

WHAT IS CLAIMED:

1. A human or humanized antibody that binds human interleukin-2 (IL-2) with an affinity K_D of 1×10^{-10} M or less and inhibits binding of IL-2 with an IL-2 receptor alpha (IL-2 R α) subunit,

wherein the antibody inhibits IL-2 signaling through IL-2 R $\alpha\beta\gamma$ and through IL-2 R $\beta\gamma$,
and

wherein the antibody inhibits IL-2 signaling through IL-2 R $\alpha\beta\gamma$ to a greater extent than through IL-2 R $\beta\gamma$.

2. The antibody of claim 1 wherein the antibody does not completely block binding of human IL-2 to cells expressing human or mouse IL-2 R β or IL-2 R $\beta\gamma$ complex.

3. The antibody of any one of the preceding claims, wherein the antibody binds at a site allosteric to binding of IL-2 to IL-2 R α , IL-2 R $\beta\gamma$ or IL-2 R $\alpha\beta\gamma$.

4. The antibody of any one of the preceding claims, wherein the antibody is a negative modulator antibody, optionally wherein the antibody is capable of weakening the binding affinity between IL-2 with IL-2 receptor α (IL-2 R α) by at least about 2-fold, optionally up to 1000-fold.

5. The antibody of any one of the preceding claims wherein IL-2 complexed to the antibody binds to CHO cells expressing IL-2 R β and γ_c with an EC50 of 5 nM or less or wherein IL-2 complexed to the antibody binds to CHO cells expressing IL-2 R β (but not γ_c) with an EC50 of 100 nM or less.

6. The antibody of any one of the preceding claims wherein the antibody binds to human IL-2 and one or more of mouse, rat or rabbit IL-2.

7. The antibody of any one of the preceding claims, wherein the antibody inhibits IL-2 stimulation of STAT5 activation in cells expressing IL-2 R α , IL-2 R β , and γ_c to a greater extent than cells expressing IL-2 R β and γ_c , but not IL-2 R α .

8. The antibody of any one of the preceding claims, wherein the antibody inhibits IL-2 stimulation of STAT5 activation in cells that express IL-2 R α , IL-2 R β , and γ_c by 200-fold or greater.

9. The antibody of any one of the preceding claims, wherein the antibody inhibits IL-2 stimulation of STAT5 activation in cells that express IL-2 R β and γ c, but not IL-2 R α by 10-fold or less.

10. The antibody of any one of the preceding claims, wherein the antibody inhibits IL-2 stimulation of proliferation in cells expressing IL-2 R α , IL-2 R β , and γ c to a greater extent than cells expressing IL-2 R β and γ c, but not IL-2 R α .

11. The antibody of any one of the preceding claims, wherein the antibody inhibits IL-2 stimulation of proliferation of NK cells that express IL-2 R α , IL-2 R β , and γ c, by greater than 15-fold.

12. The antibody of any one of the preceding claims, wherein the antibody inhibits IL-2 stimulation of proliferation of BaF3 cells that express IL-2 R β and γ c, but not IL-2 R α , by less than 10-fold.

13. The antibody of any one of the preceding claims wherein the antibody is selected from the group consisting of XPA.92.019, XPA.92.041, XPA.92.042 or XPA.92.099.

14. An antibody that binds human interleukin-2 (IL-2) comprising

(a) a heavy chain CDR1 amino acid sequence set forth in SEQ ID NOs: 17, 20, 23, or 26, or a variant thereof in which one or two amino acids have been changed;

(b) a heavy chain CDR2 amino acid sequence set forth in SEQ ID NOs: 18, 21, 24, or 27 that is from the same heavy chain variable region as (a), or a variant thereof in which one or two amino acids have been changed; and

(c) a heavy chain CDR3 amino acid sequence set forth SEQ ID NOs: 19, 22, 25, or 28 that is from the same heavy chain variable region as (a), or a variant thereof in which one or two amino acids have been changed.

15. An antibody that binds human interleukin-2 (IL-2) comprising:

(a) a heavy chain CDR1 amino acid sequence set forth in SEQ ID NOs: 17, 20, 23, or 26, or a variant thereof having at least 70% identity thereto;

(b) a heavy chain CDR2 amino acid sequence set forth in SEQ ID NOs: 18, 21, 24, or 27 that is from the same heavy chain variable region as (a), or a variant thereof having at least 70% identity thereto; and

(c) a heavy chain CDR3 amino acid sequence set forth in SEQ ID NOs: 19, 22, 25, or 28 that is from the same heavy chain variable region as (a), or a variant thereof having at least 70% identity thereto.

16. An antibody that binds human interleukin-2 (IL-2) comprising:

(a) a heavy chain CDR1 amino acid sequence set forth in SEQ ID NOs: 17, 20, 23, or 26, or a variant thereof having at least 70% identity thereto;

(b) an independently selected heavy chain CDR2 amino acid sequence set forth in SEQ ID NOs: 18, 21, 24, or 27, or a variant thereof having at least 70% identity thereto; and

(c) an independently selected heavy chain CDR3 amino acid sequence set forth in SEQ ID NOs: 19, 22, 25, or 28, or a variant thereof having at least 70% identity thereto.

17. The antibody of any one of claims 14 to 16, wherein at least two of the heavy chain CDR1, CDR2 or CDR3 amino acid sequences are set forth in any one of SEQ ID NOs: 17-28.

18. The antibody of any one of claims 14 to 16, wherein three of the heavy chain CDR1, CDR2 and CDR3 amino acid sequences are set forth in any one of SEQ ID NOs: 17-28.

19. The antibody of any one of claims 14 to 18, that comprises an amino acid sequence at least 85% identical to a heavy chain variable region amino acid sequence set forth in SEQ ID NOs: 1, 3, 5, or 7.

20. The antibody of any one of claims 14 to 19, that comprises an amino acid sequence at least 95% identical to a heavy chain variable region amino acid sequence set forth in SEQ ID NOs: 1, 3, 5, or 7.

21. The antibody of any one of claims 14 to 16, comprising a polypeptide sequence having an amino acid sequence at least 70% identical over all three HCDRs in a heavy chain variable region, or the amino acid sequences of HCDR1, HCDR2 and HCDR3 set forth in any one of SEQ ID NOs: 17-28.

22. The antibody of any one of claims 14 to 21, in which one or more heavy chain framework amino acids have been replaced with corresponding amino acid(s) from another human antibody amino acid sequence.

23. The antibody of any one of claims 14 to 22, that further comprises any one of the light chain CDR amino acid sequences set forth in any one of SEQ ID NOs: 29-40.

24. The antibody of any one of claims 14 to 23, that comprises at least two of the light chain CDR amino acid sequences set forth in any one of SEQ ID NOs: 29-40.

25. The antibody of any one of claims 14 to 24, that comprises at least three of the light chain CDR amino acid sequences set forth in any one of SEQ ID NOs: 29-40.

26. The antibody of any one of claims 14 to 22 that comprises:

(a) a light chain CDR1 amino acid sequence set forth in SEQ ID NOs: 29, 32, 35, or 38, or a variant thereof in which one or two amino acids have been changed;

(b) a light chain CDR2 amino acid sequence set forth in SEQ ID NOs: 30, 33, 36, or 39 that is from the same light chain variable region as (a), or a variant thereof in which one or two amino acids have been changed; and

(c) a light chain CDR3 amino acid sequence set forth in SEQ ID NOs: 31, 34, 37, or 40 that is from the same light chain variable region as (a), or a variant thereof in which one or two amino acids have been changed.

27. An antibody that binds human interleukin-2 (IL-2) comprising:

(a) a light chain CDR1 amino acid sequence set forth in SEQ ID NOs: 29, 32, 35, or 38, or a variant thereof having at least 70% identity thereto;

(b) a light chain CDR2 amino acid sequence set forth in SEQ ID NOs: 30, 33, 36, or 39 that is from the same light chain variable region as (a), or a variant thereof having at least 70% identity thereto; and

(c) a light chain CDR3 amino acid sequence set forth in SEQ ID NOs: 31, 34, 37, or 40 that is from the same light chain variable region as (a), or a variant thereof having at least 70% identity thereto.

28. The antibody of any one of claims 14 to 22 that comprises:

(a) a light chain CDR1 amino acid sequence set forth in SEQ ID NOs: 29, 32, 35, or 38, or a variant thereof in which one or two amino acids have been changed;

(b) an independently selected light chain CDR2 amino acid sequence set forth in SEQ ID NOs: 30, 33, 36, or 39, or a variant thereof in which one or two amino acids have been changed; and

(c) an independently selected light chain CDR3 amino acid sequence set forth in SEQ ID NOs: 31, 34, 37, or 40, or a variant thereof in which one or two amino acids have been changed.

29. The antibody of claims 26-28, wherein at least two of the light chain CDR1, CDR2 or CDR3 amino acid sequences are set forth in any one of SEQ ID NOs: 29-40.

30. The antibody of any one of claims 23 to 29, comprising an amino acid sequence at least 70% identical to a light chain variable region amino acid sequence set forth in any one of SEQ ID NOs: 9, 11, 13, or 15.

31. The antibody of claim 30, comprising an amino acid sequence at least 85% identical to a light chain variable region amino acid sequence set forth in any one of SEQ ID NOs: 9, 11, 13, or 15.

32. The antibody of claim 30, comprising an amino acid sequence at least 95% identical to a light chain variable region amino acid sequence set forth in any one of SEQ ID NOs: 9, 11, 13, or 15.

33. The antibody of claim 32, comprising a light chain variable region amino acid sequence set forth in any one of SEQ ID NOs: 9, 11, 13, or 15.

34. The antibody of any one of claims 26 to 29 comprising a polypeptide sequence having an amino acid sequence at least 70% identical over all three LCDRs of a light chain variable region, the amino acid sequences of LCDR1, LCDR2 and LCDR3 set forth in SEQ ID NOs: 29-40.

35. The antibody of any one of claims 26 to 29, comprising (i) an amino acid sequence at least 70% identical over all three LCDRs, of a light chain variable region, the amino acid sequences of LCDR1, LCDR2 and LCDR3 set forth in any one of SEQ ID NOs: 29-40 and (ii) an amino acid sequence at least 70% identical over all three HCDRs of a heavy chain

variable region, the amino acid sequences of HCDR1, HCDR2 and HCDR3 set forth in any one of SEQ ID NOs: 17-28.

36. An antibody that binds human interleukin-2 (IL-2) comprising a light chain variable region and/or a heavy chain variable region, wherein

(a) the light chain variable region comprises at least a CDR1 selected from SEQ ID NOs: 29, 32, 35, or 38, or sequences at least 80% identical thereto, a CDR2 selected from SEQ ID NOs: 30, 33, 36, or 39, or sequences at least 80% identical thereto, and/or a CDR3 selected from SEQ ID NOs: 31, 34, 37, or 40, or sequences at least 80% identical thereto; and/or wherein

(b) the heavy chain variable region comprises at least a CDR1 selected from SEQ ID NOs: 17, 20, 23, or 26, or sequences at least 80% identical thereto, a CDR2 selected from SEQ ID NOs: 18, 21, 24, or 27, or sequences at least 80% identical thereto, and/or a CDR3 selected from SEQ ID NOs: 19, 22, 25, or 28, or sequences at least 80% identical thereto.

37. The antibody of claim 31, wherein

(a) the light chain variable region comprises at least a CDR1 selected from SEQ ID NO: 29, 32, 35, or 38, or sequences at least 90% identical thereto, a CDR2 selected from SEQ ID NO: 30, 33, 36, or 39, or sequences at least 90% identical thereto, and a CDR3 selected from SEQ ID NO: 31, 34, 37, or 40, or sequences at least 90% identical thereto; and/or wherein

(b) the heavy chain variable region comprises at least a CDR1 selected from SEQ ID NO: 17, 20, 23, or 26, or sequences at least 90% identical thereto, a CDR2 selected from SEQ ID NO: 18, 21, 24, or 27, or sequences at least 90% identical thereto, and a CDR3 selected from SEQ ID NO: 19, 22, 25, or 28, or sequences at least 90% identical thereto.

38. The antibody of any one of claims 14 to 37 that inhibits binding of IL-2 to an IL-2 receptor alpha (IL-2 R- α) subunit.

39. The antibody of any one of claims 14 to 38 wherein the antibody partially inhibits binding of IL-2 to an IL-2 R $\beta\gamma$ complex.

40. The antibody of any one claims 14 to 39, wherein the antibody binds at a site allosteric to binding of IL-2 to IL-2 R α , IL-2 R $\beta\gamma$ or IL-2 R $\alpha\beta\gamma$.

41. The antibody of any one of claims 14 to 40, wherein the antibody is a negative modulator antibody, optionally wherein the antibody is capable of weakening the binding affinity between IL-2 with IL-2 receptor α (IL-2 R α) by at least about 2-fold, optionally up to 1000-fold.

42. The antibody of any one of claims 14 to 41, wherein the antibody does not shift the EC₅₀ of binding of IL-2 to IL-2 R $\beta\gamma$ complex by more than 3-fold.

43. The antibody of any one of claims 14 to 42 wherein the antibody binds to human IL-2 and one or more of mouse, rat or rabbit IL-2.

44. The antibody of any one of claims 14 to 43, wherein the antibody inhibits STAT5 activation in a cell in response to stimulation of the IL-2 R with IL-2.

45. The antibody of any one of claims 14 to 44 that is a human antibody or a humanized antibody.

46. The antibody of any one of the preceding claims, further comprising a heavy chain constant region, wherein the heavy chain constant region is a modified or unmodified IgG, IgM, IgA, IgD, IgE, a fragment thereof, or combinations thereof.

47. The antibody of any one of claims 26 to 38, in which one or more light chain framework amino acids have been replaced with corresponding amino acid(s) from another human antibody amino acid sequence.

48. The antibody of any one of claims 14 to 16, 26 to 28 or 35, wherein the antibody is selected from the group consisting of XPA.92.019, XPA.92.041, XPA.92.042 or XPA.92.099.

49. The antibody of any one of the preceding claims, further comprising a human light chain constant region attached to said light chain variable region.

50. The antibody of claim 50, wherein the light chain constant region is a modified or unmodified lambda light chain constant region, a kappa light chain constant region, a fragment thereof, or combinations thereof.

51. An antibody of any one of the claims 14-41 that binds human interleukin-2 (IL-2) with an affinity K_D of 10^{-10} M or less.

52. An isolated nucleic acid molecule comprising a nucleotide sequence that encodes the heavy chain or light chain of any one of claims 1 to 51.

53. An expression vector comprising the nucleic acid molecule of claim 52 operably linked to an expression control sequence.

54. A host cell comprising the vector of claim 53 or a nucleic acid molecule of claim 49.

55. The host cell of claim 54, comprising a nucleic acid molecule encoding a heavy chain and a light chain variable region, wherein the heavy chain and light chain nucleic acids are expressed by different nucleic acids or on the same nucleic acid.

56. A method of using the host cell of claim 54 or 55 to produce an antibody, comprising culturing the host cell of claim 54 or 55 under suitable conditions and recovering said antibody.

57. An antibody produced by the method of claim 56.

58. A sterile pharmaceutical composition comprising the antibody of any one of claims 1-52 and a pharmaceutically acceptable carrier.

59. A method for suppressing IL-2 activity in a patient in need thereof comprising the step of administering to a subject in need thereof a therapeutically effective amount of an antibody of any one of claims 1 to 52 or a pharmaceutical composition of claim 58.

60. A method for treating a disease, condition or disorder associated with increased interleukin-2 (IL-2) or interleukin-2 receptor (IL-2 R) levels or activity comprising the step of administering to a subject in need thereof a therapeutically effective amount of an antibody of any one of claims 1 to 51 or a pharmaceutical composition of claim 58.

61. The method of claim 60, wherein the disease, condition or disorder is selected from the group consisting of cancer, microbial infection, asthma and autoimmune disease.

62. The method of claim 61 wherein the cancer is selected from the group consisting of melanoma, renal cell carcinoma, lymphoma, sarcoma, breast cancer, lung cancer, bladder cancer, colon cancer, gastric cancer, non small cell lung carcinoma (NSCLC), head and neck cancer, skin cancer, and squamous cell carcinoma (SCC).

63. The method of claim 62, wherein the administration reduces tumor volume in the subject.

64. The method of any one of claims 60-63 wherein the administration increases the ratio of CD8+ T cells to CD4+ T cells in the subject.

65. The method of any one of claims 60-64 wherein the antibody is administered intravenously, intratumorally, intraarterially, intraperitoneally, intramuscularly, intradermally or subcutaneously.

66. The method of any one of claims 60-65 wherein the antibody is administered in combination with a second agent.

67. The method of claim 66 wherein the second agent is IL-2, an IL-2 variant, a checkpoint inhibitor, a CART/TIL agent, an antibody to a tumor antigen or a vaccine.

68. The method of claim 67, wherein the checkpoint inhibitor is selected from the group consisting of an anti-PD-1 antibody, an anti-PDL-1 antibody, an anti-CTLA-4 antibody, a PD-1 inhibitor, a PDL-1 inhibitor or a CTLA-4 inhibitor.

69. The method of claim 67 wherein when the second agent is IL-2 or an IL-2 variant; the antibody may be complexed with IL-2 or an IL-2 variant prior to administration or administered separately.

70. The method of claim 69, wherein the IL-2 or IL-2 variant and the IL-2 antibody are administered in a 1:1 molar ratio.

71. The method of claim 69 or 70 wherein administering the IL-2 antibody in combination with IL-2 or an IL-2 variant increases the therapeutic index (TI) of IL-2 by at least 2, 3, 4, 5, 6, 7, 8, 9, or 10-fold or more.

72. The method of claim 69 further comprising administration of a checkpoint inhibitor, a CART/TIL agent, an antibody to a tumor antigen or a vaccine.

73. The method of any one of claims 60-72, wherein the antibody is administered once per week, once every 2 weeks, twice per month, once monthly, once every two months, or once every three months.

73. A composition comprising an antibody of any one of claims 1 to 51 or a pharmaceutical composition of claim 58 for use in treating a condition or disorder associated with increased interleukin-2 (IL-2) or interleukin-2 receptor (IL-2 R).

74. A composition comprising an antibody of any one of claims 1 to 51 or a pharmaceutical composition of claim 58 for use in treating a condition or disorder associated with increased IL-2 or IL-2 R expression or activity.

75. A method for modulating IL-2 activity in a cell comprising the step of contacting the cell with an amount of an antibody of any one of claims 1 to 51 or a pharmaceutical composition of claim 58 effective to modulate IL-2 activity in the cell.