

I/WE CLAIM:

1. An isolated antibody or antibody fragment which binds to human PD-1, comprising:
light chain CDRs of SEQ ID NOs: 15, 16 and 17 and
heavy chain CDRs of SEQ ID NOs: 18, 19 and 20,
wherein said antibody or antibody fragment blocks binding of human PD-L1 and human PD-L2 to human PD-1.
2. The isolated antibody or antibody fragment of claim 1, comprising:
 - a. a heavy chain variable region comprising an amino acid sequence selected from the group consisting of:
 - i. SEQ ID NO: 7 or a variant thereof, wherein said variant has heavy chain CDRs of SEQ ID NOs: 18, 19 and 20 and comprises one, two or three conservatively modified amino acid substitutions;
 - ii. amino acid residues 20 to 139 of SEQ ID NO: 30 or a variant thereof, wherein said variant has heavy chain CDRs of SEQ ID NOs: 18, 19 and 20 and comprises one, two or three conservatively modified amino acid substitutions; and
 - iii. an amino acid sequence having heavy chain CDRs of SEQ ID NOs: 18, 19 and 20 and at least 90% homology to amino acid residues 20 to 139 of SEQ ID NO: 30;and further comprising
 - b. a light chain variable region comprising an amino acid sequence selected from the group consisting of:
 - i. SEQ ID NO: 8 or a variant thereof, wherein said variant has light chain CDRs of SEQ ID NOs: 15, 16 and 17 and comprises one, two or three conservatively modified amino acid substitutions;
 - ii. amino acid residues 20 to 130 of SEQ ID NO: 32 or a variant thereof, wherein said variant has light chain CDRs of SEQ ID NOs: 15, 16 and 17 and comprises one, two or three conservatively modified amino acid substitutions;
 - iii. amino acid residues 20 to 130 of SEQ ID NO: 33 or a variant thereof, wherein said variant has light chain CDRs of SEQ ID NOs: 15, 16 and 17 and comprises one, two or three conservatively modified amino acid substitutions;
 - iv. amino acid residues 20 to 130 of SEQ ID NO: 34 or a variant thereof, wherein said variant has light chain CDRs of SEQ ID NOs: 15, 16 and 17 and comprises one, two or three conservatively modified amino acid substitutions; and

v. an amino acid sequence having light chain CDRs of SEQ ID NOs: 15, 16 and 17 and at least 90% homology to amino acid residues 20 to 130 of SEQ ID NO: 32, 33 or 34.

3. The isolated antibody of claim 1, comprising:

a. a heavy chain comprising an amino acid sequence selected from the group consisting of:

i. amino acid residues 20 to 466 of SEQ ID NO: 31, and

ii. amino acid residues 20 to 469 of SEQ ID NO: 35; and

b. a light chain comprising an amino acid sequence selected from the group consisting of:

i. amino acid residues 20 to 237 of SEQ ID NO: 36;

ii. amino acid residues 20 to 237 of SEQ ID NO: 37, and

iii. amino acid residues 20 to 237 of SEQ ID NO: 38.

4. An isolated antibody or antibody fragment of claim 2, which binds to human PD-1, comprising

a. a heavy chain variable region comprising amino acid residues 20 to 139 of SEQ ID NO: 30; and

b. a light chain variable region comprising an amino acid sequence selected from the group consisting of:

i. amino acid residues 20 to 130 of SEQ ID NO: 32;

ii. amino acid residues 20 to 130 of SEQ ID NO: 33; and

iii. amino acid residues 20 to 130 of SEQ ID NO: 34.

5. An isolated antibody of claim 3, which binds to human PD-1 comprising:

a. a heavy chain comprising amino acid residues 20 to 466 of SEQ ID NO: 31; and

b. a light chain comprising amino acid residues 20 to 237 of SEQ ID NO: 36.

6. The isolated antibody of any of claims 1, 2 or 4, further comprising heavy chain constant region comprising a $\gamma 4$ or $\gamma 1$ human heavy chain constant region.

7. The isolated antibody or antibody fragment of any of claims 1 to 6, wherein the antibody or antibody fragment:

a. binds human PD-1 with a K_D of about 100 pM or lower;

b. binds human PD-1 with a K_D of about 30 pM or lower;

- c. binds to human PD-1 with about the same K_D as an antibody having a heavy chain comprising the amino acid sequence of SEQ ID NO: 31 and a light chain comprising the amino acid sequence of SEQ ED NO: 32;
- d. binds to human PD-1 with about the same K_D as an antibody having a heavy chain comprising the amino acid sequence of SEQ ED NO: 31 and a light chain comprising the amino acid sequence of SEQ ED NO: 33;
- e. binds to human PD-1 with a k_{assoc} of about 7.5×10^5 l/M s or faster;
- f. binds to human PD-1 with a k_{assoc} of about 1×10^6 l/ M s or faster;
- g. binds to human PD-1 with a k_{assoc} of about 2×10^{-5} 1/s or slower;
- h. binds to human PD-1 with a k_{assoc} of about 2.7×10^{-5} 1/s or slower;
- i. binds to human PD-1 with a k_{assoc} of about 3×10^{-5} 1/s or slower; or
- j. blocks binding of human PD-L1 or human PD-L2 to human PD-1 with an IC_{50} of about 1 nM or lower.

8. The isolated antibody or antibody fragment of any one of claims 1 to 7, wherein the antibody or antibody fragment is:

- a. a chimeric antibody or a fragment thereof; or
- b. a humanized antibody or a fragment thereof.

9. The isolated antibody or antibody fragment of any one of claims 1, 2, 4, 6 and 8, wherein the antibody fragment is selected from the group consisting of Fab, Fab', Fab'- SH, F(ab')₂, and a diabody.

10. An isolated polynucleotide encoding an antibody or antibody fragment which binds to human programmed death receptor 1 (PD-1), comprising SEQ ID NOs: 21, 22, 23, 24 and 27.

11. An expression vector comprising the polynucleotide of claim 10.

12. A method of producing an antibody or antibody fragment according to any one of claims 1 to 10 comprising:

- a. culturing a host cell comprising the expression vector of claim 11, wherein the host cell is cultured in culture medium under conditions wherein the polynucleotide is expressed, thereby producing polypeptides comprising the light and heavy chain variable regions of the antibody or antibody fragment; and

b. recovering the polypeptides from the host cell or culture medium.

13. A composition comprising the antibody or antibody fragment of any one of claims 1 to 9 in combination with a pharmaceutically acceptable carrier or diluent.

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To
The Controller of Patents
The Patent Office, at **Chennai**