executed by one or more processors of a computing device, cause the computing device to perform functions. The functions include: determining a structure for a plurality of residues of a protein that provides a particular receptor binding interface; determining a plurality of designed residues using a mimetic design protocol, wherein the plurality of designed residues provide the particular receptor binding interface, and wherein the plurality of designed residues differ from the plurality of residues; determining one or more connecting helix structures that connect the plurality of designed residues; determining a first protein backbone for the protein by assembling the one or more connecting helix structures and the plurality of designed residues over a plurality of combinations; designing a second protein backbone for the protein for flexibility and low energy structures based on the first protein backbone; and generating an output related to at least the second protein backbone for the protein.

In another ~~aspect~~example, a device is provided. The device includes: means for determining a structure for a plurality of residues of a protein that provides a particular receptor binding interface; means for determining a plurality of designed residues using a mimetic design protocol, wherein the plurality of designed residues provide the particular receptor binding

interface, and wherein the plurality of designed residues differ from the plurality of residues; means for determining one or more connecting helix structures that connect the plurality of designed residues; means for determining a first protein backbone for the protein by assembling the one or more connecting helix structures and the plurality of designed residues over a plurality of combinations; means for designing a second protein backbone for the protein for flexibility and low energy structures based on the first protein backbone; and means for generating an output related to at least the second protein backbone for the protein.

In another ~~aspect~~example, non-naturally occurring polypeptides are provided comprising domains X1, X2, X3, and X4, wherein:

(a) X1 is a peptide comprising the amino acid sequence at least 25%, 27%, 30%, 35%, 40%, 45%, 50%, 55%, 60%, 65%, 70%, 75%, 80%, 85%, 90%, 95%, 98%, or 100% identical to **E**HA**LYD**A**L** (SEQ ID NO:1);

(b) X2 is a helical-peptide of at least 8 amino acids in length;

(c) X3 is a peptide comprising the amino acid sequence at least 25%%, 27%, 30%, 35%, 40%, 45%, 50%, 55%, 60%, 65%, 70%, 75%, 80%, 85%, 90%, 95%, 98%, or 100% identical to **Y**AF**N**FE**LI** (SEQ ID NO:2);

(d) X4 is a peptide comprising the amino acid sequence at least 25%, 27%, 30%, 35%, 40%, 45%, 50%, 55%, 60%, 65%, 70%, 75%, 80%, 85%, 90%, 95%, 98%, or 100% identical to **I**TIL**Q**S**W**IF (SEQ ID NO:3);

wherein X1, X2, X3, and X4 may be in any order in the polypeptide;

wherein amino acid linkers may be present between any of the domains; and

wherein the polypeptide binds to IL-2 receptor $\beta\gamma_c$ heterodimer (IL-2R$\beta\gamma_c$), IL-4 receptor $\alpha\gamma_c$ heterodimer (IL-4R$\alpha\gamma_c$), or IL-13 receptor α subunit (IL-13Rα).

In one aspect, the present disclosure refers to a non-naturally occurring polypeptide comprising domains X1, X2, X3, and X4, wherein:

X1 is a peptide comprising an amino acid sequence at least 60%, at least 65%, at least 70%, at least 75%, at least 80%, at least 85%, at least 90%, at least 95%, at least 98%, or 100% identical to the peptide PKKKIQLHAEHALYDALMILNI (SEQ ID NO: 4);

X2 is a helical-peptide of at least 8 amino acids in length;

X3 is a peptide comprising an amino acid sequence at least 60%, at least 65%, at least 70%, at least 75%, at least 80%, at least 85%, at least 90%, at least 95%, at least 98%, or 100% identical to the peptide LEDYAFNFELILEEIARLFESG (SEQ ID NO:5); and

X4 is a peptide comprising an amino acid sequence at least 60%, at least 65%, at least 70%, at least 75%, at least 80%, at least 85%, at least 90%, at least 95%, at least 98%, or 100% identical to the peptide EDEQEEMANAIITILQSWIFS (SEQ ID NO:6),

wherein X1, X2, X3, and X4 may be in any order in the polypeptide;

wherein amino acid linkers may be present between any of the domains; and

wherein the polypeptide binds to IL-2 receptor $\beta\gamma_c$ heterodimer (IL-2R$\beta\gamma_c$) or IL-4 receptor $\alpha\gamma_c$heterodimer (IL-4R$\alpha\gamma_c$).

In one aspect, the present disclosure refers to a non-naturally occurring polypeptide comprising domains X1, X2, X3, and X4, wherein:

(a) X1 is a peptide comprising an amino acid sequence at least 60%, at least 65%, at least 70%, at least 75%, at least 80%, at least 85%, at least 90%, at least 95%, at least 98%, or 100% identical to EHALYDAL (SEQ ID NO:1);

(b) X2 is a helical-peptide of at least 8 amino acids in length;

(c) X3 is a peptide comprising an amino acid sequence at least 60%, at least 65%, at least 70%, at least 75%, at least 80%, at least 85%, at least 90%, at least 95%, at least 98%, or 100% identical to YAFNFELI (SEQ ID NO:2);

(d) X4 is a peptide comprising an amino acid sequence at least 60%, at least 65%, at least 70%, at least 75%, at least 80%, at least 85%, at least 90%, at least 95%, at least 98%, or 100% identical to ITILQSWIF (SEQ ID NO:3);

wherein X1, X2, X3, and X4 may be in any order in the polypeptide;

wherein amino acid linkers may be present between any of the domains; and

wherein the polypeptide binds to IL-2 receptor $\beta\gamma_c$ heterodimer (IL-2R$\beta\gamma_c$).

In one aspect, the present disclosure refers to a non-naturally occurring polypeptide comprising an amino acid sequence at least 90%, at least 95%, at least 98% or 100% identical to the amino acid sequence set forth in SEQ ID NO: 90 wherein the polypeptide binds to IL-2 receptor $\beta\gamma_c$ heterodimer (IL-2R$\beta\gamma_c$).

In one aspect, the present disclosure refers to a non-naturally occurring polypeptide comprising an amino acid sequence at least 90%, at least 95%, at least 98% or 100% identical to the amino acid sequence set forth in SEQ ID NO: 181 wherein the polypeptide binds to IL-2 receptor $\beta\gamma_c$ heterodimer (IL-2R$\beta\gamma_c$).

In one aspect, the present disclosure refers to a recombinant nucleic acid encoding any one of the polypeptides disclosed herein.

In one aspect, the present disclosure refers to a recombinant host cell comprising the nucleic acid disclosed herein.

In one aspect, the present disclosure refers to a pharmaceutical composition comprising any one of the polypeptides disclosed herein that binds to IL-2 receptor $\beta\gamma_c$ heterodimer (IL-2R$\beta\gamma_c$) or a recombinant nucleic acid disclosed herein that encodes a polypeptide that binds to IL-2 receptor $\beta\gamma_c$ heterodimer (IL-2R$\beta\gamma_c$), and a pharmaceutically acceptable carrier.

In one aspect, the present disclosure refers to use of any one of the polypeptides disclosed herein that binds to IL-2 receptor $\beta\gamma_c$ heterodimer (IL-2R$\beta\gamma_c$), a recombinant nucleic acid disclosed herein that encodes a polypeptide that binds to IL-2 receptor $\beta\gamma_c$ heterodimer (IL-2R$\beta\gamma_c$), or the pharmaceutical composition disclosed herein in the manufacture of a medicament for treating cancer that expresses IL-2 receptor $\beta\gamma$c heterodimer (IL-2R$\beta\gamma$c) in a subject having said cancer.

In other ~~aspect~~examples are provided pharmaceutical compositions comprising one or more polypeptide disclosed herein and a pharmaceutically acceptable carrier, recombinant nucleic acids encoding a polypeptide disclosed herein, expression vectors comprising the recombinant nucleic acids disclosed herein, and recombinant host cells comprising one or more expression vector disclosed herein. In a further ~~aspect~~example, methods for treating cancer are provided, comprising administering to a subject having cancer one or more polypeptide, recombinant nucleic acid, expression vector comprising the recombinant nucleic acid, and/or recombinant host cells disclosed herein or a pharmaceutical composition thereof in an amount effective to treat the tumor.

We claim

1. A non-naturally occurring polypeptide comprising domains X1, X2, X3, and X4, wherein:

(a) X1 is a peptide comprising the amino acid sequence at least 25%, 27%, 30%, 35%, 40%, 45%, 50%, 55%, 60%, 65%, 70%, 75%, 80%, 85%, 90%, 95%, 98%, or 100% identical to **E**HA**LYD**A**L** (SEQ ID NO:1);

(b) X2 is a helical peptide of at least 8 amino acids in length;

(c) X3 is a peptide comprising the amino acid sequence at least 25%, 27%, 30%, 35%, 40%, 45%, 50%, 55%, 60%, 65%, 70%, 75%, 80%, 85%, 90%, 95%, 98%, or 100% identical to **Y**AF**N**FE**LI** (SEQ ID NO:2);

(d) X4 is a peptide comprising the amino acid sequence at least 25%, 27%, 30%, 35%, 40%, 45%, 50%, 55%, 60%, 65%, 70%, 75%, 80%, 85%, 90%, 95%, 98%, or 100% identical to **I**TIL**Q**S**W**IF (SEQ ID NO:3);

wherein X1, X2, X3, and X4 may be in any order in the polypeptide;

wherein amino acid linkers may be present between any of the domains; and

wherein the polypeptide binds to IL-2 receptor $\beta\gamma_c$ heterodimer (IL-2R$\beta\gamma_c$), IL-4 receptor $\alpha\gamma_c$heterodimer (IL-4R$\alpha\gamma_c$), or IL-13 receptor α subunit (IL-13Rα).

2. The polypeptide of claim 1, wherein:

(i) X1 includes one or both of the following: H at residue 2 and Y at residue 5; and/or

(ii) X3 includes 1, 2, 3, 4, or all 5 of the following: Y at residue 1, F at residue 3, N at residue 4, L at residue 7, and I at residue 8.

3. The polypeptide of claim 1 or 2, wherein:

(iii) X4 includes I at residue 8.

4. The polypeptide of claim 1, wherein:

(i) X1 includes E at residue 2 and K at residue 5; and

(ii) X3 includes F at residue 1, K at residue 3, R at residue 4, R at residue 7, and N at residue 8.

5. The polypeptide of claim 1 or 4, wherein

(iii) X4 includes F at residue 8.

6. The polypeptide of any one of claims 1-5, wherein:

X1 is a peptide comprising the amino acid sequence at least 25%, 27%, 30%, 35%, 40%, 45%, 50%, 55%, 60%, 65%, 70%, 75%, 80%, 85%, 90%, 95%, 98%, or 100% identical along its length to the peptide PKKKIQLHA**E**HA**LYD**A**L**MILNI (SEQ ID NO: 4) ;

X3 is a peptide comprising the amino acid sequence at least 25%, 27%, 30%, 35%, 40%, 45%, 50%, 55%, 60%, 65%, 70%, 75%, 80%, 85%, 90%, 95%, 98%, or 100% identical along its length the peptide **L**ED**Y**AF**N**FE**LI**LEE**I**ARLFESG (SEQ ID NO:5) ; and

X4 is a peptide comprising the amino acid sequence at least 25%, 27%, 30%, 35%, 40%, 45%, 50%, 55%, 60%, 65%, 70%, 75%, 80%, 85%, 90%, 95%, 98%, or 100% identical along its length to the peptide EDEQEEMANAI**I**TIL**Q**S**W**IFS (SEQ ID NO:6) .

7. The polypeptide of claim 6, wherein:

(i) X1 includes 1, 2, 3, 4, or all 5 of the following: L at residue 7, H at residue 8, H at residue 11, Y at residue 14; M at residue 18; and/or

(ii) X3 includes 1, 2, 3, 4, 5, 6, 7, or all 8 of the following: D at residue 3, Y at residue 4, F at residue 6, N at residue 7, L at residue 10, I at residue 11, E at residue 13, or E at residue 14.

8. The polypeptide of claim 6 or 7, wherein:

(iii) X4 includes I at residue 19.

9. The polypeptide of claim 6, wherein:

X1 is a peptide comprising the amino acid sequence at least 25%, 27%, 30%, 35%, 40%, 45%, 50%, 55%, 60%, 65%, 70%, 75%, 80%, 85%, 90%, 95%, 98%, or 100% identical along its length to the peptide PKKKIQIMA**EEALKDAL**SILNI (SEQ ID NO: 8);

X3 is a peptide comprising the amino acid sequence at least 37% 40%, 45%, 50%, 55%, 60%, 65%, 70%, 75%, 80%, 85%, 90%, 95%, 98%, or 100% identical along its length the peptide LER**FAKRFERN**LWGIARLFESG (SEQ ID NO: 9); and

X4 is a peptide comprising the amino acid sequence at least 25%, 27%, 30%, 35%, 40%, 45%, 50%, 55%, 60%, 65%, 70%, 75%, 80%, 85%, 90%, 95%, 98%, or 100% identical along its length to the peptide EDEQEEMANA**IITILQSWFF**S (SEQ ID NO: 10).

wherein

(i) X1 includes I at residue 7, T or M at residue 8, E at residue 11, K at residue 14 and S at residue 18; and

(ii) X3 includes R at residue 3, F at residue 4, K at residue 6, R at residue 7, R at residue 10, N at residue 11, W at residue 13, and G at residue 14.

10. The polypeptide of claim 9, wherein

(iii) X4 includes F at residue 19.

11. The polypeptide of any one of claims 1-7, wherein amino acid substitutions relative to the reference peptide domains do not occur at AA residues marked in bold font.

12. The polypeptide of any one of claims 1-11, wherein amino acid substitutions relative to the reference peptide domains are conservative amino acid substitutions.

13. The polypeptide of any one of claims 1-12, wherein the domains are arranged N-terminal to C-terminal in an arrangement selected from the group consisting of X1-X2-X3-X4; X1-X3-X2-X4; X1-X4-X2-X3; X3-X2-X1-X4; X4-X3-X2-X1; X2-X3-X4-X1; and X2-X1-X4-X3.

14. The polypeptide of any one of claims 6-13, wherein amino acid residues relative to SEQ ID NO:4 are selected from the group consisting of:

Position 01: A F I L M P Q R S W

Position 02: A D E G V K

Position 03: D E F W K

Position 04: D E K N P R W

Position 05: D E H I K L M S

Position 06: A D E G L P S W Q

Position 07: D E L Q Y I

Position 08: A F H W Y M T

Position 09: C F P A

Position 10: C D E F K P

Position 11: D F H E

Position 12: A D E P S T V

Position 13: H I L M P R V W

~~Position 14: F R W Y K~~

~~Position 15: D E N Y~~

~~Position 16: A C L M S~~

~~Position 17: F I L M P R~~

~~Position 18: G M Q Y S~~

~~Position 19: I L M P Q V~~

~~Position 20: A K L M Q R S~~

~~Position 21: G K N P R S W~~

~~Position 22: D E I K M N W Y~~

~~15. The polypeptide of claim 14, wherein position 7 is I, position 8 is M or T, position 11 is E, position 14 is K, and position 18 is S.~~

~~16. The polypeptide of claim 14, wherein 1, 2, 3, 4, or 5 of the following are not true: position 7 is I, position 8 is M or T, position 11 is E, position 14 is K, and position 18 is S.~~

~~17. The polypeptide of any one of claims 6-16, wherein amino acid residues relative to SEQ ID NO:5 are selected from the group consisting of:~~

~~Position 01: A L~~

~~Position 02: D E G K M T~~

~~Position 03: D E N Y R~~

~~Position 04: C D G T Y F~~

~~Position 05: A F H S V W Y~~

~~Position 06: A F I M T V Y K~~

~~Position 07: D K N S T R~~

~~Position 08: A C G L M S V F~~

~~Position 09: C H K L R S T V E~~

~~Position 10: F I L M Y R~~

~~Position 11: I L N T Y~~

~~Position 12: F K L M S V~~

~~Position 13: A D F G I N P Q S T E W~~

~~Position 14: A E F G H S V~~

~~Position 15: C I L M V W~~

~~Position 16: A D G S T V~~

~~Position 17: H K L N R~~

~~Position 18: C D G I L Q R T W~~

~~Position 19: D F M N W~~

~~Position 20: A C E F G M S Y~~

~~Position 21: D E G H L M R S T V W~~

~~Position 22: A D G K N S Y~~

~~18. The polypeptide of any one of claims 6 to 17 comprising a cysteine substitution at position 17 or 20 relative to SEQ ID NO:5.~~

~~19. The polypeptide of claim 17 or 18, wherein position 3 is R, position 4 is F, position 6 is K, position 7 is R, position 10 is R, position 11 is N, position 13 is W, and position 14 is G.~~

~~20. The polypeptide of claim 17 or 18, wherein 1, 2, 3, 4, 5, 6, 7, or all 8 of the following are not true: position 3 is R, position 4 is F, position 6 is K, position 7 is R, position 10 is R, position 11 is N, position 13 is W, and position 14 is G.~~

~~21. The polypeptide of any one of claims 6-20, wherein amino acid residues relative to SEQ ID NO:6 are selected from the group consisting of:~~

~~Position 01: D E G K V~~

~~Position 02: D I M S~~

~~Position 03: E G H K~~

~~Position 04: E G I K Q R S~~

~~Position 05: A D E G H S V~~

~~Position 06: C D E G I M Q R T V~~

~~Position 07: C E L M P R T~~

~~Position 08: A F L M W~~

~~Position 09: A G L N Q R T~~

~~Position 10: A C D E F H I W~~

~~Position 11: I M N S V W~~

~~Position 12: I K L S V~~

~~Position 13: C L M R S T~~

~~Position 14: I L P T Y~~

~~Position 15: F G I L M N V~~

~~Position 16: H K Q R~~

~~Position 17: C F K S W Y~~

~~Position 18: K Q T W~~

~~Position 19: C G N I~~

~~Position 20: C F G L Y~~

~~Position 21: A F G H S Y~~

~~22. The polypeptide of any one of claims 6 to 21 comprising a cysteine substitution at position 3 relative to SEQ NO:6.~~

~~23. The polypeptide of claim 21 or 22 where position 19 is I.~~

~~24. The polypeptide of claim 21 or 22 where position 19 is not I.~~

~~25. The polypeptide of any one of claims 1-24, wherein X2 is a peptide comprising the amino acid sequence at least 25%, 27%, 30%, 35%, 40%, 45%, 50%, 55%, 60%, 65%, 70%, 75%, 80%, 85%, 90%, 95%, 98%, or 100% identical along its length to KDEAEKAKRMKEWMKRIKT (SEQ ID NO:7) .~~

~~26. The polypeptide of claim 25, wherein amino acid residues relative to SEQ ID NO:7 are selected from the group consisting of:~~

~~Position 01: A H L M R S V K~~

~~Position 02: A D E Q R S T V W Y~~

~~Position 03: C E G K L N Q R W~~

~~Position 04: A F G N S T V Y~~

~~Position 05: A E G I M R V C~~

~~Position 06: C E K L N R V~~

~~Position 07: A C E I L S T V W~~

~~Position 08: H K L M S T W Y~~

~~Position 09: A I L M Q S R~~

~~Position 10: A I M S W Y~~

~~Position 11: C I K L S V~~

~~Position 12: C E K L P Q R T~~

~~Position 13: A D H N W~~

~~Position 14: A C G I L S T V M~~

~~Position 15: A E G I K L M R V~~

~~Position 16: G H L R S T V C~~

~~Position 17: A I L V~~

~~Position 18: A C D E G H I K M S~~

~~Position 19: D E G L N V T~~

~~27. The polypeptide of claim 25 or 26 comprising a cysteine substitution at position 1, 2, 5, 9, 12, or 16 relative to SEQ NO:7.~~

~~28. The polypeptide of claim 26 or 27, wherein position 11 is I.~~

~~29. The polypeptide of claim 26 or 27, wherein position 11 is not I.~~

~~30. The polypeptide of any one of claims 1-29, wherein the polypeptide comprises a polypeptide at least 25%, 27%, 30%, 35%, 40%, 45%, 50%, 55%, 60%, 65%, 70%, 75%, 80%, 85%, 90%, 95%, 98%, or 100% identical to the amino acid sequence selected from the group consisting of SEQ ID NOS:11-94, 103-184, 190-243, and 245-247.~~

~~31. The polypeptide of any one of claims 1-29, wherein the polypeptide comprises a polypeptide at least 25%, 27%, 30%, 35%, 40%, 45%, 50%, 55%, 60%, 65%, 70%, 75%, 80%, 85%, 90%, 95%, 98%, or 100% identical to the amino acid sequence selected from the group consisting of SEQ ID NOS:90 and 181.~~

~~32. The polypeptide of any one of claims 1-31, wherein the polypeptide comprises a polypeptide at least 25%, 27%, 30%, 35%, 40%, 45%, 50%, 55%, 60%, 65%, 70%, 75%, 80%, 85%, 90%, 95%, 98%, or 100% identical to the full length of the amino acid sequence of SEQ ID NO:90, and wherein one, two, or more of the following mutations are present:~~

~~R50C;~~

~~E53C;~~

~~E62C;~~

~~E69C;~~

~~R73C; and/or~~

~~E82C.~~

~~33. The polypeptide of any one of claims 1-31, wherein the polypeptide comprises a polypeptide at least 25%, 27%, 30%, 35%, 40%, 45%, 50%, 55%, 60%, 65%, 70%, 75%, 80%, 85%, 90%, 95%, 98%, or 100% identical to the full length of the amino acid sequence of SEQ ID NO:181, and wherein one, two, or more of the following mutations are present~~

~~D56C;~~

~~K58C;~~

~~D59C;~~

~~R66C;~~

~~T77C;~~

~~E85C;~~

~~R50C;~~

~~E53C;~~

~~E62C;~~

~~E69C;~~

~~R73C; and/or~~

~~E82C.~~

~~34. The polypeptide of claim 32 or 33, wherein the polypeptide comprises a polypeptide at least 25%, 27%, 30%, 35%, 40%, 45%, 50%, 55%, 60%, 65%, 70%, 75%, 80%, 85%, 90%, 95%, 98%, or 100% identical to the full length of the amino acid sequence selected from the group consisting of SEQ ID NOS: 190-243; or wherein the polypeptide comprises a polypeptide at least 25%, 27%, 30%, 35%, 40%, 45%, 50%, 55%, 60%, 65%, 70%, 75%, 80%, 85%, 90%, 95%, 98%, or 100% identical to the full length of the amino acid sequence selected from the group consisting of SEQ ID NO:195 and 222; or wherein the polypeptide comprises a polypeptide at least 25%, 27%, 30%, 35%, 40%, 45%, 50%, 55%, 60%, 65%, 70%, 75%, 80%, 85%, 90%, 95%, 98%, or 100% identical to the full length of the amino acid sequence of SEQ ID NO:195.~~

35. The polypeptide of any one of claims 1-34, wherein the polypeptide is linked to a stabilization compound, including but not limited to a polyethylene glycol ("PEG") containing moiety.

36. The polypeptide of claim 35, wherein the stabilization compound, including but not limited to a PEG-containing moiety, is linked at a cysteine residue in the polypeptide.

37. The polypeptide of claim 36, wherein the cysteine residue is present in X2.

38. The polypeptide of any one of claims 35-37, wherein the stabilization compound, including but not limited to a PEG-containing moiety, is linked to the cysteine reside via a maleimide group, including but not limited to linked to a cysteine residue present at amino acid residue 62 relative to SEQ ID NO:90.

39. The polypeptide of any one of claims 1-38, wherein the polypeptide comprises a polypeptide at least 25%, 27%, 30%, 35%, 40%, 45%, 50%, 55%, 60%, 65%, 70%, 75%, 80%, 85%, 90%, 95%, 98%, or 100% identical to the amino acid sequence selected from the group consisting of SEQ ID NO:92, 93, 183, and 184.

40. The polypeptide of any one of claims 30-39, wherein position 7 is I, position 8 is T or M, position 11 is E, position 14 is K, position 18 is S, position 33 is Q, position 36 is R, position 37 is F, position 39 is K, position 40 is R, position 43 is R, position 44 is N, position 46 is W, and position 47 is G.

41. The polypeptide of claim 40, wherein position 68 is I and position 98 is F.

42. The polypeptide of any one of claims 30-39, wherein 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, or all1-4 of the following are not true: position 7 is I, position 8 is T or M, position 11 is E, position 14 is K, position 18 is S, position 33 is Q, position 36 is R, position 37 is F, position 39 is K, position 40 is R, position 43 is R, position 44 is N, position 46 is W, and position 47 is G.

43. The polypeptide of claim 42, wherein one or both of the following are not true: position 68 is I and position 98 is F.

44. The polypeptide of claim 1, wherein the polypeptide comprises a polypeptide at least 80% identical to the amino acid sequence selected from the group consisting of SEQ ID NOS:11-94, 103-184, 190-243, and 245-247.

45. The polypeptide of claim 44, wherein the polypeptide comprises a polypeptide at least 90% identical to the amino acid sequence selected from the group consisting of SEQ ID NOS:11-94, 103-184, 190-243, and 245-247.

46. The polypeptide of claim 44 or 45 wherein the polypeptide binds to IL-2 receptor $\beta\gamma_c$ heterodimer (IL-2R$\beta\gamma_c$).

47. The polypeptide of claim 1, wherein:

(a) X1 is a peptide comprising the amino acid sequence at least 85% identical to **E**HA**LYD**A**L** (SEQ ID NO:1);

(b) X2 is a helical peptide of at least 8 amino acids in length;

(c) X3 is a peptide comprising the amino acid sequence at least 85% identical to **Y**AF**N**FE**LI** (SEQ ID NO:2);

(d) X4 is a peptide comprising the amino acid sequence at least 85% identical to **I**TIL**Q**S**W**IF (SEQ ID NO:3);

wherein X1, X2, X3, and X4 may be in any order in the polypeptide;

wherein amino acid linkers may be present between any of the domains; and

wherein the polypeptide binds to IL-2 receptor $\beta\gamma_c$ heterodimer (IL-2R$\beta\gamma_c$).

48. The polypeptide of claim 1, wherein:

X1 is a peptide comprising the amino acid sequence at least 80% identical along its length to the peptide PKKKIQLHA**E**HA**LYD**A**L**MILNI (SEQ ID NO: 4) ;

X3 is a peptide comprising the amino acid sequence at least 80% identical along its length to the peptide **L**ED**Y**AF**N**FE**LI**LEE**I**ARLFESG (SEQ ID NO:5) ; and

X4 is a peptide comprising the amino acid at least 80% identical along its length to the peptide EDEQEEMANA**I**TIL**Q**S**W**IFS (SEQ ID NO:6) .

49. The polypeptide of claim 48, wherein:

X1 is a peptide comprising the amino acid sequence at least 90% identical along its length to the peptide PKKKIQLHA**E**HA**LYD**A**L**MILNI (SEQ ID NO: 4) ;

X3 is a peptide comprising the amino acid sequence at least 90% identical along its length to the peptide **L**ED**Y**AF**N**FE**LI**LEE**I**ARLFESG (SEQ ID NO:5) ; and

X4 is a peptide comprising the amino acid at least 90% identical along its length to the peptide EDEQEEMANAI**I**TIL**Q**S**W**IFS (SEQ ID NO:6) .

50. The polypeptide of any one of claims 47 to 49, wherein X2 is a peptide comprising the amino acid sequence at least 90% identical along its length to KDEAEKAKRMKE**W**MKRIKT (SEQ ID NO:7) .

51. The polypeptide of any one of claims 44 50, wherein the polypeptide is linked to a polyethylene glycol ("PEG") containing moiety at a cysteine residue in X2 of the polypeptide.

52. The polypeptide of claim 51 wherein the polypeptide comprises a polypeptide at least 90% identical to the amino acid sequence selected from the group consisting of SEQ ID NOS:195 and 222 and wherein the PEG-containing moiety, is linked to the cysteine reside at amino acid residue 62 relative to SEQ ID NO:195.

53. The polypeptide of any one of claims 44 to 52, wherein the domains are arranged N-terminal to C-terminal in an arrangement selected from the group consisting of X1-X3-X2-X4.

54. The polypeptide of any one of claims 2-3, 6-8, 11-14, 16-17, 20-21, 24-26, 29-38, 42-43 and 47--53 having a three dimensional structure with structural coordinates having a root mean square deviation of common residue backbone atoms or alpha carbon atoms of less than 2.5 Angstroms when superimposed on backbone atoms or alpha carbon atoms of the three dimensional structure of native IL-2.

55. The polypeptide of any one of claims 2-3, 6-8, 11-14, 16-17, 20-21, 24-26, 29-38, 42-44 and 47-53 having a three dimensional structure with structural coordinates having a root mean square deviation of common residue backbone atoms or alpha carbon atoms of less than

2.5 Angstroms when superimposed on backbone atoms or alpha carbon atoms of a three dimensional structure having the structural coordinates of Table E2.

56. The polypeptide of any one of claims 2-3, 6-8, 11-14, 16-17, 20-21, 24-26, 29-38, 42-45, and 47-53, wherein when in ternary complex with the mouse IL-2 receptor $\beta\gamma_c$, the polypeptide has a three dimensional structure with structural coordinates having a root mean square deviation of common residue backbone atoms or alpha carbon atoms of less than 2.5 Angstroms when superimposed on backbone atoms or alpha carbon atoms of the three dimensional structure of native IL-2 when in ternary complex with the mouse IL-2 receptor $\beta\gamma_c$.

57. The polypeptide of any one of claims 54-56 wherein the root mean square deviation is less than 1.5 Angstroms.

58. The polypeptide of claim 57 wherein the root mean square deviation is less than 1 Angstrom.

59. The polypeptide of any one of claims 4-6, 9-15, 17-19, 21-23, 25-28, 30, and 39-41 having a three dimensional structure with structural coordinates having a root mean square deviation of common residue backbone atoms or alpha carbon atoms of less than 2.5 Angstroms when superimposed on backbone atoms or alpha carbon atoms of the three dimensional structure of native IL-4.

60. The polypeptide of claim 59 wherein the root mean square deviation is less than 1.5 Angstroms.

61. The polypeptide of claim 59 or 60 wherein the root mean square deviation is less than 1 Angstrom.

62. The polypeptide of any one of claims 54-61 wherein the three dimensional structure of the polypeptide is determined using computational modeling.

63. The polypeptide of any one of claims 1-62, wherein X1, X2, X3, and X4 are alpha-helical domains.

64. The polypeptide of any one of claims 1-63 wherein the amino acid length of each of X1, X2, X3 and X4 is at least about 8 amino acids in length.

65. The polypeptide of any one of claims 1-64 wherein the amino acid length of each of X1, X2, X3 and X4 is at least about 19 amino acids in length.

66 The polypeptide of any one of claims 1-65 wherein the amino acid length of each of X1, X2, X3 and X4 is no more than 1000 amino acids in length, no more than 500 amino acids in length, no more than 400 amino acids in length, no more than 300 amino acids in length, no more than 200 amino acids in length, no more than 100 amino acids in length, or amino acids in length 50 amino acids in length.

67. The polypeptide of any one of claims 2-3, 6-8, 11-14, 16-18, 20-22, 24-27, 29-38, 42-55, and 62-66, wherein X1 binds to the beta and the gamma subunit of the human IL-2 receptor.

68. The polypeptide of any one of claims 2-3, 6-8, 11-14, 16-18, 20-22, 24-27, 29-38, 42-555, and 62-67 wherein X2 does not bind to the human IL-2 receptor.

69. The polypeptide of any one of claims 2-3, 6-8, 11-14, 16-18, 20-22, 24-27, 29-38, 42-55, and 62-68, wherein X3 binds to the beta subunit of the human IL-2 receptor.

70. The polypeptide of any one of claims 2-3, 6-8, 11-14, 16-18, 20-22, 24-27, 29-38, 42-55, and 62-69, wherein X4 binds to the gamma subunit of the human IL-2 receptor.

71. The polypeptide of any one of claims 2-3, 6-8, 11-14, 16-18, 20-22, 24-27, 29-38, 42-55, and 62-70 that does not bind to the alpha subunit of the human or murine IL-2 receptor.

72 The polypeptide of any one of claims 67-71 wherein the binding is specific binding as determined by surface plasmon resonance at biologically relevant concentrations.

73. The polypeptide of any one of claims 2-3, 6-8, 11-14, 16-18, 20-22, 24-27, 29-38, 42-55, and 62-72 that binds to that binds to the IL-2 receptor $\beta\gamma_c$ heterodimer (IL-2R$\beta\gamma_c$) with a binding affinity of 200 nm or less, 100 nm or less, 50 nM or less, or 25 nM or less.

74. The polypeptide of any one of claims 2-3, 6-8, 11-14, 16-18, 20-22, 24-27, 29-38, 42-55, and 62-73 wherein the polypeptide's affinity for the human and mouse IL-2 receptors is about equal to or greater than that of native IL-2.

75. The polypeptide of any one of claims 4-6, 9-15, 17-19, 21-23, 25-28, 30, 35-37, 39-41, and 59-66 that binds to that binds to the IL-4 receptor $\alpha\gamma_c$heterodimer (IL-4R$\alpha\gamma_c$) with a binding affinity of 200 nm or less, 100 nm or less, 50 nM or less, or 25 nM or less.

76. The polypeptide of any one of claims 4-6, 9-15, 17-19, 21-23, 25-28, 30, 35-37, 39-41, 59-66, and 75, wherein the polypeptide's affinity for the human and mouse IL-4 receptors is about equal to or greater than that of native IL-4.

77. The polypeptide of any one of claims 2-3, 6-8, 11-14, 16-18, 20-22, 24-27, 29-38, 42-55, and 62-74, wherein the polypeptide stimulates STAT5 phosphorylation in cells expressing the IL-2 receptor with potency about equal to or greater than native IL-2.

78. The polypeptide of any one of claims 2-3, 6-8, 11-14, 16-18, 20-22, 24-27, 29-38, 42-55, 62-74, and 77 wherein the polypeptide stimulates STAT5 phosphorylation in cells expressing the IL-2 receptor with potency about equal to or greater than native IL-2 in cells expressing IL-2 receptor $\beta\gamma_c$ heterodimer but lacking the IL-2 receptor α.

79. The polypeptide of any one of claims 2-3, 6-8, 11-14, 16-18, 20-22, 24-27, 29-38, 42-55, 62-74, and 77-78, wherein the polypeptide demonstrates thermal stability about equal to or greater than the thermal stability of native IL-2.

80. The polypeptide of any one of claims 1-79, that maintains or recovers at least 70% of its folded structure after thermal stability testing.

81. The polypeptide of any one of claims 1-80 that maintains or recovers at least 80% of its folded structure after thermal stability testing.

~~82. The polypeptide of any one of claims 1-81 that maintains or recovers at least 90% of its folded structure after thermal stability testing.~~

~~83. The polypeptide of any one of claims 1-82 that maintains or recovers at least 80% of its ellipticity spectrum after thermal stability testing.~~

~~84. The polypeptide of any one of claims 1-83 that maintains or recovers at least 70% activity after thermal stability testing.~~

~~85. The polypeptide of any one of claims 1-84 that maintains or recovers at least 80% activity after thermal stability testing.~~

~~86 The polypeptide of any one of claims 84 or 85 wherein activity is determined by a STAT5 phosphorylation assay.~~

~~87. The polypeptide of any one of claims 79-85 wherein thermal stability is measured by circular dichroism (CD) spectroscopy at 222 nM~~

~~88. The polypeptide of claim 87 wherein the thermal stability test comprises heating the polypeptide from 25 degrees Celsius to 95 degrees Celsius in one hour time frame , cooling the polypeptide to 25 degrees Celsius in a 5-minute time frame and monitoring ellipticity at 222 nm.~~

~~89. The polypeptide of claim 1, wherein the polypeptide comprises a polypeptide at least 90% identical, at least 95% identical or 100% identical to the amino acid sequence of SEQ ID NO:90, 181, or 247 wherein the polypeptide (i) does not bind to human or murine IL-2Ralpha, (ii) binds to human IL2RB with an affinity of about 11.2 nM (iii) binds to murine IL2RB with an affinity of about 16.1 nm (IV) binds to human IL-2Rβγ_c with an affinity of about 18.8 nM and (V) binds to murine IL-2Rβγ_c with an affinity of about 3.4 nM.~~

~~90. The polypeptide of any one of claims 1-89, wherein the polypeptide includes at least one disulfide bond.~~

91. The polypeptide of claim 90 wherein the disulfide bond links two of the X1, X2, X3, and X4 domains together.

92. The polypeptide of claim 90 or 91 wherein the disulfide bond links the X1 domain to the X4 domain.

93. The polypeptide of claim 90-92 wherein the disulfide linkage improves the thermal stability of the polypeptide as compared to a substantially similar polypeptide with no disulfide bond linking two domains together.

94. The polypeptide of any one of claims 1-93, wherein the polypeptide further comprises a targeting domain.

95. The polypeptide of claim 94, wherein the targeting domain is a translational fusion with the polypeptide.

96. The polypeptide of claim 94 or 95 wherein the targeting domain binds to a cell surface protein.

97. The polypeptide of claim 96, wherein the cell surface protein is present on the surface of cells selected from the group consisting of tumor cells, vascular components, tumor microenvironment (e.g. fibroblasts, infiltrating immune cells, or stromal elements), other cancer cells and immune cells (including but not limited to CD8+ T cells, T regulatory cells, dendritic cells, NK cells, or macrophages), such immune cell surface markers including but not limited to CD3, CD4, CD8, CD19, CD20, CD21, CD25, CD37, CD30, CD33, CD40, CD68, CD123, CD254, PD-1, B7-H3, and CTLA-4.

98. The polypeptide of claim 96, wherein the targeting domain binds to a tumor cell, tumor vascular component cell, or tumor microenvironment cell surface marker.

99. The polypeptide of claim 98, wherein the cell surface marker is selected from the group including but not limited to EGFR, EGFRvIII, Her2, HER3, EpCAM, MSLN, MUC16, PSMA, TROP2, ROR1, RON, PD-L1, CD47, CTLA-4,CD5, CD19, CD20, CD25, CD37, CD30, CD33, CD40, CD45, CAMPATH-1, BCMA, CS-1, PD-L1, B7-H3, B7-DC, HLD-

DR, carcinoembryonic antigen (CEA), TAG-72, EpCAM, MUC1, folate-binding protein, A33, G250, prostate-specific membrane antigen (PSMA), ferritin, GD2, GD3, GM2, Le^{y}, CA-125, CA19-9, epidermal growth factor, p185HER2, IL-2 receptor, EGFRvIII (de2-7 EGFR), fibroblast activation protein, tenascin, a metalloproteinase, endosialin, vascular endothelial growth factor, avB3, WT1, LMP2, HPV-E6, HPV-E7, Her-2/neu, MAGE-A3, p53 nonmutant, NY-ESO-1, MelanA/MART1, Ras mutant, gp100, p53 mutant, PR1, bcr-abl, tyronsinase, survivin, PSA, hTERT, a Sarcoma translocation breakpoint protein, EphA2, PAP, ML-IAP, AFP, ERG, NA17, PAX3, ALK, androgen receptor, cyclin B-1, polysialic acid, MYCN, RhoC, TRP-2, fucosyl-GM1, mesothelin (MSLN), PSCA, MAGE-A1, sLe(animal), CYP1B1, PLAV1, GM3, BORIS, Tn, GloboH, ETV6-AML, NY-BR-1, RGS5, SART3, STn, Carbonic anhydrase IX, PAX5, OY-TESL Sperm protein 17, LCK, HMWMAA, AKAP-4, SSX2, XAGE-1, Legumain, Tie-3, VEGFR2, MAD-CT-1, PDGFR-B, MAD-CT-2, ROR2, TRAIL1, MUC16, MAGE-A4, MAGE-C2, GAGE, EGFR, CMET, HER3, MUC15, CA6, NAPI2B, TROP2, CLDN6, CLDN16, CLDN18.2, CLorf186, RON, LY6E, FRA, DLL3, PTK7, STRA6, TMPRSS3, TMPRSS4, TMEM238, UPK1B, VTCN1, LIV1, ROR1, Fos-related antigen 1, and the markers listed below:

(1) BMPR1B (bone morphogenetic protein receptor-type IB, Genbank accession no. NM.sub.--001203);

(2) E16 (LAT1, SLC7A5, Genbank accession no. NM.sub.--003486);

(3) STEAP1 (six transmembrane epithelial antigen of prostate, Genbank accession no. NM.sub.--012449);

(4) 0772P (CA125, MUC16, Genbank accession no. AF361486);

(5) MPF (MPF, MSLN, SMR, megakaryocyte potentiating factor, mesothelin, Genbank accession no. NM.sub.--005823);

(6) Napi3b (NAPI-3B, NPTIIb, SLC34A2, solute carrier family 34 (sodium phosphate), member 2, type II sodium-dependent phosphate transporter 3b, Genbank accession no. NM.sub.--006424);

(7) Sema 5b (FLJ10372, KIAA1445, Mm. 42015, SEMA5B, SEMAG, Semaphorin 5b Hlog, sema domain, seven thrombospondin repeats (type 1 and type 1-like), transmembrane domain (TM) and short cytoplasmic domain, (semaphorin) 5B, Genbank accession no. AB040878);

(8) PSCA hlg (2700050C12Rik, C530008O16Rik, RIKEN cDNA 2700050C12, RIKEN cDNA 2700050C12 gene, Genbank accession no. AY358628);

(9) ETBR (Endothelin type B receptor, Genbank accession no. AY275463);

(10) MSG783 (RNF124, hypothetical protein FLJ20315, Genbank accession no. NM.sub.--

017763);

(11) STEAP2 (HGNC.sub.-8639, IPCA-1, PCANAP1, STAMP1, STEAP2, STMP, prostate cancer associated gene 1, prostate cancer associated protein 1, six transmembrane epithelial antigen of prostate 2, six transmembrane prostate protein, Genbank accession no. AF455138);

(12) TrpM4 (BR22450, FLJ20041, TRPM4, TRPM4B, transient receptor potential cation channel, subfamily M, member 4, Genbank accession no. NM.sub.-017636);

(13) CRIPTO (CR, CR1, CRGF, CRIPTO, TDGF1, teratocarcinoma-derived growth factor, Genbank accession no. NP.sub.--003203 or NM.sub.--003212);

(14) CD21 (CR2 (Complement receptor 2) or C3DR(C3d/Epstein-Barr virus receptor) or Hs. 73792, Genbank accession no. M26004);

(15) CD79b (IGb (immunoglobulin-associated beta), B29, Genbank accession no. NM.sub.-000626);

(16) FcRH2 (IFGP4, IRTA4, SPAP1A (SH2 domain containing phosphatase anchor protein 1a), SPAP1B, SPAP1C, Genbank accession no. NM.sub.-030764);

(17) HER2 (Genbank accession no. M11730);

(18) NCA (Genbank accession no. M18728);

(19) MDP (Genbank accession no. BC017023);

(20) IL20R.alpha. (Genbank accession no. AF184971);

(21) Brevican (Genbank accession no. AF229053);

(22) Ephb2R (Genbank accession no. NM.sub.-004442);

(23) ASLG659 (Genbank accession no. AX092328);

(24) PSCA (Genbank accession no. AJ297436);

(25) GEDA (Genbank accession no. AY260763);

(26) BAFF-R (Genbank accession no. NP.sub.-443177.1);

(27) CD22 (Genbank accession no. NP-001762.1);

(28) CD79a (CD79A, CD79.alpha., immunoglobulin-associated alpha, a B-cell-specific protein that covalently interacts with Ig beta (CD79B) and forms a complex on the surface with Ig M molecules, transduces a signal involved in B-cell differentiation, Genbank accession No. NP.sub.-001774.1);

(29) CXCR5 (Burkitt's lymphoma receptor-1, a G-protein-coupled receptor that is activated by the CXCL13 chemokine, functions in lymphocyte migration and humoral defense, plays a role in HIV-2 infection and perhaps development of AIDS, lymphoma, myeloma, and leukemia, Genbank accession No. NP.sub.-001707.1);

(30) HLA-DOB (Beta subunit of MHC class II molecule (Ia antigen) that binds peptides and

presents them to CD4+ T lymphocytes, Genbank accession No. NP.sub. 002111.1);
(31) P2X5 (Purinergic receptor P2X ligand-gated ion channel 5, an ion channel gated by extracellular ATP, may be involved in synaptic transmission and neurogenesis, deficiency may contribute to the pathophysiology of idiopathic detrusor instability, Genbank accession No. NP.sub. 002552.2);
(32) CD72 (B-cell differentiation antigen CD72, Lyb-2, Genbank accession No. NP.sub. 001773.1);
(33) LY64 (Lymphocyte antigen 64 (RP105), type I membrane protein of the leucine rich repeat (LRR) family, regulates B-cell activation and apoptosis, loss of function is associated with increased disease activity in patients with systemic lupus erythematosis, Genbank accession No. NP.sub. 005573.1);
(34) FCRH1 (Fc receptor-like protein 1, a putative receptor for the immunoglobulin Fc domain that contains C2 type Ig-like and ITAM domains, may have a role in B-lymphocyte differentiation, Genbank accession No. NP.sub. 443170.1); and
(35) IRTA2 (Immunoglobulin superfamily receptor translocation associated 2, a putative immunoreceptor with possible roles in B-cell development and lymphomagenesis; deregulation of the gene by translocation occurs in some B-cell malignancies, Genbank accession No. NP.sub.-112571.1).

100. The polypeptide of claim 96, wherein the targeting domain binds to an immune cell surface marker (including but not limited to CD8+ T cells, T-regulatory cells, dendritic cells, NK cells, or macrophages), wherein the immune cell surface marker may include but is not limited to CD3, CD4, CD8, CD19, CD20, CD21, CD25, CD37, CD30, CD33, CD40, CD68, CD123, CD254, PD-1, B7-H3, and CTLA-4, and/or wherein the targeting domain binds to PD-1, PDL-1, CTLA-4, TROP2, B7-H3, CD33, CD22, carbonic anhydrase IX, CD123, Nectin-4, tissue factor antigen, CD154, B7-H3, B7-H4, FAP (fibroblast activation protein) or MUC16.

101. The polypeptide of any one of claims 94-100, wherein the targeting domain may include but is not limited to an scFv, a F(ab), a $F(ab')_2$, a B-cell receptor (BCR), a DARPin, an affibody, a monobody, a nanobody, diabody, an antibody (including a monospecific or bispecific antibody); a cell-targeting oligopeptide including but not limited to RGD integrin-binding peptides, de novo designed binders, aptamers, a bicycle peptide, conotoxins, small molecules such as folic acid, and a virus that binds to the cell surface.

~~102. A recombinant nucleic acid encoding the polypeptide of any one of claims 1-101.~~

~~103. An expression vector comprising the recombinant nucleic acid of claim 102 operatively linked to a promoter.~~

~~104. A recombinant host cell comprising the nucleic acid of claim 102 and/or the expression vector of claim 103.~~

~~105. A pharmaceutical composition, comprising the polypeptide of any one of claims 1-101, the recombinant nucleic acid of claim 102, the expression vector of claim 103, or the recombinant host cell of claim 104, and a pharmaceutically acceptable carrier.~~

~~106. A method for treating cancer, comprising administering to a subject having cancer the polypeptide of any one of claims 1-101, the recombinant nucleic acid of claim 102, the expression vector of claim 103, the recombinant host cell of claim 104, or the pharmaceutical composition of claim 105 in an amount effective to treat the tumor.~~

~~107. The method of claim 106, where the cancer is selected from the group consisting of colon cancer, melanoma, renal cell cancer, head and neck squamous cell cancer, gastric cancer, urothelial carcinoma, Hodgkin lymphoma, non-small cell lung cancer, small cell lung cancer, hepatocellular carcinoma, pancreatic cancer, Merkel cell carcinoma, colorectal cancer, acute myeloid leukemia, acute lymphoblastic leukemia, chronic lymphocytic leukemia, non-Hodgkin lymphoma, multiple myeloma, ovarian cancer, cervical cancer, and any tumor types selected by a diagnostic test, such as microsatellite instability, tumor mutational burden, PD-L1 expression level, or the immunoscore assay (as developed by the Society for Immunotherapy of Cancer).~~

~~108. The polypeptide of any one of claims 1-101, the recombinant nucleic acid of claim 102, the expression vector of claim 103, the recombinant host cell of claim 104, or the pharmaceutical composition of claim 105 for use as a medicament for treating cancer and/or for modulating an immune response in a subject.~~

~~109. A method for modulating an immune response in a subject comprising administering to the subject the polypeptide of any one of claims 1-101, the recombinant nucleic acid of claim 102, the expression vector of claim 103, the recombinant host cell of claim 014, or the pharmaceutical composition of claim 105.~~

~~110. The method of claim 109 wherein the immune response is an anti-cancer immune response, a tissue reparative immune response or a wound healing immune response.~~

~~111. The method of claim 109 or 110, wherein the polypeptide, recombinant nucleic acid, expression vector, recombinant host cell, or pharmaceutical composition is administered as a component of a biomaterial.~~

~~112. The method of any one of claims 109-111 further comprising administering a second therapeutic agent to the subject.~~

~~113. The method of claim 112 wherein the polypeptide enhances the subject's immune response to the second therapeutic agent.~~

~~114. The method of any one of claims 112-113 wherein the second therapeutic agent comprises a chemotherapeutic agent or an antigen-specific immunotherapeutic agent including but not limited to a chimeric antigen receptor T cell.~~

~~115. A method, comprising:~~

~~determining a structure for a plurality of residues of a protein using a computing device, wherein the structure of the plurality of residues provides a particular receptor binding interface;~~

~~determining a plurality of designed residues using a mimetic design protocol provided by the computing device, wherein the plurality of designed residues provide the particular receptor binding interface, and wherein the plurality of designed residues differ from the plurality of residues;~~

~~determining one or more connecting helix structures that connect the plurality of designed residues using the computing device;~~

~~determining a first protein backbone for the protein by assembling the one or more connecting helix structures and the plurality of designed residues over a plurality of combinations using the computing device;~~

~~designing a second protein backbone for the protein for flexibility and low energy structures based on the first protein backbone using the computing device; and~~

~~generating an output related to at least the second protein backbone.~~

~~116. The method of claim 115, wherein determining the plurality of designed residues using the mimetic design protocol comprises determining an idealized residue using a database of idealized residues, wherein the idealized residue is related to a designed residue of the plurality of designed residues.~~

~~117. The method of claim 116, wherein determining the idealized residue using the database of idealized residues comprises:~~

~~retrieving one or more idealized fragments related to the idealized residue from the database of idealized residues; and~~

~~determining the idealized residue by reconstructing the related designed residue using the one or more idealized fragments.~~

~~118. The method of claim 117, wherein reconstructing the related designed residue using the one or more idealized fragments comprises:~~

~~reconnecting pairs of the one or more idealized fragments by: use of combinatorial fragment assembly of the pairs of the one or more idealized fragments; and~~

~~using Cartesian-constrained backbone minimization to determine whether the pairs of the one or more idealized fragments link two or more of the plurality of designed residues.~~

~~119. The method of claim 118, wherein reconstructing the related designed residue using the one or more idealized fragments comprises:~~

~~verifying that overlapping fragments of the idealized residue are idealized fragments using the database of idealized residues;~~

~~verifying whether the idealized residue does not clash with a target receptor associated with the particular receptor binding interface; and~~

after verifying that the idealized residue does not clash with a target receptor associated with the particular receptor binding interface, determining a most probable amino acid at each position of the idealized residue using the database of idealized residues.

120. The method of claim 118, wherein determining the first protein backbone for the protein by assembling the one or more connecting helix structures and the plurality of designed residues over the plurality of combinations comprises:

recombining the pairs of the one or more idealized fragments by combinatorially recombining the pairs of the one or more idealized fragments; and

determining the first protein backbone for the protein using the recombined pairs of the one or more idealized fragments.

121. The method of claim 120, wherein combinatorially recombining the pairs of the one or more idealized fragments comprises ranking the pairs of the one or more idealized fragments based on an interconnection length between idealized fragments of the pairs of the one or more idealized fragments.

122. The method of claim 115, wherein determining the plurality of designed residues using the mimetic design protocol comprises:

determining an idealized residue using one or more parametric equations that represent a shape of a designed residue of the plurality of designed residues; and

determining a single fragment that closes the idealized residue with at least one designed residue of the plurality of designed residues.

123. The method of claim 122, wherein the designed residue comprises a helical structure, and wherein the one or more parametric equations comprise an equation related to phi and psi angles of the helical structure.

124. The method of claim 123, wherein the equation related to phi and psi angles of the helical structure includes one or more terms related to an angular pitch of the phi and psi angles of the helical structure

~~125. The method of claim 115, wherein generating the output related to the second protein backbone for the protein comprises designing one or more molecules based on the second protein backbone for the protein.~~

~~126. The method of claim 115, wherein generating the output related to the second protein backbone for the protein comprises:~~

~~generating a synthetic gene for the protein that is based the second protein backbone for the protein;~~

~~expressing a particular protein *in vivo* using the synthetic gene; and~~

~~purifying the particular protein.~~

~~127. The method of claim 126, wherein expressing the particular protein sequence *in vivo* using the synthetic gene comprises expressing the particular protein sequence in one or more *Escherichia coli* that include the synthetic gene.~~

~~128. The method of claim 115, wherein generating the output related to the second protein backbone for the protein comprises generating one or more images that include at least part of the second protein backbone for the protein.~~

~~129. The method of claim 115, wherein the computing device comprises a protein synthesis device, and wherein generating the output related to at least the second protein backbone for the protein comprises synthesizing at least the second protein backbone for the protein using the protein synthesis device.~~

~~130. The method of any one of claims 115 to 129 wherein the method is for designing a protein mimetic.~~

~~131. A non-naturally occurring protein mimetic identified by the method of claim 130.~~

~~132. The non-naturally protein of claim 131 that is a cytokine mimetic.~~

~~133. The non-naturally protein of claim 122 that is an IL-2 mimetic or an IL-4 mimetic.~~

134. A computing device, comprising:

one or more processors; and

data storage, configured to store at least computer-readable instructions that, when executed, cause the computing device to perform functions comprising:

determining a structure for a plurality of residues of a protein that provides a particular receptor binding interface;

determining a plurality of designed residues using a mimetic design protocol, wherein the plurality of designed residues provide the particular receptor binding interface, and wherein the plurality of designed residues differ from the plurality of residues;

determining one or more connecting helix structures that connect the plurality of designed residues;

determining a first protein backbone for the protein by assembling the one or more connecting helix structures and the plurality of designed residues over a plurality of combinations;

designing a second protein backbone for the protein for flexibility and low energy structures based on the first protein backbone; and

generating an output related to at least the second protein backbone for the protein.

135. The computing device of claim 134, wherein determining the plurality of designed residues using the mimetic design protocol comprises determining an idealized residue using a database of idealized residues, wherein the idealized residue is related to a designed residue of the plurality of designed residues.

136. The computing device of claim 134, wherein determining the plurality of designed residues using the mimetic design protocol comprises:

determining an idealized residue using one or more parametric equations that represent a shape of a designed residue of the plurality of designed residues; and

determining a single fragment that closes the idealized residue with at least one designed residue of the plurality of designed residues.

137. The computing device of claim 135, wherein the computing device further comprises a protein synthesis device, and wherein generating the output related to at least the second

~~protein backbone for the protein comprises synthesizing at least the second protein backbone for the protein using the protein synthesis device.~~

~~138. A non-transitory computer-readable medium, configured to store at least computer-readable instructions that, when executed by one or more processors of a computing device, cause the computing device to perform functions comprising:~~

~~determining a structure for a plurality of residues of a protein that provides a particular receptor binding interface;~~

~~determining a plurality of designed residues using a mimetic design protocol, wherein the plurality of designed residues provide the particular receptor binding interface, and wherein the plurality of designed residues differ from the plurality of residues;~~

~~determining one or more connecting helix structures that connect the plurality of designed residues;~~

~~determining a first protein backbone for the protein by assembling the one or more connecting helix structures and the plurality of designed residues over a plurality of combinations;~~

~~designing a second protein backbone for the protein for flexibility and low energy structures based on the first protein backbone; and~~

~~generating an output related to at least the second protein backbone for the protein.~~

1. A non-naturally occurring polypeptide comprising domains X1, X2, X3, and X4, wherein:

X1 is a peptide comprising an amino acid sequence at least 60%, at least 65%, at least 70%, at least 75%, at least 80%, at least 85%, at least 90%, at least 95%, at least 98%, or 100% identical to the peptide PKKKIQLHAEHALYDALMILNI (SEQ ID NO: 4);

X2 is a helical-peptide of at least 8 amino acids in length;

X3 is a peptide comprising an amino acid sequence at least 60%, at least 65%, at least 70%, at least 75%, at least 80%, at least 85%, at least 90%, at least 95%, at least 98%, or 100% identical to the peptide LEDYAFNFELILEEIARLFESG (SEQ ID NO:5); and

X4 is a peptide comprising an amino acid sequence at least 60%, at least 65%, at least 70%, at least 75%, at least 80%, at least 85%, at least 90%, at least 95%, at least 98%, or 100% identical to the peptide EDEQEEMANAIITILQSWIFS (SEQ ID NO:6),

wherein X1, X2, X3, and X4 may be in any order in the polypeptide;

wherein amino acid linkers may be present between any of the domains; and

wherein the polypeptide binds to IL-2 receptor $\beta\gamma_c$ heterodimer (IL-2R$\beta\gamma_c$) or IL-4 receptor $\alpha\gamma_c$heterodimer (IL-4R$\alpha\gamma_c$).

2. The polypeptide of claim 1, provided that:

(a) X1 comprises an amino acid sequence at least 25%, at least 27%, at least 30%, at least 35%, at least 40%, at least 45%, at least 50%, at least 55%, at least 60%, at least 65%, at least 70%, at least 75%, at least 80%, at least 85%, at least 90%, at least 95%, at least 98%, or 100% identical to EHALYDAL (SEQ ID NO:1);

(b) X3 comprises an amino acid sequence at least 25%, at least 27%, at least 30%, at least 35%, at least 40%, at least 45%, at least 50%, at least 55%, at least 60%, at least 65%, at least 70%, at least 75%, at least 80%, at least 85%, at least 90%, at least 95%, at least 98%, or 100% identical to YAFNFELI (SEQ ID NO:2); and

(c) X4 comprises an amino acid sequence at least 25%, at least 27%, at least 30%, at least 35%, at least 40%, at least 45%, at least 50%, at least 55%, at least 60%, at least 65%, at least 70%, at least 75%, at least 80%, at least 85%, at least 90%, at least 95%, at least 98%, or 100% identical to ITILQSWIF (SEQ ID NO:3).

3. A non-naturally occurring polypeptide comprising domains X1, X2, X3, and X4, wherein:

(a) X1 is a peptide comprising an amino acid sequence at least 60%, at least 65%, at least 70%, at least 75%, at least 80%, at least 85%, at least 90%, at least 95%, at least 98%, or 100% identical to EHALYDAL (SEQ ID NO:1);

(b) X2 is a helical-peptide of at least 8 amino acids in length;

(c) X3 is a peptide comprising an amino acid sequence at least 60%, at least 65%, at least 70%, at least 75%, at least 80%, at least 85%, at least 90%, at least 95%, at least 98%, or 100% identical to YAFNFELI (SEQ ID NO:2);

(d) X4 is a peptide comprising an amino acid sequence at least 60%, at least 65%, at least 70%, at least 75%, at least 80%, at least 85%, at least 90%, at least 95%, at least 98%, or 100% identical to ITILQSWIF (SEQ ID NO:3);

wherein X1, X2, X3, and X4 may be in any order in the polypeptide;

wherein amino acid linkers may be present between any of the domains; and

wherein the polypeptide binds to IL-2 receptor $\beta\gamma_c$ heterodimer (IL-2R$\beta\gamma_c$).

4. The polypeptide of claim 2 or 3, wherein:

(i) X1 includes both of the following: H at residue 2 and Y at residue 5 relative to SEQ ID NO:1; and/or

(ii) X3 includes all 5 of the following: Y at residue 1, F at residue 3, N at residue 4, L at residue 7, and I at residue 8 relative to SEQ ID NO:2; wherein the polypeptide binds to IL-2 receptor $\beta\gamma_c$ heterodimer (IL-2R$\beta\gamma_c$).

5. The polypeptide of any one of claims 1-3 wherein,

X1 comprises the amino acid sequence EHALYDAL (SEQ ID NO:1);

X3 is comprises the amino acid sequence YAFNFELI (SEQ ID NO:2); and

X4 comprises the amino acid sequence ITILQSWIF (SEQ ID NO:3); wherein the polypeptide binds to IL-2 receptor $\beta\gamma_c$ heterodimer (IL-2R$\beta\gamma_c$).

6. The polypeptide of any one of claims 1 - 5, wherein:

X1 comprises an amino acid sequence at least 80%, at least 85%, at least 90%, at least 95%, at least 98%, or 100% identical to the peptide PKKKIQLHAEHALYDALMILNI (SEQ ID NO: 4);

X3 comprises an amino acid sequence at least 80%, at least 85%, at least 90%, at least 95%, at least 98%, or 100% identical to the peptide LEDYAFNFELILEEIARLFESG (SEQ ID NO:5); and

X4 comprises an amino acid at least 80%, at least 85%, at least 90%, at least 95%, at least 98%, or 100% identical to the peptide EDEQEEMANAIITILQSWIFS (SEQ ID NO:6); wherein the polypeptide binds to IL-2 receptor $\beta\gamma_c$ heterodimer (IL-2R$\beta\gamma_c$).

7. The polypeptide of any one of claims 1-2 or 6, wherein:

(i) X1 includes all 5 of the following: L at residue 7, H at residue 8, H at residue 11, Y at residue 14; M at residue 18 relative to SEQ ID NO:4; and/or

(ii) X3 includes all 8 of the following: D at residue 3, Y at residue 4, F at residue 6, N at residue 7, L at residue 10, I at residue 11, E at residue 13, or E at residue 14 relative to SEQ ID NO:5; wherein the polypeptide binds to IL-2 receptor $\beta\gamma_c$ heterodimer (IL-2R$\beta\gamma_c$).

8. The polypeptide of any one of claims 1 or 2, wherein:

X1 comprises an amino acid sequence at least 80%, at least 85%, at least 90%, at least

95%, at least 98%, or 100% identical to the peptide PKKKIQIMAEEALKDALSILNI (SEQ ID NO: 8);

X3 comprises an amino acid sequence at least 80%, at least 85%, at least 90%, at least 95%, at least 98%, or 100% identical to the peptide LERFAKRFERNLWGIARLFESG (SEQ ID NO: 9); and

X4 comprises an amino acid sequence at least 80%, at least 85%, at least 90%, at least 95%, at least 98%, or 100% identical to the peptide EDEQEEMANAIITILQSWFFS (SEQ ID NO: 10).

wherein

(i) X1 includes I at residue 7, T or M at residue 8, E at residue 11, K at residue 14 and S at residue 18 relative to SEQ ID NO:8; and

(ii) X3 includes R at residue 3, F at residue 4, K at residue 6, R at residue 7, R at residue 10, N at residue 11, W at residue 13, and G at residue 14 relative to SEQ ID NO:9, wherein the polypeptide binds to IL-4 receptor $\alpha\gamma_c$heterodimer (IL-4R$\alpha\gamma_c$).

9. The polypeptide of any one of claims 1-2 or 6-7, wherein amino acid substitutions relative to the reference peptide domains do not occur at positions 10, 13, 14, 15, and 17 relative to SEQ ID NO:4; positions 1, 4, 7, 10, 11, and 15 relative to SEQ ID NO:5; and positions 12, 16, and 18 relative to SEQ ID NO:6.

10. The polypeptide of any one of claims 1-9, wherein amino acid substitutions relative to the reference peptide domains are conservative amino acid substitutions.

11. The polypeptide of any one of claims 1-10, wherein the domains are arranged N-terminal to C-terminal in an arrangement selected from X1-X3-X2-X4.

12. The polypeptide of any one of claims 1-11, wherein X2 is a peptide comprising an amino acid sequence at least 25%, at least 27%, at least 30%, at least 35%, at least 40%, at least 45%, at least 50%, at least 55%, at least 60%, at least 65%, at least 70%, at least 75%, at least 80%, at least 85%, at least 90%, at least 95%, at least 98%, or 100% identical to KDEAEKAKRMKEWMKRIKT (SEQ ID NO:7).

13. The polypeptide of claim 12, wherein X2 comprises an amino acid sequence at least

80%, at least 85%, at least 90%, at least 95%, at least 98%, or 100% identical to KDEAEKAKRMKEWMKRIKT (SEQ ID NO:7).

14. The polypeptide of claim 1 or 2, wherein

X1 comprises an amino acid sequence at least 60%, at least 65%, at least 70%, at least 75%, at least 80%, at least 85%, at least 90%, at least 95%, at least 98%, or 100% identical to the peptide PKKKIQLHAEHALYDALMILNI (SEQ ID NO: 4) wherein amino acid residues relative to SEQ ID NO:4 are selected from:

Position 01:	A	F	I	L	M	P	Q	R	S	W
Position 02:	A	D	E	G	V	K				
Position 03:	D	E	F	W	K					
Position 04:	D	E	K	N	P	R	W			
Position 05:	D	E	H	I	K	L	M	S		
Position 06:	A	D	E	G	L	P	S	W	Q	
Position 07:	D	E	L	Q	Y	I				
Position 08:	A	F	H	W	Y	M	T			
Position 09:	C	F	P	A						
Position 10:	C	D	E	F	K	P				
Position 11:	D	F	H	E						
Position 12:	A	D	E	P	S	T	V			
Position 13:	H	I	L	M	P	R	V	W		
Position 14:	F	R	W	Y	K					
Position 15:	D	E	N	Y						
Position 16:	A	C	L	M	S					
Position 17:	F	I	L	M	P	R				
Position 18:	G	M	Q	Y	S					
Position 19:	I	L	M	P	Q	V				
Position 20:	A	K	L	M	Q	R	S			
Position 21:	G	K	N	P	R	S	W			
Position 22:	D	E	I	K	M	N	W	Y;		

X3 comprises an amino acid sequence at least 60%, at least 65%, at least 70%, at least 75%, at least 80%, at least 85%, at least 90%, at least 95%, at least 98%, or 100% identical to the peptide LEDYAFNFELILEEIARLFESG (SEQ ID NO:5) wherein amino acid residues relative to SEQ ID NO:5 are selected from:

Position 01: A L

Position 02: D E G K M T

Position 03: D E N Y R

Position 04: C D G T Y F

Position 05: A F H S V W Y

Position 06: A F I M T V Y K

Position 07: D K N S T R

Position 08: A C G L M S V F

Position 09: C H K L R S T V E

Position 10: F I L M Y R

Position 11: I L N T Y

Position 12: F K L M S V

Position 13: A D F G I N P Q S T E W

Position 14: A E F G H S V

Position 15: C I L M V W

Position 16: A D G S T V

Position 17: H K L N R

Position 18: C D G I L Q R T W

Position 19: D F M N W

Position 20: A C E F G M S Y

Position 21: D E G H L M R S T V W

Position 22: A D G K N S Y;

wherein X4 comprises an amino acid sequence at least 60%, at least 65%, at least 70%, at least 75%, at least 80%, at least 85%, at least 90%, at least 95%, at least 98%, or 100% identical to the peptide EDEQEEMANAIITILQSWIFS (SEQ ID NO:6) wherein amino acid residues relative to SEQ ID NO:6 are selected from:

Position 01: D E G K V

Position 02: D I M S

Position 03: E G H K

Position 04: E G I K Q R S

Position 05: A D E G H S V

Position 06: C D E G I M Q R T V

Position 07: C E L M P R T

Position 08: A F L M W

Position 09: A G L N Q R T

Position 10: A C D E F H I W

Position 11: I M N S V W

Position 12: I K L S V

Position 13: C L M R S T

Position 14: I L P T Y

Position 15: F G I L M N V

Position 16: H K Q R

Position 17: C F K S W Y

Position 18: K Q T W

Position 19: C G N I

Position 20: C F G L Y

Position 21: A F G H S Y; and

wherein X2 comprises an amino acid sequence at least 60%, at least 65%, at least 70%, at least 75%, at least 80%, at least 85%, at least 90%, at least 95%, at least 98%, or 100% identical to KDEAEKAKRMKEWMKRIKT (SEQ ID NO:7) wherein amino acid residues relative to SEQ ID NO:7 are selected from:

Position 01: A H L M R S V K

Position 02: A D E Q R S T V W Y

Position 03: C E G K L N Q R W

Position 04: A F G N S T V Y

Position 05: A E G I M R V C

Position 06: C E K L N R V

Position 07: A C E I L S T V W

Position 08: H K L M S T W Y

Position 09: A I L M Q S R

Position 10: A I M S W Y

Position 11: C I K L S V

Position 12: C E K L P Q R T

Position 13: A D H N W

Position 14: A C G I L S T V M

Position 15: A E G I K L M R V

Position 16: G H L R S T V C

Position 17: A I L V

Position 18: A C D E G H I K M S

Position 19: D E G L N V T

15. The polypeptide of any one of claims 1-14, wherein the polypeptide comprises an amino acid sequence at least 70%, at least 75%, at least 80%, at least 85%, at least 90%, at least 95%, at least 98%, or 100% identical to the amino acid sequence set forth in SEQ ID NOS: 76, 168, 90, 181, 91, 182, 94 or 246 wherein the polypeptide binds to IL-2 receptor $\beta\gamma_c$ heterodimer (IL-2R$\beta\gamma_c$) or SEQ ID NOS: 92, 93, 183, or 184 wherein the polypeptide binds to IL-4 receptor $\alpha\gamma_c$heterodimer (IL-4R$\alpha\gamma_c$).

16. A non-naturally occurring polypeptide comprising an amino acid sequence at least 90%, at least 95%, at least 98% or 100% identical to the amino acid sequence set forth in SEQ ID NO: 90 wherein the polypeptide binds to IL-2 receptor $\beta\gamma_c$ heterodimer (IL-2R$\beta\gamma_c$).

17. A non-naturally occurring polypeptide comprising an amino acid sequence at least 90%, at least 95%, at least 98% or 100% identical to the amino acid sequence set forth in SEQ ID NO: 181 wherein the polypeptide binds to IL-2 receptor $\beta\gamma_c$ heterodimer (IL-2R$\beta\gamma_c$).

18. The polypeptide of any one of claims 1-5, wherein the polypeptide comprises an amino acid sequence at least 60%, at least 65%, at least 70%, at least 75%, at least 80%, at least 85%, at least 90%, at least 95%, or at least 98%, identical to the amino acid sequence set forth in SEQ ID NO:181, and wherein one of the following mutations are present

D56C;

K58C;

D59C;

R66C;

T77C;

E85C;

R50C;

E53C;

E62C;

E69C;

R73C; or

E82C.

19. The polypeptide of any one of claims 1-18, wherein the polypeptide is linked to a stabilization compound, including but not limited to a polyethylene glycol ("PEG") containing moiety.

20. The polypeptide of claim 19, wherein the polypeptide comprises a cysteine residue and one or more polyethylene glycol chains is linked to the cysteine residue via a maleimide group.

21. The polypeptide of any one of claims 1-7, or 9-19 wherein the polypeptide binds to the human IL-2 receptor $\beta\gamma_c$ heterodimer (IL-2R$\beta\gamma_c$) and wherein the polypeptide's affinity for the human IL-2 receptor $\beta\gamma_c$ heterodimer is greater than that of native IL-2.

22. The polypeptide of claim 21, wherein the polypeptide stimulates STAT5 phosphorylation in cells expressing the human IL-2 receptor $\beta\gamma_c$ heterodimer (IL-2R$\beta\gamma_c$) with potency greater than native IL-2.

23. The polypeptide of claim 1, comprising the amino acid sequence set forth in SEQ ID NO:190, 191, 195, 197, 198, or SEQ ID NO:200.

24. The polypeptide of any one of claims 1-22, wherein the polypeptide includes at least one disulfide bond.

25. The polypeptide of claim 1 comprising the amino acid sequence set forth in SEQ ID NO:195 wherein a polyethylene glycol containing moiety is linked to the cysteine reside at position 62 of SEQ ID NO:195.

26. The polypeptide of any one of claims 1-25, wherein the polypeptide further comprises a targeting domain.

27. The polypeptide of claim 26, wherein the targeting domain is a translational fusion with the polypeptide.

28. The polypeptide of claim 26 or claim 27, wherein the targeting domain binds to a cell surface protein present on the surface of a tumor cell, a tumor vascular component cell, or a tumor microenvironment cell .

29. The polypeptide of claim 26 or claim 27, wherein the targeting domain binds to a tumor cell, tumor vascular component cell, or tumor microenvironment cell surface marker wherein the cell surface marker is EGFR, EGFRvIII, Her2, HER3, EpCAM, MSLN, MUC16, PSMA, TROP2, ROR1, RON, PD-L1, CD47, CTLA-4,CD5, CD19, CD20, CD25, CD37, CD30, CD33, CD40, CD45, CAMPATH-1, BCMA, CS-1, PD-L1, B7-H3, B7-DC, HLD-DR, carcinoembryonic antigen (CEA), TAG-72, EpCAM, MUC1, folate-binding protein, A33, G250, prostate-specific membrane antigen (PSMA), ferritin, GD2, GD3, GM2, Le^y, CA-125, CA19-9, epidermal growth factor, p185HER2, IL-2 receptor, EGFRvIII (de2-7 EGFR), fibroblast activation protein, tenascin, a metalloproteinase, endosialin, vascular endothelial growth factor, avB3, WT1, LMP2, HPV E6, HPV E7, Her-2/neu, MAGE A3, p53 nonmutant, NY-ESO-1, MelanA/MART1, Ras mutant, gp100, p53 mutant, PR1, bcr-abl, tyronsinase, survivin, PSA, hTERT, a Sarcoma translocation breakpoint protein, EphA2, PAP, ML-IAP, AFP, ERG, NA17, PAX3, ALK, androgen receptor, cyclin B 1, polysialic acid, MYCN, RhoC, TRP-2, fucosyl GM1, mesothelin (MSLN), PSCA, MAGE Al, sLe(animal), CYP1B1, PLAV1, GM3, BORIS, Tn, GloboH, ETV6-AML, NY-BR-1, RGS5, SART3, STn, Carbonic anhydrase IX, PAX5, OY-TESL Sperm protein 17, LCK, HMWMAA, AKAP-4, SSX2, XAGE 1, Legumain, Tie 3, VEGFR2, MAD-CT-1, PDGFR-B, MAD-CT-2, ROR2, TRAIL1, MUC16, MAGE A4, MAGE C2, GAGE, EGFR, CMET, HER3, MUC15, CA6, NAPI2B, TROP2, CLDN6, CLDN16, CLDN18.2, CLorf186, RON, LY6E, FRA, DLL3, PTK7, STRA6, TMPRSS3, TMPRSS4, TMEM238, UPK1B, VTCN1, LIV1, ROR1, Fos-related antigen 1, or one of the markers listed below:

(1) BMPR1B (bone morphogenetic protein receptor-type IB, Genbank accession no. NM.sub.--001203);

(2) E16 (LAT1, SLC7A5, Genbank accession no. NM.sub.--003486);

(3) STEAP1 (six transmembrane epithelial antigen of prostate, Genbank accession no. NM.sub.--012449);

(4) 0772P (CA125, MUC16, Genbank accession no. AF361486);

(5) MPF (MPF, MSLN, SMR, megakaryocyte potentiating factor, mesothelin, Genbank accession no. NM.sub.--005823);

(6) Napi3b (NAPI-3B, NPTIIb, SLC34A2, solute carrier family 34 (sodium phosphate), member 2, type II sodium-dependent phosphate transporter 3b, Genbank accession no. NM.sub.--006424);

(7) Sema 5b (FLJ10372, KIAA1445, Mm. 42015, SEMA5B, SEMAG, Semaphorin 5b Hlog, sema domain, seven thrombospondin repeats (type 1 and type 1-like), transmembrane domain (TM) and short cytoplasmic domain, (semaphorin) 5B, Genbank accession no. AB040878);

(8) PSCA hlg (2700050C12Rik, C530008O16Rik, RIKEN cDNA 2700050C12, RIKEN cDNA 2700050C12 gene, Genbank accession no. AY358628);

(9) ETBR (Endothelin type B receptor, Genbank accession no. AY275463);

(10) MSG783 (RNF124, hypothetical protein FLJ20315, Genbank accession no. NM.sub.--017763);

(11) STEAP2 (HGNC.sub.--8639, IPCA-1, PCANAP1, STAMP1, STEAP2, STMP, prostate cancer associated gene 1, prostate cancer associated protein 1, six transmembrane epithelial antigen of prostate 2, six transmembrane prostate protein, Genbank accession no. AF455138);

(12) TrpM4 (BR22450, FLJ20041, TRPM4, TRPM4B, transient receptor potential cation channel, subfamily M, member 4, Genbank accession no. NM.sub.--017636);

(13) CRIPTO (CR, CR1, CRGF, CRIPTO, TDGF1, teratocarcinoma-derived growth factor, Genbank accession no. NP.sub.--003203 or NM.sub.--003212);

(14) CD21 (CR2 (Complement receptor 2) or C3DR(C3d/Epstein Barr virus receptor) or Hs. 73792, Genbank accession no. M26004);

(15) CD79b (IGb (immunoglobulin-associated beta), B29, Genbank accession no. NM.sub.--000626);

(16) FcRH2 (IFGP4, IRTA4, SPAP1A (SH2 domain containing phosphatase anchor protein 1a), SPAP1B, SPAP1C, Genbank accession no. NM.sub.--030764);

(17) HER2 (Genbank accession no. M11730);

(18) NCA (Genbank accession no. M18728);

(19) MDP (Genbank accession no. BC017023);

(20) IL20R.alpha. (Genbank accession no. AF184971);

(21) Brevican (Genbank accession no. AF229053);

(22) Ephb2R (Genbank accession no. NM.sub.--004442);

(23) ASLG659 (Genbank accession no. AX092328);

(24) PSCA (Genbank accession no. AJ297436);

(25) GEDA (Genbank accession no. AY260763);

(26) BAFF-R (Genbank accession no. NP.sub.--443177.1);

(27) CD22 (Genbank accession no. NP-001762.1);

(28) CD79a (CD79A, CD79.alpha., immunoglobulin-associated alpha, a B cell-specific protein that covalently interacts with Ig beta (CD79B) and forms a complex on the surface with Ig M molecules, transduces a signal involved in B-cell differentiation, Genbank accession No. NP.sub.--001774.1);

(29) CXCR5 (Burkitt's lymphoma receptor 1, a G protein-coupled receptor that is activated by the CXCL13 chemokine, functions in lymphocyte migration and humoral defense, plays a role in HIV-2 infection and perhaps development of AIDS, lymphoma, myeloma, and leukemia, Genbank accession No. NP.sub.--001707.1);

(30) HLA-DOB (Beta subunit of MHC class II molecule (Ia antigen) that binds peptides and presents them to CD4+ T lymphocytes, Genbank accession No. NP.sub.--002111.1);

(31) P2X5 (Purinergic receptor P2X ligand-gated ion channel 5, an ion channel gated by extracellular ATP, may be involved in synaptic transmission and neurogenesis, deficiency may contribute to the pathophysiology of idiopathic detrusor instability, Genbank accession No. NP.sub.--002552.2);

(32) CD72 (B-cell differentiation antigen CD72, Lyb-2, Genbank accession No. NP.sub.--001773.1);

(33) LY64 (Lymphocyte antigen 64 (RP105), type I membrane protein of the leucine rich repeat (LRR) family, regulates B-cell activation and apoptosis, loss of function is associated with increased disease activity in patients with systemic lupus erythematosis, Genbank accession No. NP.sub.--005573.1);

(34) FCRH1 (Fc receptor-like protein 1, a putative receptor for the immunoglobulin Fc domain that contains C2 type Ig-like and ITAM domains, may have a role in B-lymphocyte differentiation, Genbank accession No. NP.sub.--443170.1); or

(35) IRTA2 (Immunoglobulin superfamily receptor translocation associated 2, a putative immunoreceptor with possible roles in B cell development and lymphomagenesis; deregulation of the gene by translocation occurs in some B cell malignancies, Genbank accession No. NP.sub.--112571.1).

30. The polypeptide of claim 26 or 27, wherein the targeting domain binds to an immune cell surface marker.

31. A recombinant nucleic acid encoding the polypeptide of any one of claims 1-30.

32. A recombinant host cell comprising the nucleic acid of claim 31.

33. A pharmaceutical composition comprising a polypeptide of any one of claims 1-7 or 9-30 that binds to IL-2 receptor $\beta\gamma_c$ heterodimer (IL-2R$\beta\gamma_c$) or a recombinant nucleic acid of claim 31 that encodes a polypeptide that binds to IL-2 receptor $\beta\gamma_c$ heterodimer (IL-2R$\beta\gamma_c$), and a pharmaceutically acceptable carrier.

34. Use of a polypeptide of any one of claims 1-7 or 9-30 that binds to IL-2 receptor $\beta\gamma_c$ heterodimer (IL-2R$\beta\gamma_c$), a recombinant nucleic acid of claim 31 that encodes a polypeptide that binds to IL-2 receptor $\beta\gamma_c$ heterodimer (IL-2R$\beta\gamma_c$), or the pharmaceutical composition of claim 33 in the manufacture of a medicament for treating cancer that expresses IL-2 receptor $\beta\gamma$c heterodimer (IL-2R$\beta\gamma$c) in a subject having said cancer.