

WHAT IS CLAIMED IS:

1. An IL2 agonist comprising:
 - (a) an Fc domain; an
 - (b) an IL2 moiety C-terminal to the Fc domain, wherein the IL2 moiety comprises an IL2 domain and an IL2-R α domain.
2. The IL2 agonist of claim 1, wherein the IL2 domain is N-terminal to the IL2-R α domain.
3. The IL2 agonist of claim 1, wherein the IL2 domain is C-terminal to the IL2-R α domain.
4. The IL2 agonist of any one of claims 1 to 3, wherein the IL2 moiety comprises an IL2 domain comprising an amino acid sequence having:
 - (a) at least about 90% or at least about 95% sequence identity to mature human IL2,
 - (b) an N-terminal alanine deletion as compared to mature human IL2;
 - (c) an IL2 variant which has an amino acid substitution at position N88 as compared to wild type IL2, optionally wherein the amino acid substitution is N88D;
 - (d) the amino acid substitution C125S, C125A or C125V as compared to wild type IL2; or
 - (e) any combination of (a), (b), (c) and/or (d).
5. The IL2 agonist of any one of claims 1 to 4, wherein the IL2-R α domain comprises or consists of an amino acid sequence having at least about 90%, at least about 95%, at least about 96%, at least about 97%, at least about 98%, at least about 99% or 100% sequence identity to an IL2 binding portion of human IL-2R α , optionally wherein said binding portion has:
 - (a) at least 160 amino acids, at least 161 amino acids, at least 162 amino acids, at least 164 amino acids or at least 165 amino acids of human IL2-R α ; and/or
 - (b) up to 251, up to 240, up to 230, up to 220, up to 210, up to 200, up to 190, up to 180 or up to 170 amino acids of the extracellular domain of human IL2-R α .
6. The IL2 agonist of any one of claims 1 to 5, wherein the IL2 domain and the IL2-R α domain are connected via a linker ("the IL2 moiety linker").

7. The IL2 agonist of claim 6, wherein the IL2 moiety linker is at least 10 or at least 15 amino acids in length.
8. The IL2 agonist of claim 6 or claim 7, wherein the IL2 moiety linker is or comprises a glycine-serine linker.
9. The IL2 agonist of any one of claims 6 to 8, wherein the IL2 moiety linker comprises the amino acid sequence G₄S (SEQ ID NO:57).
10. The IL2 agonist of claim 9, wherein the IL2 moiety linker is or comprises a multimer of the amino acid sequence G₄S (SEQ ID NO:57).
11. The IL2 agonist of claim 10, wherein the multimer comprises 2, 3, 4, 5, 6 or more repeats of the amino acid sequence G₄S (SEQ ID NO:57).
12. The IL2 agonist of any one of claims 1 to 11, wherein the Fc domain and the IL2 moiety are connected via a linker (the "Fc-IL2 linker").
13. The IL2 agonist of claim 12, wherein the Fc-IL2 linker is at least 5 or at least 10 amino acids in length.
14. The IL2 agonist of claim 12 or claim 13, wherein the Fc-IL2 linker is or comprises a glycine-serine linker.
15. The IL2 agonist of any one of claims 12 to 14, wherein the Fc-IL2 linker comprises the amino acid sequence G₄S (SEQ ID NO:57).
16. The IL2 agonist of claim 9, wherein the Fc-IL2 linker is or comprises a multimer of the amino acid sequence G₄S (SEQ ID NO:57).
17. The IL2 agonist of claim 10, wherein the multimer comprises 2, 3, 4, 5, 6 or more repeats of the amino acid sequence G₄S (SEQ ID NO:57).
18. The IL2 agonist of any one of claims 1 to 17, wherein the Fc domain is an IgG1, IgG2, IgG3 or IgG4 Fc domain.
19. The IL2 agonist of claim 18, wherein the Fc domain has reduced effector function.

20. The IL2 agonist of any one of claims 1 to 19 which is a dimer.
21. The IL2 agonist of claim 20, which is a homodimer.
22. The IL2 agonist of claim 20, which is a heterodimer.
23. The IL2 agonist of any one of claims 1 to 22, which is bivalent for the IL2 moiety.
24. The IL2 agonist of any one of claims 1 to 23, which comprises a targeting moiety.
25. The IL2 agonist of claim 24, wherein the targeting moiety is N-terminal to the Fc domain.
26. The IL2 agonist of claim 24 or claim 25, wherein the targeting moiety:
- (a) binds to a tumor associated antigen;
 - (b) binds to a tumor microenvironment antigen;
 - (c) binds to a cell surface molecule of tumor reactive lymphocytes;
 - (d) binds to a checkpoint inhibitor;
 - (e) binds to a peptide-MHC complex;
 - (f) is a peptide-MHC complex; or
 - (g) binds to an antigen associated with or targeted by an autoimmune response.
27. The IL2 agonist of claim 26, wherein the targeting moiety binds to a tumor associated antigen.
28. The IL2 agonist of claim 27, wherein the tumor associated antigen is Fibroblast Activation Protein (FAP), the A1 domain of Tenascin-C (TNC A1), the A2 domain of Tenascin-C (TNC A2), the Extra Domain B of Fibronectin (EDB), the Melanoma-associated Chondroitin Sulfate Proteoglycan (MCSP), MART-1/Melan-A, gp100, Dipeptidyl peptidase IV (DPPIV), adenosine deaminase-binding protein (ADA bp), cyclophilin b, colorectal associated antigen (CRC)-C017-1A/GA733, Carcinoembryonic Antigen (CEA) and its immunogenic epitopes CAP-1 and CAP-2, etv6, aml1, Prostate Specific Antigen (PSA) or an immunogenic epitopes thereof PSA-1, PSA-2, and PSA-3, prostate-specific membrane antigen (PSMA), T-cell receptor/CD3-zeta chain, MAGE-family of tumor antigens (e.g., MAGE-A1, MAGE-A2, MAGE-A3, MAGE-A4, MAGE-A5, MAGE-A6, MAGE-A7, MAGE-A8, MAGE-A9, MAGE-A10, MAGE-A11, MAGE-A12, MAGE-Xp2 (MAGE-B2), MAGE-Xp3 (MAGE-B3), MAGE-Xp4 (MAGE-B4),

MAGE-C1, MAGE-C2, MAGE-C3, MAGE-C4, MAGE-C5), GAGE-family of tumor antigens (*e.g.*, GAGE-1, GAGE-2, GAGE-3, GAGE-4, GAGE-5, GAGE-6, GAGE-7, GAGE-8, GAGE-9), BAGE, RAGE, LAGE-1, NAG, GnT-V, MUM-1, CDK4, tyrosinase, p53, MUC family, HER2/neu, p21ras, RCAS1, α -fetoprotein, E-cadherin, α -catenin, β -catenin and γ -catenin, p120ctn, gp100 Pmel117, PRAME, NY-ESO-1, cdc27, adenomatous polyposis coli protein (APC), fodrin, Connexin 37, Ig-idiotypic, p15, gp75, GM2 and GD2 gangliosides, viral products such as human papilloma virus proteins, Smad family of tumor antigens, Imp-1, P1A, EBV-encoded nuclear antigen (EBNA)-1, brain glycogen phosphorylase, SSX-1, SSX-2 (HOM-MEL-40), SSX-1, SSX-4, SSX-5, SCP-1 and CT-7, c-erbB-2, Her2, EGFR, IGF-1R, CD2 (T-cell surface antigen), CD3 (heteromultimer associated with the TCR), CD22 (B-cell receptor), CD23 (low binding affinity IgE receptor), CD30 (cytokine receptor), CD33 (myeloid cell surface antigen), CD40 (tumor necrosis factor receptor), IL-6R-(IL6 receptor), CD20, MCSP, PDGF β R (β -platelet-derived growth factor receptor), ErbB2 epithelial cell adhesion molecule (EpCAM), EGFR variant III (EGFRvIII), CD19, disialoganglioside GD2, ductal-epithelial mucine, gp36, TAG-72, glioma-associated antigen, β -human chorionic gonadotropin, alphafetoprotein (AFP), lectin-reactive AFP, thyroglobulin, MN-CA IX, human telomerase reverse transcriptase, RU1, RU2 (AS), intestinal carboxyl esterase, mut hsp70-2, M-CSF, prostase, prostase specific antigen (PSA), PAP, LAGA-1a, p53, prostein, PSMA, surviving and telomerase, prostate-carcinoma tumor antigen-1 (PCTA-1), ELF2M, neutrophil elastase, ephrin B2, insulin growth factor (IGF1)-I, IGF-II, IGF1 receptor, 5T4, ROR1, Nkp30, NKG2D, tumor stromal antigens, the extra domain A (EDA) or extra domain B (EDB) of fibronectin, or the A1 domain of tenascin-C(TnC A1).

29. The IL2 agonist of claim 26 or claim 27, wherein the tumor associated antigen is a viral antigen.

30. The IL2 agonist of claim 29, wherein the viral antigen is Epstein-Barr virus LMP-1, hepatitis C virus E2 glycoprotein, HIV gp160, or HIV gp120, HPV E6, HPV E7, CMV early membrane antigen (EMA) or CMV late membrane antigen (LMA).

31. The IL2 agonist of claim 26, wherein the targeting moiety binds to a tumor microenvironment antigen.

32. The IL2 agonist of claim 31, wherein the tumor microenvironment antigen is an extracellular matrix protein.

33. The IL2 agonist of claim 32, wherein the extracellular matrix protein is syndecan, heparanase, integrins, osteopontin, link, cadherins, laminin, laminin type EGF, lectin, fibronectin, notch, tenascin, collagen and matrixin.

34. The IL2 agonist of claim 26, wherein the targeting moiety binds to a cell surface molecule of tumor lymphocytes.

35. The IL2 agonist of claim 34, wherein the cell surface molecule is CD27, CD28, 4-1BB (CD137), OX40, CD30, CD40, PD1, ICOS, lymphocyte function-associated antigen-1 (LFA-1), CD2, CD7, LIGHT, NKG2C, LAG3, TIM3, or B7-H3.

36. The IL2 agonist of claim 35, wherein the cell surface molecule is PD1.

37. The IL2 agonist of claim 36, wherein targeting moiety is an anti-PD1 antibody or antigen binding fragment thereof.

38. The IL2 agonist of claim 35, wherein the cell surface molecule is LAG3.

39. The IL2 agonist of claim 26, wherein the targeting moiety binds to a checkpoint inhibitor.

40. The IL2 agonist of claim 39, wherein the checkpoint inhibitor is CTLA-4, PD1, PDL1, PDL2, PD1, B7-H3, B7-H4, BTLA, HVEM, TIM3, GAL9, LAG3, VISTA, KIR, 2B4, CD160, CGEN-15049, CHK1, VISTA, PSGL1, or CHK2.

41. The IL2 agonist of claim 40, wherein the checkpoint inhibitor is PD1.

42. The IL2 agonist of claim 40, wherein the checkpoint inhibitor is LAG3.

43. The IL2 agonist of claim 41, wherein the targeting moiety binds to an MHC-peptide complex.

44. The IL2 agonist of claim 43 wherein the peptide in the peptide-MHC complex comprises a tumor neoantigen.

45. The IL2 agonist of claim 44, wherein the tumor neoantigen is LCMV derived peptide gp33-41, APF (126-134), BALF(276-284), CEA (571-579), CMV pp65 (495-503), FLU-M1 (58-66), gp100 (154-162), gp100 (209-217), HBV Core (18-27), Her2/neu (369-377;V2v9);

HPV E7 (11-20), HPV E7 (11-19), HPV E7 (82-90), KLK4 (11-19), LMP1 (125-133), MAG-A3 (112-120), NYESO1 (157-165, C165A), NYESO1 (157-165, C165V), p54 WT (264-272), PAP-3 (136-143), PSMA (4-12), PSMA (135-145), Survivin (96-014), Tyrosinase (369-377, 371D), or WT1 (126-134).

46. The IL2 agonist of any one of claims 26 to 45, wherein the targeting moiety is an antibody or antigen binding fragment thereof.

47. The IL2 agonist of claim 46, wherein the targeting moiety is a Fab.

48. The IL2 agonist of claim 46, wherein the targeting moiety is a scFv.

49. The IL2 agonist of claim 26, wherein the targeting moiety is a peptide-MHC complex.

50. The IL2 agonist of claim 49, wherein the peptide-MHC complex binds to the T cell receptor of tumor lymphocytes.

51. The IL2 agonist of claim 49 or claim 50, wherein the peptide in the peptide-MHC complex comprises a tumor neoantigen.

52. The IL2 agonist of claim 51, wherein the tumor neoantigen is LCMV derived peptide gp33-41, APF (126-134), BALF(276-284), CEA (571-579), CMV pp65 (495-503), FLU-M1 (58-66), gp100 (154-162), gp100 (209-217), HBV Core (18-27), Her2/neu (369-377;V2v9); HPV E7 (11-20), HPV E7 (11-19), HPV E7 (82-90), KLK4 (11-19), LMP1 (125-133), MAG-A3 (112-120), NYESO1 (157-165, C165A), NYESO1 (157-165, C165V), p54 WT (264-272), PAP-3 (136-143), PSMA (4-12), PSMA (135-145), Survivin (96-014), Tyrosinase (369-377, 371D), or WT1 (126-134).

53. The IL2 agonist of claim 49, wherein the peptide in peptide-MHC complex comprises a viral antigen.

54. The IL2 agonist of claim 53, wherein the viral antigen is CMVpp65 or HPV16E7.

55. The IL2 agonist of any one of claims 49 to 54, wherein the peptide-MHC complex further comprises β 2 microglobulin or a fragment thereof.

56. The IL2 agonist of claim 55, wherein the peptide MHC complex comprises a type I MHC domain.

57. The IL2 agonist of claim 56, wherein the peptide MHC complex comprises, in an N- to C-terminal orientation a MHC peptide, a linker, a β 2-microglobulin domain, a linker, and a type I MHC domain.

58. The IL2 agonist of claim 57, wherein the linker connecting the MHC peptide and the β 2-microglobulin domain comprises the amino acid sequence GCGGS.

59. The IL2 agonist of any one of claim 49 to 54, wherein the peptide-MHC complex does not comprise β 2 microglobulin or a fragment thereof.

60. The IL2 agonist of claim 59, wherein the peptide MHC complex comprises a type II MHC domain.

61. A nucleic acid or plurality of nucleic acids encoding the IL2 agonist of any one of claims 1 to 60.

62. A host cell engineered to express the IL2 agonist of any one of claims 1 to 60 or the nucleic acid(s) of claim 61.

63. A method of producing the IL2 agonist of any one of claims 1 to 60, comprising culturing the host cell of claim 62 and recovering the IL2 agonist expressed thereby.

64. A pharmaceutical composition comprising the IL2 agonist of any one of claims 1 to 60 and an excipient.

65. A method of treating cancer, comprising administering to a subject in need thereof the IL2 agonist of any one of claims 1 to 60 or the pharmaceutical composition of claim 64.

66. A method of treating cancer, comprising administering to a subject in need thereof:

- (a) chimeric antigen receptor ("CAR") T cells ("CART cells"); and
- (b) an IL2 agonist according to any one of claims 1 to 26 comprising a targeting moiety that binds to the T cell receptor of the CART cells or another cell surface

molecule on the CART cells, optionally wherein the targeting moiety is capable of binding to the extracellular domain of the CAR.

67. The method of claim 65 or claim 66, which further comprises administering an anti-PD1 antibody to the subject.

68. The method of claim 67, wherein the anti-PD1 antibody is MDX-1106 (nivolumab), MK-3475 (pembrolizumab), MEDI-0680 (AMP-514), PDR001, REGN2810, or BGB-108.