

What is claimed:

1. An isolated antibody or antigen binding portion thereof, which specifically binds to an alpha-chain of a human IL-7 receptor ("anti-IL-7R antibody"), comprising a heavy chain CDR1, CDR2, and CDR3 and a light chain CDR1, CDR2, and CDR3, wherein the antibody

- (a) is capable of binding to T cells ($CD4^+CD45RA^+$, $CD4^+CD45RA^-$, $CD8^+CD45RA^+$, and/or $CD8^+CD45RA^-$) in whole blood with an EC_{50} of about 5 nM or less (*e.g.*, less than about 3 nM);
- (b) is not capable of binding to non-T cells in whole blood;
- (c) is not capable of effectively blocking thymic stromal lymphopoietin (TSLP)-mediated activation of monocytes;
- (d) does not agonize IL-7 receptor signaling upon binding to the IL-7 receptor, *e.g.*, minimal pSTAT5 activation; or
- (e) any combination thereof.

2. The antibody of claim 1, wherein the heavy chain CDR3 comprises the amino acid sequence set forth in SEQ ID NO: 15 (DEYSRGYYVLDV).

3. The antibody of claim 1 or 2, wherein the antibody has one or more properties selected from the group consisting of:

- (a) is capable of selectively binding to an alpha-chain of a human and cynomolgus IL-7 receptor (IL-7R);
- (b) is capable of binding to an alpha-chain of soluble and membrane bound IL-7R;
- (c) is capable of blocking an expansion and/or survival of pathogenic T cells when administered to a subject in need thereof;
- (d) is capable of restoring a T regulatory cell (Treg) function and/or promoting a Treg survival when administered to a subject in need thereof;
- (e) is capable of maintaining a drug free remission longer than that by CTLA4-Ig (ORENCIA[®]);
- (f) is capable of blocking inflammation and mucosal damage, *e.g.*, induced by pathogenic T cells, within an intestinal tissue of a subject in need thereof;
- (g) is capable of decreasing a frequency of T effector cells in the mesenteric lymph nodes (MLN) and/or lamina propria (LP) in a subject in need thereof;
- (h) is capable of reducing or inhibiting IL-7 mediated pSTAT activation in T cells (*e.g.*, $CD4^+CD45RA^+$);
- (i) is capable of blocking expansion of IL-17 and/or IFN-gamma producing cells;
- (j) is capable of treating a subject with an inflammatory disease (*e.g.*, inflammatory bowel disease); and
- (k) any combination thereof.

4. The antibody of any one of claims 1 to 3, wherein the heavy chain CDR1 comprises the amino acid sequence set forth in SEQ ID NO: 13 (DHAMH).
5. The antibody of any one of claims 1 to 4, wherein the heavy chain CDR2 comprises the amino acid sequence set forth in SEQ ID NO: 14 (GISWNSRGIGYADSVKG).
6. The antibody of any one of claims 1 to 5, wherein the light chain CDR1 comprises the amino acid sequence set forth in SEQ ID NO: 16 (RASQGISSALA).
7. The antibody of any one of claims 1 to 6, wherein the light chain CDR2 comprises the amino acid sequence set forth in SEQ ID NO: 17 (DASSLES).
8. The antibody of any one of claims 1 to 7, wherein the light chain CDR3 comprises the amino acid sequence set forth in SEQ ID NO: 18 (QQFNSYPLWIT).
9. The antibody of any one of claims 1 to 8, comprising a heavy chain variable region (VH) and a light chain variable region (VL), wherein the VH comprises an amino acid sequence which is at least about 80%, at least about 85%, 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 about 100% identical to the amino acid sequence set forth in SEQ ID NO: 19.
10. The antibody of any one of claims 1 to 8, wherein the VL comprises an amino acid sequence which is at least about 80%, at least about 85%, 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 about 100% identical to the amino acid sequence set forth in SEQ ID NO: 20.
11. The antibody of any one of claims 1 to 10, which specifically binds to the alpha-chain of the human IL-7 receptor at an epitope selected from the group consisting of: ²⁴SQLEVNGSQHSLTCAF³⁹ (SEQ ID NO: 8); ⁷³FIETKKFLLIGKSNIC⁸⁸ (SEQ ID NO: 9); ⁸⁹VKVGEKSLTCKKIDLT¹⁰⁵ (SEQ ID NO: 10); ¹³⁶QKKYVKVLMHDVAY¹⁴⁹ (SEQ ID NO: 11); ¹⁸¹YEIKVRSIPDHYFKGF¹⁹⁶ (SEQ ID NO: 12); and combinations thereof.
12. The antibody of any one of claims 1 to 11, which specifically binds to the alpha-chain of the human IL-7 receptor at an epitope comprising one or more amino acid residues selected from the group consisting of H33, E75, F79, I82, K84, M144, R186, H191, Y192, and combinations thereof.
13. The antibody of any one of claims 1 to 12, wherein the antibody is selected from the group consisting of an IgG1, IgG2, IgG3, IgG4, and a variant thereof.
14. The antibody of claim 13, wherein the antibody is an IgG1 antibody.
15. The antibody of claim 14, comprising an effectorless IgG1 Fc.
16. An isolated antibody or antigen binding portion thereof, which specifically binds to an alpha-chain of a human IL-7 receptor ("anti-IL-7R antibody"), comprising a heavy chain and a light chain, wherein the heavy chain comprises the amino acid sequence set forth in SEQ ID NO: 21 and wherein the light chain comprises the amino acid sequence set forth in SEQ ID NO: 22.

17. The antibody of any one of claims 1 to 16, which binds to the alpha-chain of the human IL-7 receptor with a K_D of less than 10 nM, 9 nM, 8 nM, 7 nM, 6 nM, 5 nM, 4 nM, 3 nM, 2 nM, or 1 nM (*e.g.*, 1.3 nM), as measured by surface plasmon resonance.

18. The antibody of any one of claims 1 to 17, which binds to the alpha-chain of the cynomolgus IL-7 receptor with a K_D of less than 10 nM, 9 nM, 8 nM, 7 nM, 6 nM, 5 nM, 4 nM, 3 nM, 2 nM, or 1 nM (*e.g.*, 1.7 nM), as measured by surface plasmon resonance.

19. The antibody of claim 17 or 18, wherein the binding to the alpha-chain of the human IL-7 receptor or the alpha-chain of the cynomolgus IL-7 receptor is pH-dependent.

20. The antibody of claim 19, which binds to the alpha-chain of the human IL-7 receptor with a K_D of about 1.3 nM at pH 7.4 and with a K_D of about 5.3 nM at pH 6.

21. The antibody of claim 19 or 20, which binds to the alpha-chain of the cynomolgus IL-7 receptor with a K_D of about 1.7 nM at pH 7.4 and with a K_D of about 7.0 nM at pH 6.

22. An isolated antibody or antigen binding portion thereof, which specifically binds to an alpha-chain of a human IL-7 receptor ("anti-IL-7R antibody") comprising a heavy chain (HC) CDR1, CDR2, and CDR3, and a light chain (LC) CDR1, CDR2, and CDR3, wherein the HC CDR1 comprises the amino acid sequence $GX_1X_2FDDHAX_3H$ (SEQ ID NO: 260), wherein X_1 is F or Y; X_2 is T, P, A, S, V, L, I, M, H, F, Y, N, D, E, or Q; and X_3 is L or M.

23. The antibody of claim 22, wherein X_2 is D or E.

24. The antibody of claim 22 or 23, wherein the HC CDR2 comprises the amino acid sequence $GIX_1WX_2SRGX_3GYX_4X_5X_6X_7X_8X_9$ (SEQ ID NO: 261), wherein X_1 is S or T; X_2 is H or N; X_3 is I or V; X_4 is G, A, S, T, V, L, I, R, H, or N; X_5 is P, T, N, D, E, Q, S, H, or Y; X_6 is P, G, A, S, T, V, R, H, F, Y, N, D, or E; X_7 is V or I; X_8 is A, S, T, V, L, I, M, K, R, H, F, Y, N, D, E, or Q; and X_9 is G, H, D, or Q.

25. The antibody of claim 24, wherein X_1 is T.

26. The antibody of any one of claims 22 to 25, wherein the HC CDR3 comprises the amino acid sequence $DEYX_1X_2GYX_3LDX_4$ (SEQ ID NO: 262), wherein X_1 is S, T, N, D, or E; X_2 is L, M, R, or S; X_3 is G, A, S, T, V, M, N, E, or Q; and X_4 is A, S, T, V, R, H, Y, W, N, E, Q, or M.

27. The antibody of claim 26, wherein X_3 is A, S, or T.

28. The antibody of claim 26 or 27, wherein X_4 is E.

29. The antibody of any one of claims 22 to 28, wherein the LC CDR1 comprises the amino acid sequence $X_1X_2X_3X_4X_5X_6X_7SX_8X_9A$ (SEQ ID NO: 263), wherein X_1 is S, T, V, K, R, H, Y, or I; X_2 is A, S, T, or V; X_3 is P, G, A, S, T, V, L, I, M, K, R, H, N, E, or Q; X_4 is P, G, A, S, T, V, L, I, M, H, F, Y, N, D, E, or Q; X_5 is P, G, A, S, T, H, E, Q, M, N, or D; X_6 is P, G, A, S, T, V, L, I, or N; X_7 is S, T, V, L, I, M, H, F, Y, N, D, E, or Q; X_8 is P or A; and X_9 is A, L, or V.

30. The antibody of claim 29, wherein X_6 is P.

31. The antibody of claim 29 or 30, wherein X_8 is P.

32. The antibody of any one of claims 29 to 31, wherein X_7 is D or E.

33. The antibody of any one of claims 22 to 32, wherein the LC CDR2 comprises the amino acid sequence $DX_1X_2X_3X_4X_5X_6$ (SEQ ID NO: 264), wherein X_1 is G, A, S, M, H, N, D, E, or Q; X_2 is G, A, S, T, V, M, H, F, Y, N, D, E, or Q; X_3 is A, S, F, Y, W, N, D, E, or L; X_4 is P, S, T, L, K, H, or N; X_5 is D, E, or Q; and X_6 is G, S, T, N, D, Q, P, or E.

34. The antibody of any one of claims 22 to 33, wherein the LC CDR3 comprises the amino acid sequence $X_1X_2FX_3X_4YPLX_5X_6X_7$ (SEQ ID NO: 265), wherein X_1 is M or Q; X_2 is G, A, D, E, or Q; X_3 is N or E; X_4 is P, A, or S; X_5 is T, I, M, K, W, N, E, or Q; X_6 is L or I; and X_7 is T, M, K, H, Y, E, or Q.

35. The antibody of claim 34, wherein X_2 is A.

36. The antibody of claim 34 or 35, wherein X_4 is P or A.

37. The antibody of any one of claims 22 to 36, wherein the heavy chain CDR1 comprises an amino acid sequence set forth in SEQ ID NOs: 31 to 46.

38. The antibody of claim 37, wherein the heavy chain CDR1 comprises an amino acid sequence set forth in SEQ ID NO: 43 or SEQ ID NO: 44.

39. The antibody of any one of claims 22 to 38, wherein the heavy chain CDR2 comprises an amino acid sequence set forth in SEQ ID NOs: 47 to 96.

40. The antibody of claim 39, wherein the heavy chain CDR2 comprises an amino acid sequence set forth in SEQ ID NO: 47.

41. The antibody of any one of claims 22 to 40, wherein the heavy chain CDR3 comprises an amino acid sequence set forth in SEQ ID NOs: 97 to 122.

42. The antibody of claim 41, wherein the heavy chain CDR3 comprises an amino acid sequence set forth in SEQ ID NO: 105, SEQ ID NO: 106, SEQ ID NO: 107, or SEQ ID NO: 120.

43. The antibody of any one of claims 22 to 42, wherein the light chain CDR1 comprises an amino acid sequence set forth in SEQ ID NOs: 123 to 194.

44. The antibody of claim 43, wherein the light chain CDR1 comprises an amino acid sequence set forth in SEQ ID NO: 172, SEQ ID NO: 189, SEQ ID NO: 190, or SEQ ID NO: 192.

45. The antibody of any one of claims 22 to 44, wherein the light chain CDR2 comprises an amino acid sequence set forth in SEQ ID NOs: 195 to 237.

46. The antibody of any one of claims 22 to 45, wherein the light chain CDR3 comprises an amino acid sequence set forth in SEQ ID NOs: 238 to 259.

47. The antibody of claim 46, wherein the light chain CDR3 comprises an amino acid sequence set forth in SEQ ID NO: 240, SEQ ID NO: 244, or SEQ ID NO: 245.

48. An isolated antibody or antigen binding portion thereof, which specifically binds to an alpha-chain of a human IL-7 receptor ("anti-IL-7R antibody") comprising a heavy chain (HC) CDR1, CDR2, and CDR3, and a light chain (LC) CDR1, CDR2, and CDR3, wherein:

(i) the heavy chain CDR1 comprises an amino acid sequence set forth in SEQ ID NOs: 31 to 46;

- (ii) the heavy chain CDR2 comprises an amino acid sequence set forth in SEQ ID NO: 14;
- (iii) the heavy chain CDR3 comprises an amino acid sequence set forth in SEQ ID NO: 15;
- (iv) the light chain CDR1 comprises an amino acid sequence set forth in SEQ ID NO: 16;
- (v) the light chain CDR2 comprises an amino acid sequence set forth in SEQ ID NO: 17; and
- (vi) the light chain CDR3 comprises an amino acid sequence set forth in SEQ ID NO: 18.

49. The antibody of claim 48, wherein the heavy chain CDR1 comprises an amino acid sequence set forth in SEQ ID NO: 43 or SEQ ID NO: 44.

50. An isolated antibody or antigen binding portion thereof, which specifically binds to an alpha-chain of a human IL-7 receptor ("anti-IL-7R antibody") comprising a heavy chain (HC) CDR1, CDR2, and CDR3, and a light chain (LC) CDR1, CDR2, and CDR3, wherein:

- (i) the heavy chain CDR1 comprises an amino acid sequence set forth in SEQ ID NO: 13;
- (ii) the heavy chain CDR2 comprises an amino acid sequence set forth in SEQ ID NOs: 47 to 96;
- (iii) the heavy chain CDR3 comprises an amino acid sequence set forth in SEQ ID NO: 15;
- (iv) the light chain CDR1 comprises an amino acid sequence set forth in SEQ ID NO: 16;
- (v) the light chain CDR2 comprises an amino acid sequence set forth in SEQ ID NO: 17; and
- (vi) the light chain CDR3 comprises an amino acid sequence set forth in SEQ ID NO: 18.

51. The antibody of claim 50, wherein the heavy chain CDR2 comprises an amino acid sequence set forth in SEQ ID NO: 47.

52. An isolated antibody or antigen binding portion thereof, which specifically binds to an alpha-chain of a human IL-7 receptor ("anti-IL-7R antibody") comprising a heavy chain (HC) CDR1, CDR2, and CDR3, and a light chain (LC) CDR1, CDR2, and CDR3, wherein:

- (i) the heavy chain CDR1 comprises an amino acid sequence set forth in SEQ ID NO: 13;
- (ii) the heavy chain CDR2 comprises an amino acid sequence set forth in SEQ ID NO: 14;
- (iii) the heavy chain CDR3 comprises an amino acid sequence set forth in SEQ ID NOs: 97 to 122;
- (iv) the light chain CDR1 comprises an amino acid sequence set forth in SEQ ID NO: 16;
- (v) the light chain CDR2 comprises an amino acid sequence set forth in SEQ ID NO: 17; and
- (vi) the light chain CDR3 comprises an amino acid sequence set forth in SEQ ID NO: 18.

53. The antibody of claim 52, wherein the heavy chain CDR3 comprises an amino acid sequence set forth in SEQ ID NO: 105, SEQ ID NO: 106, SEQ ID NO: 107, or SEQ ID NO: 120.

54. An isolated antibody or antigen binding portion thereof, which specifically binds to an alpha-chain of a human IL-7 receptor ("anti-IL-7R antibody") comprising a heavy chain (HC) CDR1, CDR2, and CDR3, and a light chain (LC) CDR1, CDR2, and CDR3, wherein:

- (i) the heavy chain CDR1 comprises an amino acid sequence set forth in SEQ ID NO: 13;
- (ii) the heavy chain CDR2 comprises an amino acid sequence set forth in SEQ ID NO: 14;

- (iii) the heavy chain CDR3 comprises an amino acid sequence set forth in SEQ ID NO: 15;
- (iv) the light chain CDR1 comprises an amino acid sequence set forth in SEQ ID NOs: 123 to 194;
- (v) the light chain CDR2 comprises an amino acid sequence set forth in SEQ ID NO: 17; and
- (vi) the light chain CDR3 comprises an amino acid sequence set forth in SEQ ID NO: 18.

55. The antibody of claim 54, wherein the light chain CDR1 comprises an amino acid sequence set forth in SEQ ID NO: 172, SEQ ID NO: 189, SEQ ID NO: 190, or SEQ ID NO: 192.

56. An isolated antibody or antigen binding portion thereof, which specifically binds to an alpha-chain of a human IL-7 receptor ("anti-IL-7R antibody") comprising a heavy chain (HC) CDR1, CDR2, and CDR3, and a light chain (LC) CDR1, CDR2, and CDR3, wherein:

- (i) the heavy chain CDR1 comprises an amino acid sequence set forth in SEQ ID NO: 13;
- (ii) the heavy chain CDR2 comprises an amino acid sequence set forth in SEQ ID NO: 14;
- (iii) the heavy chain CDR3 comprises an amino acid sequence set forth in SEQ ID NO: 15;
- (iv) the light chain CDR1 comprises an amino acid sequence set forth in SEQ ID NO: 16;
- (v) the light chain CDR2 comprises an amino acid sequence set forth in SEQ ID NOs: 195 to 237; and

- (vi) the light chain CDR3 comprises an amino acid sequence set forth in SEQ ID NO: 18.

57. An isolated antibody or antigen binding portion thereof, which specifically binds to an alpha-chain of a human IL-7 receptor ("anti-IL-7R antibody") comprising a heavy chain (HC) CDR1, CDR2, and CDR3, and a light chain (LC) CDR1, CDR2, and CDR3, wherein:

- (i) the heavy chain CDR1 comprises an amino acid sequence set forth in SEQ ID NO: 13;
- (ii) the heavy chain CDR2 comprises an amino acid sequence set forth in SEQ ID NO: 14;
- (iii) the heavy chain CDR3 comprises an amino acid sequence set forth in SEQ ID NO: 15;
- (iv) the light chain CDR1 comprises an amino acid sequence set forth in SEQ ID NO: 16;
- (v) the light chain CDR2 comprises an amino acid sequence set forth in SEQ ID NO: 17; and
- (vi) the light chain CDR3 comprises an amino acid sequence set forth in SEQ ID NOs: 238 to 259.

58. The antibody of claim 57, wherein the light chain CDR3 comprises an amino acid sequence set forth in SEQ ID NO: 240, SEQ ID NO: 244, or SEQ ID NO: 245.

59. A nucleic acid encoding the antibody of any one of claims 1 to 58.

60. A vector comprising the nucleic acid of claim 59.

61. A cell comprising the vector of claim 60.

62. The cell of claim 61, wherein the cell is CHO cells, HEK293 cells, HBK cells, COS cells, NSO cells, or HT1080 cells.

63. An immunoconjugate comprising the antibody of any one of claims 1 to 58, linked to an agent.

64. A composition comprising the antibody of any one of claims 1 to 58, the nucleic acid of claim 59, the vector of claim 60, the cell of claim 61 or 62, or the immunoconjugate of claim 63, and a carrier.

65. A kit comprising the antibody of any one of claims 1 to 58, the nucleic acid of claim 59, the vector of claim 60, the cell of claim 61 or 62, or the immunoconjugate of claim 63, and an instruction for use.

66. A method of inhibiting IL-7 activity in a subject in need thereof, comprising administering the antibody of any one of claims 1 to 58, the nucleic acid of claim 59, the vector of claim 60, the cell of claim 61 or 62, or the immunoconjugate of claim 63 to the subject.

67. A method of inhibiting proliferation of effector T cells and/or inducing generation and/or survival of regulatory T cells in a subject in need thereof, comprising administering the antibody of any one of claims 1 to 58, the nucleic acid of claim 59, the vector of claim 60, the cell of claim 61 or 62, or the immunoconjugate of claim 63 to the subject.

68. A method of treating an inflammatory disease or an autoimmune disease in a subject in need thereof, comprising administering the antibody of any one of claims 1 to 58, the nucleic acid of claim 59, the vector of claim 60, the cell of claim 61 or 62, or the immunoconjugate of claim 63 to the subject.

69. The method of claim 68, wherein the inflammatory disease or the autoimmune disease is selected from the group consisting of an inflammatory bowel disease (IBD), irritable bowel syndrome, rheumatoid arthritis (RA), psoriasis, psoriatic arthritis, systemic lupus erythematosus (SLE), lupus nephritis, vasculitis, sepsis, systemic inflammatory response syndrome (SIRS), type I diabetes, Grave's disease, multiple sclerosis (MS), autoimmune myocarditis, Kawasaki disease, coronary artery disease, chronic obstructive pulmonary disease, interstitial lung disease, autoimmune thyroiditis, scleroderma, systemic sclerosis, osteoarthritis, atopic dermatitis, vitiligo, graft versus host disease, Sjogren's syndrome, autoimmune nephritis, Goodpasture syndrome, chronic inflammatory demyelinating polyneuropathy, allergy, asthma, other autoimmune diseases that are a result of either acute or chronic inflammation, and any combinations thereof.

70. The method of claim 69, wherein the inflammatory disease or the autoimmune disease is inflammatory bowel disease.

71. The method of claim 69 or 70, wherein the inflammatory bowel disease is ulcerative colitis or Crohn's disease.

72. The method of any one of claims 66 to 71, wherein the subject did not adequately respond to previous TNF- α inhibitor therapy (anti-TNF- α inadequate responder).

73. The method of any one of claims 66 to 72, further comprising administering one or more additional therapeutics.

74. The method of claim 73, wherein the additional therapeutics comprise an anti-TNF- α antibody.

75. The method of any one of claims 66 to 74, wherein the antibody is administered to the subject at a flat dose or a body weight based dose.

76. The method of any one of claims 66 to 75, wherein the antibody is administered intravenously, subcutaneously, intramuscularly, intradermally, or intraperitoneally.

77. The method of claim 76, wherein the antibody is administered intravenously or subcutaneously.

78. A method of producing an antibody which specifically binds to an alpha-chain of a human IL-7 receptor ("anti-IL-7R antibody"), comprising culturing the cell of claim 61 or 62 under suitable conditions and isolating the antibody.