

WHAT IS CLAIMED:

1. An isolated antibody or antigen-binding fragment thereof that specifically binds to human PILRA, wherein the antibody or antigen-binding fragment thereof blocks binding of PILRA to one or more of its ligands and downregulates cell surface PILRA.
2. The antibody or antigen-binding fragment thereof of claim 1, wherein the antibody or antigen-binding fragment thereof blocks binding of residue Arg126 of human PILRA (SEQ ID NO:1) to one or more ligands of PILRA.
3. The antibody or antigen-binding fragment thereof of claim 1 or 2, wherein the antibody or antigen-binding fragment thereof blocks binding of PILRA-Fc to human T-cells by at least 70%, at least 75%, at least 80%, at least 85%, at least 90%, at least 95% or at least 98%.
4. The antibody or antigen-binding fragment thereof of any one of claims 1-3, wherein the antibody or antigen-binding fragment thereof downregulates cell surface PILRA by at least 10%, at least 20%, at least 30%, at least 40%, or at least 50% after 30 minutes at 37°C.
5. An isolated antibody or antigen-binding fragment thereof that specifically binds to human PILRA and comprises the heavy chain variable region (VH) complementarity determining region (CDR) 1, VH CDR2, VH CDR3 and light chain variable region (VL) CDR1, CDR2, and CDR3 sequences of:
 - (a) SEQ ID NOs:4-9, respectively;
 - (b) SEQ ID NOs:10-15, respectively;
 - (c) SEQ ID NOs:16-21, respectively; or
 - (d) SEQ ID NOs:22-27, respectively.
6. An isolated antibody or antigen-binding fragment thereof that competitively inhibits binding of a reference antibody to human PILRA, wherein the reference antibody comprises a heavy chain variable region and a light chain variable region comprising the amino acid sequences of:
 - (a) SEQ ID NOs:28 and 29, respectively;
 - (b) SEQ ID NOs:30 and 31, respectively;

- (c) SEQ ID NOs:32 and 33, respectively; or
 - (d) SEQ ID NOs:34 and 35, respectively.
7. An isolated antibody or antigen-binding fragment thereof that binds to the same human PILRA epitope as an antibody comprising a heavy chain variable region and a light chain variable region comprising the amino acid sequences of:
- (a) SEQ ID NOs:28 and 29, respectively;
 - (b) SEQ ID NOs:30 and 31, respectively;
 - (c) SEQ ID NOs:32 and 33, respectively; or
 - (d) SEQ ID NOs:34 and 35, respectively.
8. An isolated antibody or antigen-binding fragment thereof that specifically binds to human PILRA, wherein the antibody or antigen-binding fragment thereof comprises the VH CDR1, VH CDR2, VH CDR3, VL CDR1, VL CDR2, and VL CDR3 of an antibody selected from the group consisting of hPA-002, hPA-005, hPA-004, or hPA-001.
9. The antibody or antigen-binding fragment thereof of claim 8, wherein the CDRs are the Kabat-defined CDRs, the Chothia-defined CDRs, the IMGT-defined CDRs, or the AbM-defined CDRs.
10. The antibody or antigen-binding fragment thereof of any one of claims 1-9, wherein the antibody or antigen-binding fragment thereof comprises a VH comprising the amino acid sequence of SEQ ID NO:28, 30, 32, or 34.
11. The antibody or antigen-binding fragment thereof of any one of claims 1-10, wherein the antibody or antigen-binding fragment thereof comprises a VL comprising the amino acid sequence of SEQ ID NO:29, 31, 33, or 35.
12. The antibody or antigen-binding fragment thereof of any one of claims 1-11, wherein the antibody or antigen-binding fragment comprises a heavy chain variable region and a light chain variable region comprising the amino acid sequences of:
- (e) SEQ ID NOs:28 and 29, respectively;
 - (f) SEQ ID NOs:30 and 31, respectively;

- (g) SEQ ID NOs:32 and 33, respectively; or
 - (h) SEQ ID NOs:34 and 35, respectively.
13. A humanized form of the antibody of claim 12.
 14. An isolated antibody or antigen-binding fragment thereof that specifically binds to human PILRA, wherein the antibody or antigen-binding fragment thereof comprises a heavy chain variable region and a light chain variable region, wherein the heavy chain variable region comprises the amino acid sequence of SEQ ID NO:28, 30, 32, or 34.
 15. An isolated antibody or antigen-binding fragment thereof that specifically binds to human PILRA, wherein the antibody comprises a heavy chain variable region and a light chain variable region, wherein the light chain variable region comprises the amino acid sequence of SEQ ID NO:29, 31, 33, or 35.
 16. The antibody or antigen-binding fragment thereof of any one of claims 5-15, wherein the antibody or antigen-binding fragment thereof blocks binding of PILRA to one or more of its ligands and downregulates cell surface PILRA.
 17. The antibody or antigen-binding fragment thereof of claim 16, wherein the antibody or antigen-binding fragment thereof blocks binding of residue Arg126 of human PILRA (SEQ ID NO:1) to one or more of its ligands.
 18. The antibody or antigen-binding fragment thereof of claim 16 or 17, wherein the antibody or antigen-binding fragment thereof blocks binding of PILRA-Fc to human T-cells by at least 70%, at least 75%, at least 80%, at least 85%, at least 90%, at least 95% or at least 98%.
 19. The antibody or antigen-binding fragment thereof of any one of claims 5-18, wherein the antibody or antigen-binding fragment thereof downregulates cell surface PILRA by at least 10%, at least 20%, at least 30%, at least 40%, or at least 50% after 30 minutes at 37°C.
 20. The antibody or antigen-binding fragment thereof of any one of claims 1-4 and 16-19, wherein the downregulation is dose-dependent.

21. The antibody or antigen-binding fragment thereof of any one of claims 1-4 and 16-20, wherein the blocking is dose-dependent.
22. The antibody or antigen-binding fragment thereof of any one of claims 1-21, wherein the antibody or antigen-binding fragment thereof activates myeloid cells.
23. The antibody or antigen-binding fragment thereof of any one of claims 1-22, wherein the antibody or antigen-binding fragment thereof promotes myeloid cell differentiation.
24. The antibody or antigen-binding fragment thereof of any one of claims 1-23, wherein the antibody or antigen-binding fragment thereof increases MIP1b production by myeloid cells.
25. The antibody or antigen-binding fragment thereof of any one of claims 1-24, wherein the antibody or antigen-binding fragment thereof blocks binding of PILRA to NPDC1.
26. The antibody or antigen-binding fragment thereof of any one of claims 22-25, wherein the activation of myeloid cells, the promotion of myeloid cell differentiation, the increase in MIP1b production, and/or the blocking of ligand binding is dose-dependent.
27. The antibody or antigen-binding fragment thereof of any one of claims 1-26, wherein the antibody or antigen-binding fragment thereof binds to cynomolgus monkey PILRA.
28. The antibody or antigen-binding fragment thereof of any one of claims 1-27, wherein the antibody or antigen-binding fragment thereof does not bind to human PILRB.
29. The antibody or antigen-binding fragment thereof of any one of claims 1-28, wherein the antibody or antigen-binding fragment thereof binds to an epitope in amino acids 20-197 of SEQ ID NO:1.
30. The antibody or antigen-binding fragment thereof of any one of claims 1-29, wherein antibody 2175B does not competitively inhibit binding of the antibody or antigen-binding fragment thereof to human PILRA.

31. The antibody or antigen-binding fragment thereof of any one of claims 1-30, wherein the antibody or antigen-binding fragment comprises a heavy chain constant region and a light chain constant region.
32. The antibody or antigen-binding fragment thereof of claim 31, wherein the heavy chain constant region is an isotype selected from the group consisting of human IgG₁, IgG₂, IgG₃, and IgG₄ isotypes.
33. The antibody or antigen-binding fragment thereof of claim 32, which comprises an Fc domain that is engineered to reduce effector function.
34. The antibody or antigen-binding fragment thereof of any one of claims 1-33, wherein the antibody or antigen-binding fragment comprises a heavy chain constant region and a light chain constant region, wherein the heavy chain constant region is a human IgG₁ heavy chain constant region, and wherein the light chain constant region is a human IgG_κ light chain constant region.
35. The antibody or antigen-binding fragment thereof of any one of claims 1-34, wherein the antibody or antigen-binding fragment is a monoclonal antibody.
36. The antibody or antigen-binding fragment thereof of any one of claims 1-35 wherein the antibody or antigen-binding fragment thereof is a murine, chimeric, humanized, or human antibody or antigen-binding fragment thereof.
37. The antibody or antigen binding fragment thereof of any one of claims 1-36, which is a full length antibody.
38. The antibody or antigen binding fragment thereof of any one of claims 1-36, which is an antigen binding fragment.
39. The antigen binding fragment of claim 38, wherein the antigen binding fragment is a Fab, Fab', F(ab')₂, single chain Fv (scFv), disulfide linked Fv, V-NAR domain, IgNar, intrabody, IgGΔCH2, minibody, F(ab')₃, tetrabody, triabody, diabody, single-domain antibody, DVD-Ig, Fcab, mAb², (scFv)₂, or scFv-Fc.

40. The antibody or antigen-binding fragment thereof of any one of claims 1-39, further comprising a detectable label.
41. An isolated polynucleotide comprising a nucleic acid molecule encoding the heavy chain variable region or heavy chain of the antibody or antigen-binding fragment thereof of any one of claims 1-40.
42. The isolated polynucleotide of claim 41, wherein the nucleic acid molecule encodes the VH of SEQ ID NO:28, 30, 32, or 34.
43. An isolated polynucleotide comprising a nucleic acid molecule encoding the light chain variable region or light chain of the antibody or antigen-binding fragment thereof of any one of claims 1-40.
44. The isolated polynucleotide of claim 43, wherein the nucleic acid molecule encodes the VL of SEQ ID NO:29, 31, 33, or 35.
45. An isolated polynucleotide comprising a nucleic acid molecule encoding the heavy chain variable region or heavy chain of the antibody or antigen-binding fragment thereof of any one of claims 1-35 and the light chain variable region or light chain of the antibody or antigen-binding fragment thereof of any one of claims 1-40.
46. An isolated vector comprising the polynucleotide of any one of claims 41-45.
47. A host cell comprising (a) the polynucleotide of any one of claims 41-45, (b) the vector of claim 46, or (c) a first vector comprising the polynucleotide of claim 41 or 42 and a second vector comprising the polynucleotide of claim 43 or 44.
48. The host cell of claim 47, which is selected from the group consisting of *E. coli*, *Pseudomonas*, *Bacillus*, *Streptomyces*, yeast, CHO, YB/20, NS0, PER-C6, HEK-293T, NIH-3T3, HeLa, BHK, Hep G2, SP2/0, R1.1, B-W, L-M, COS 1, COS 7, BSC1, BSC40, BMT10 cell, plant cell, insect cell, and human cell in tissue culture.

49. A method of producing an antibody or antigen-binding fragment thereof that binds to human PILRA comprising culturing the host cell of claim 47 or 48 so that the nucleic acid molecule is expressed and the antibody or antigen-binding fragment thereof is produced, optionally wherein the method further comprises isolating the antibody or antigen-binding fragment thereof from the culture.
50. An isolated antibody or antigen-binding fragment thereof that specifically binds to human PILRA and is encoded by the polynucleotide of any one of claims 41-45 or produced by the method of claim 49.
51. A pharmaceutical composition comprising the antibody or antigen-binding fragment thereof of any one of claims 1-40 and 50 and a pharmaceutically acceptable excipient.
52. A method for downregulating cell surface PILRA comprising contacting a cell expressing PILRA on its surface with the antibody or antigen-binding fragment thereof of any one of claims 1-40 and 50 or the pharmaceutical composition of claim 51.
53. A method for inhibiting binding of PILRA to a PILRA ligand comprising contacting PILRA with the antibody or antigen-binding fragment thereof of any one of claims 1-40 and 50 or the pharmaceutical composition of claim 51 in the presence of the PILRA ligand, optionally wherein the PILRA and/or the PILRA ligand is expressed on a cell.
54. The method of claim 53, wherein the PILRA ligand is NPDC1 and/or wherein the PILRA ligand is expressed on a T cell.
55. A method for increasing myeloid cell activation comprising contacting the myeloid cell with the antibody or antigen-binding fragment thereof of any one of claims 1-40 and 50 or the pharmaceutical composition of claim 51.
56. A method for promoting myeloid cell differentiation comprising contacting the myeloid cell with the antibody or antigen-binding fragment thereof of any one of claims 1-40 and 50 or the pharmaceutical composition of claim 51.

57. A method for increasing myeloid cell production of MIP1b comprising contacting the myeloid cell with the antibody or antigen-binding fragment thereof of any one of claims 1-40 and 50 or the pharmaceutical composition of claim 51.
58. The method of any one of claims 52-57, wherein the contacting is *in vitro*.
59. The method of any one of claims 52-57, wherein the contacting is in a subject.
60. A method of treating cancer in a patient, the method comprising administering to the patient a therapeutically effective amount of the antibody or antigen binding fragment thereof of any one of claims 1-40 and 50 or the pharmaceutical composition of claim 51.
61. The method of claim 60, wherein the cancer is a solid tumor in which myeloid cells have infiltrated the tumor microenvironment.
62. The method of claim 60 or claim 61, wherein the cancer is selected from glioblastoma, head and neck cancer, kidney cancer (optionally wherein the kidney cancer is kidney clear cell cancer), pancreatic cancer, and breast cancer.
63. The method of any one of claims 60-62, further comprising administering an antagonist of an inhibitory immune checkpoint molecule, optionally wherein the immune checkpoint molecule is PD-1 or PD-L1.
64. The method of claim 63, wherein the antagonist is an antagonist of PD-1, which is an anti-PD-1 antibody or antigen-binding fragment thereof, optionally wherein the anti-PD-1 antibody or antigen-binding fragment thereof is selected from the group consisting of nivolumab, pembrolizumab, MEDI-0680 (AMP-514), camrelizumab (SHR-1210), tislelizumab (BGB-A317), and spartalizumab (NPVPDR001, NVS240118, PDR001).
65. The method of claim 63, wherein the antagonist is an antagonist of PD-L1, which is an anti-PD-L1 antibody or antigen-binding fragment thereof, optionally wherein the anti-PD-L1 antibody or antigen-binding fragment thereof is selected from the group consisting of atezolizumab, durvalumab (MEDI4736), BMS-936559, MSB0010718C and rHigM12B7.

66. The method of any one of claims 63-65, wherein the antibody or antigen-binding fragment thereof that specifically binds to human PILRA and the antagonist of the inhibitory immune checkpoint molecule are administered simultaneously.
67. The method of any one of claims 63-65, wherein the antibody or antigen-binding fragment thereof that specifically binds to human PILRA and the antagonist of the inhibitory immune checkpoint molecule are administered sequentially.
68. A method of treating a disease or condition in which myeloid cells are dysfunctional or deficient in a patient, the method comprising administering to the patient a therapeutically effective amount of the antibody or antigen binding fragment thereof of any one of claims 1-40 and 50 or the pharmaceutical composition of claim 51.
69. The method of claim 68, wherein the disease or condition is a neurodegenerative disease.
70. The method of claim 69, wherein the neurodegenerative disease is Alzheimer's disease, optionally wherein the patient carries the G78 variant of PILRA.
71. A method of activating the innate immune system in a patient, the method comprising administering to the patient an effective amount of the antibody or antigen binding fragment thereof of any one of claims 1-40 and 50 or the pharmaceutical composition of claim 51.
72. A method for detecting PILRA in a sample comprising contacting the sample with the antibody or antigen-binding fragment thereof of any one of claims 1-40 and 50 or the pharmaceutical composition of claim 51.
73. The method of claim 72, wherein the sample is obtained from a human subject, optionally wherein the sample is a cancer sample.
74. The method of claim 55, wherein the myeloid cell activation is Fc receptor-mediated.