

Claims

1. An antibody, or a variant of said antibody that maintains the binding specificity of the antibody that comprises:
 - 5 - a variable domain that can bind to an extracellular part of a protein of the CD28 family (first membrane protein); and
 - a variable domain that can bind to an extracellular part of a protein of the B7 family (second membrane protein),
 wherein said first and second membrane proteins are binding partners (i.e. a ligand and
 10 receptor pair), and wherein the binding of the variable domain that can bind to an extracellular part of said first membrane protein blocks the binding of said first membrane protein to said second membrane protein and/or the binding of the variable domain that can bind to an extracellular part of said second membrane protein blocks the binding of said first membrane protein to said second membrane protein; and
 15 wherein the antibody, or a variant of said antibody has a stronger T cell activation potential in a Staphylococcus enterotoxin B (SEB) assay as compared to an equimolar mix of:
 - bivalent monospecific antibody that comprises two of said variable domains that bind to an extracellular part of a protein of the CD28 family (first membrane
 20 protein), and
 - bivalent monospecific antibody that comprises two of said variable domains that bind to an extracellular part of a protein of the B7 family (second membrane protein).
- 25 2. The antibody or variant thereof of claim 1, wherein the binding of the antibody or variant thereof reduces an inhibitory activity of the binding of the receptor-ligand pair.
3. The antibody or variant thereof of claim 1 or claim 2, that comprises:
 - a variable domain that can bind to an extracellular part of PD-1; CTLA-4;
 30 BTLA; or TMIGD2; and
 - a variable domain that can bind to an extracellular part of PD-L1; PD-L2; CD80; CD86; B7-H4; TNFRSF14; or B7-H7.
4. The antibody or variant thereof of claim 3, that comprises:
 35 - a variable domain that can bind to an extracellular part of PD-1; and

- a variable domain that can bind to an extracellular part of PD-L1 or PD-L2.

5. The antibody or variant thereof of claim 3 or claim 4, wherein the binding of the variable domain that binds PD-1 blocks the binding of PD-1 to PD-L1 and/or the binding of the variable domain that binds PD-L1 blocks the binding of PD-L1 to PD-1.

6. The antibody or variant thereof of claim 5, wherein the binding of the variable domain that binds PD-1 blocks the binding of PD-1 to PD-L1 and the binding of the variable domain that binds PD-L1 blocks the binding of PD-L1 to PD-1.

7. The antibody or variant thereof of any one of claims 1-6, that comprises a variable domain that can bind to an extracellular part of PD-1, wherein the binding of said variable domain to PD-1 blocks the binding of PD-1 to PD-L2.

8. The antibody or variant thereof of any one of claims 1-7, that comprises a variable domain that can bind to an extracellular part of PD-L1, wherein the binding of said variable domain to PD-L1 blocks the binding of PD-L1 to CD80.

9. The antibody or variant thereof of any one of claims 1-8, that comprises a variable domain that can bind to an extracellular part of PD-1 and a variable domain that can bind to an extracellular part of PD-L1, and that is able to activate T cells in an antigen-specific CD4⁺ T cell assay more strongly than benchmark antibody 5C4 or benchmark antibody YW243.55.S70 or a combination of benchmark antibodies 5C4 and YW243.55.S70.

10. The antibody or variant thereof of any one of claims 1-9, that comprises a variable domain that can bind to an extracellular part of PD-1 and a variable domain that can bind to an extracellular part of PD-L1, and that has a stronger CD4⁺ T cell activation potential in a mixed lymphocyte reaction (MLR) assay as compared to benchmark antibody 5C4 or benchmark antibody YW243.55.S70.

11. The antibody or variant thereof of any one of claims 1-10, that comprises a variable domain that has a binding affinity for an extracellular part of PD-L1 with an equilibrium dissociation constant (K_D) of lower than or equal to 4.27 nM, preferably of

lower than or equal to 1.31 nM, preferably of lower than or equal to 1.27 nM, as measured by SPR.

12. The antibody or variant thereof of any one of claims 1-11, that comprises a variable domain that can bind to an extracellular part of PD-1 and a variable domain that can bind to an extracellular part of PD-L1, and that is capable of enhancing the proliferation of CD4⁺ and/or CD8⁺ tumor-infiltrating T cells.

13. The antibody or variant thereof of any one of claims 1-12, that comprises a variable domain that can bind to an extracellular part of PD-1 and a variable domain that can bind to an extracellular part of PD-L1, and that is capable of inducing a stronger T cell mediated anti-tumor response *in vivo* as compared to a combination of benchmark antibodies MK-3475 and YW243.55.S70.

14. The antibody or variant thereof of any one of claims 3-13, wherein the variable domain that binds an extracellular part of PD-1 is defined as a variable domain that when in a bivalent monospecific antibody format that comprises two of said variable domains that bind PD-1, inhibits PD-1/PD-L1 mediated inhibition of T cell receptor mediated activation of a Jurkat cell in a range of 20-150% when compared to the inhibition obtained with the antibody Nivolumab on a Jurkat cell.

15. The antibody or variant thereof of any one of claims 3-14, wherein the variable domain that binds an extracellular part of PD-L1 is defined as a variable domain that when in a bispecific antibody that has a second variable domain that binds an irrelevant antigen such as Tetanus Toxoid, provides the bispecific antibody with a K_d of 0.1-14 nM for PD-L1 binding (as measured by biacore).

16. The antibody or variant thereof of any one of claims 1-15, that comprises a variable domain that can bind to an extracellular part of PD-1, wherein said variable domain that binds PD-1 comprises a heavy chain variable region with a CDR1, CDR2 and CDR3 region that comprises the amino acid sequence of the CDR1, CDR2 and CDR3 of a variable heavy chain region of one of the VH depicted for MF6076; MF6236; MF6256; MF6226; MF6930; MF6932; MF6935; MF6936; MF6972; MF6974; MF6982; MF6929; MF7699; MF7698; MF7687; MF7686; MF7685; or MF7684 in figure 3 and/or figure 13,;

and wherein the variable domain that binds PD-1 comprises a light chain comprising a light chain variable region CDR1 comprising sequence QSISSY, CDR2 comprising sequence AAS and CDR3 comprising sequence QQSYSTPPT.

5 17. An antibody or variant thereof of claim 16, that comprises a variable domain that can bind to an extracellular part of PD-1 and comprises a heavy chain variable region that comprises the amino acid sequence of the variable heavy chain region as depicted for MF6076; MF6236; MF6256; MF6226; MF6930; MF6932; MF6935; MF6936; MF6972; MF6974; MF6982; MF6929; MF7699; MF7698; MF7687; MF7686; MF7685; or MF7684
10 (as depicted in figure 3 and/or figure 13) having at most 15, preferably 0, 1, 2, 3, 4, 5, 6, 7, 8, 9 or 10 and preferably having 0, 1, 2, 3, 4 or 5 amino acid insertions, deletions, substitutions or a combination thereof with respect to the amino acid sequence of the VH for the aforementioned antibodies indicated by their MF designation, wherein said insertions, deletions, or substitutions or a combination thereof are not in the CDR1,
15 CDR2 or CDR3 of the variable heavy chain region.

18. An antibody or variant thereof of any one of claims 1-17, that comprises a variable domain that can bind to an extra-cellular part of PD-L1 and that comprises a heavy chain variable region with a CDR1, CDR2 and CDR3 region that comprises the amino acid sequence of the CDR1, CDR2 and CDR3 of a variable heavy chain region of one of the VH depicted for MF5359; MF5361; MF5377; MF5382; MF5424; MF5426; MF5439; MF5442; MF5553; MF5557; MF5561; MF5576; MF5594; MF5708; MF5442; MF7691; MF7690; MF7689; MF7688; MF7700; MF7701; MF7703; MF7694; MF7693; MF7692; MF7697; MF7696; or MF7695 of Figure 3 and/or figure 13,;

25 and wherein the variable domain that can bind to an extra-cellular part of PD-L1 comprises a light chain comprising a light chain variable region CDR1 comprising sequence QSISSY, CDR2 comprising sequence AAS and CDR3 comprising sequence QQSYSTPPT.

30 19. An antibody or variant thereof of claim 18, that comprises a variable domain that can bind to an extra cellular part of PD-L1 and comprises a heavy chain variable region that comprises the amino acid sequence of the variable heavy chain region as depicted for MF5359; MF5361; MF5377; MF5382; MF5424; MF5426; MF5439; MF5442; MF5553; MF5557; MF5561; MF5576; MF5594; MF5708; MF5442; MF7691; MF7690; MF7689; MF7688; MF7700; MF7701; MF7703; MF7694; MF7693; MF7692; MF7697; MF7696; or
35 MF7688; MF7700; MF7701; MF7703; MF7694; MF7693; MF7692; MF7697; MF7696; or

MF7695 (of Figure 3 and/or figure 13) having at most 15, preferably 0, 1, 2, 3, 4, 5, 6, 7, 8, 9 or 10 and preferably having 0, 1, 2, 3, 4 or 5 amino acid insertions, deletions, substitutions or a combination thereof with respect to the amino acid sequence of the aforementioned antibodies indicated by their MF designation, wherein said insertions, deletions, or substitutions or a combination thereof are not in the CDR1, CDR2 or CDR3 of the variable heavy chain region.

20. The antibody or variant thereof of any one of claims 16-19, that comprises a variable domain that can bind to an extracellular part of PD-1 and wherein said variable domain that can bind to an extracellular part of PD-1 comprises:

- heavy chain CDR1, CDR2 and CDR3 sequences that are identical to the heavy chain CDR1, CDR2 and CDR3 sequences of a variable region selected from the group consisting of MF6974, MF6076 and MF7686 and
- a light chain variable region CDR1 comprising sequence QSISSY, CDR2 comprising sequence AAS and CDR3 comprising sequence QQSYSTPPT.

21. The antibody or variant thereof of claim 20 that comprises a variable domain that can bind to an extracellular part of PD-1 and wherein said variable domain that can bind to an extracellular part of PD-1 comprises:

- a heavy chain variable region that comprises the amino acid sequence of MF6974 or MF6076 or MF7686, or
- a heavy chain variable region having a sequence that is at least 90% identical to the amino acid sequence of MF6974 or MF6076 or MF7686, and comprises the CDR1, CDR2, and CDR3 sequences of the heavy chain variable region of MF6974 or MF6076 or MF7686.

22. An antibody, or variant thereof that maintains the binding specificity of the antibody, that comprises a variable domain that can bind to an extracellular part of PD-1 and a variable domain that can bind to an extracellular part of PD-L1 or PD-L2, wherein said variable domain that can bind to an extracellular part of PD-1 comprises: a heavy chain comprising heavy chain CDR1, CDR2 and CDR3 sequences that are identical to the heavy chain CDR1, CDR2 and CDR3 sequences of MF6974, and a light chain variable region CDR1 comprising sequence QSISSY, CDR2 comprising sequence AAS and CDR3 sequence comprising QQSYSTPPT.

23. An antibody or variant thereof that maintains the binding specificity of the antibody, that comprises a variable domain that can bind to an extracellular part of PD-1 and a variable domain that can bind to an extracellular part of PD-L1 or PD-L2, wherein said variable domain that can bind to an extracellular part of PD-1 comprises:
- 5 a heavy chain comprising heavy chain CDR1, CDR2 and CDR3 sequences that are identical to the heavy chain CDR1, CDR2 and CDR3 sequences of MF6076, and a light chain variable region CDR1 sequence comprising QSISSY, CDR2 sequence comprising AAS and CDR3 sequence comprising QQSYSTPPT.
- 10 24. An antibody or variant thereof that maintains the binding specificity of the antibody, that comprises a variable domain that can bind to an extracellular part of PD-1 and a variable domain that can bind to an extracellular part of PD-L1 or PD-L2, and wherein said variable domain that can bind to an extracellular part of PD-1 comprises:
- 15 a heavy chain comprising heavy chain CDR1, CDR2 and CDR3 sequences that are identical to the heavy chain CDR1, CDR2 and CDR3 sequences of MF7686, and a light chain variable region CDR1 sequence comprising QSISSY, CDR2 sequence comprising AAS and CDR3 sequence comprising QQSYSTPPT.
25. The antibody or variant thereof of any one of claims 16-24, that comprises a
- 20 variable domain that can bind to an extracellular part of PD-L1 and wherein said variable domain that can bind to an extracellular part of PD-L1 comprises:
- heavy chain CDR1 and CDR2 and CDR3 sequences that are identical to the heavy chain CDR1 and CDR2 and CDR3 sequences of a variable region selected from the group consisting of MF7689 and MF7703 and
 - 25 - a light chain variable region CDR1 comprising sequence QSISSY, CDR2 comprising sequence AAS and CDR3 comprising sequence QQSYSTPPT.
26. The antibody or variant thereof of claim 25 that comprises a variable domain that can bind to an extracellular part of PD-L1 and wherein said variable domain that
- 30 can bind to an extracellular part of PD-L1 comprises:
- a heavy chain variable region that comprises the amino acid sequence of MF7689 or MF7703, or
 - a heavy chain variable region having a sequence that is at least 90% identical to the amino acid sequence of MF7689 or MF7703, and comprises the CDR1, CDR2, and CDR3
 - 35 sequences of the heavy chain variable region of MF7689 or MF7703.

27. An antibody or variant thereof that maintains the binding specificity of the antibody, that comprises a variable domain that can bind to an extracellular part of PD-1 and a variable domain that can bind to an extracellular part of PD-L1, and wherein
 5 said variable domain that can bind to an extracellular part of PD-L1 comprises:
 a heavy chain comprising heavy chain CDR1, CDR2 and CDR3 sequences that are identical to the heavy chain CDR1, CDR2 and CDR3 sequences MF7689,
 and a light chain variable region CDR1 sequence comprising QSISSY, CDR2 sequence comprising AAS and CDR3 sequence comprising QQSYSTPPT.

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28. An antibody or variant thereof that maintains the binding specificity of the antibody, that comprises a variable domain that can bind to an extracellular part of PD-1 and a variable domain that can bind to an extracellular part of PD-L1, and wherein
 15 said variable domain that can bind to an extracellular part of PD-L1 comprises:
 a heavy chain CDR1, CDR2 and CDR3 sequences that are identical to the heavy chain CDR1, CDR2 and CDR3 sequences MF7703,
 and a light chain variable region CDR1 sequence comprising QSISSY, CDR2 sequence comprising AAS and CDR3 sequence comprising QQSYSTPPT.

20 29. The antibody or variant thereof of any one of claims 16-28 that comprises a variable domain that can bind to an extracellular part of PD-L1 and a variable domain that can bind to an extracellular part of PD-1,

wherein said variable domain that can bind to an extracellular part of PD-L1 comprises a heavy chain variable region that comprises the amino acid sequence of
 25 MF7689 having at most 15, preferably 0, 1, 2, 3, 4, 5, 6, 7, 8, 9 or 10 and preferably having 0, 1, 2, 3, 4 or 5 amino acid insertions, deletions, substitutions or a combination thereof with respect to the amino acid sequence of the aforementioned antibodies indicated by their MF designation, wherein said insertions, deletions, or substitutions or a combination thereof are not in the CDR1, CDR2 or CDR3 of the variable heavy chain
 30 region;

wherein the variable domain that can bind to an extracellular part of PD-1 comprises a heavy chain variable region that comprises the amino acid sequence of MF6974 having at most 15, preferably 0, 1, 2, 3, 4, 5, 6, 7, 8, 9 or 10 and preferably
 35 having 0, 1, 2, 3, 4 or 5 amino acid insertions, deletions, substitutions or a combination thereof with respect to the amino acid sequence of the aforementioned antibodies

indicated by their MF designation, wherein said insertions, deletions, or substitutions or a combination thereof are not in the CDR1, CDR2 or CDR3 of the variable heavy chain region, and

wherein the antibody or variant thereof comprises a light chain variable region CDR1 comprising sequence QSISSY, CDR2 comprising sequence AAS and CDR3 comprising sequence QQSYSTPPT.

30. The antibody or variant thereof of any one of claims 16-28 that comprises a variable domain that can bind to an extracellular part of PD-L1 and a variable domain that can bind to an extracellular part of PD-1,

wherein said variable domain that can bind to an extracellular part of PD-L1 comprises a heavy chain variable region that comprises the amino acid sequence of MF7689 having at most 15, preferably 0, 1, 2, 3, 4, 5, 6, 7, 8, 9 or 10 and preferably having 0, 1, 2, 3, 4 or 5 amino acid insertions, deletions, substitutions or a combination thereof with respect to the amino acid sequence of the aforementioned antibodies indicated by their MF designation, wherein said insertions, deletions, or substitutions or a combination thereof are not in the CDR1, CDR2 or CDR3 of the variable heavy chain region;

wherein the variable domain that can bind to an extracellular part of PD-1 comprises a heavy chain variable region that comprises the amino acid sequence of MF7686 having at most 15, preferably 0, 1, 2, 3, 4, 5, 6, 7, 8, 9 or 10 and preferably having 0, 1, 2, 3, 4 or 5 amino acid insertions, deletions, substitutions or a combination thereof with respect to the amino acid sequence of the aforementioned antibodies indicated by their MF designation, wherein said insertions, deletions, or substitutions or a combination thereof are not in the CDR1, CDR2 or CDR3 of the variable heavy chain region, and

wherein the antibody or variant thereof comprises a light chain variable region CDR1 comprising sequence QSISSY, CDR2 comprising sequence AAS and CDR3 comprising sequence QQSYSTPPT.

31. The antibody or variant thereof of any one of claims 16-28 that comprises a variable domain that can bind to an extracellular part of PD-L1 and a variable domain that can bind to an extracellular part of PD-1,

wherein said variable domain that can bind to an extracellular part of PD-L1 comprises a heavy chain variable region that comprises the amino acid sequence of MF7689 having at most 15, preferably 0, 1, 2, 3, 4, 5, 6, 7, 8, 9 or 10 and preferably

having 0, 1, 2, 3, 4 or 5 amino acid insertions, deletions, substitutions or a combination thereof with respect to the amino acid sequence of the aforementioned antibodies indicated by their MF designation, wherein said insertions, deletions, or substitutions or a combination thereof are not in the CDR1, CDR2 or CDR3 of the variable heavy chain region;

wherein the variable domain that can bind to an extracellular part of PD-1 comprises a heavy chain variable region that comprises the amino acid sequence of MF6076 having at most 15, preferably 0, 1, 2, 3, 4, 5, 6, 7, 8, 9 or 10 and preferably having 0, 1, 2, 3, 4 or 5 amino acid insertions, deletions, substitutions or a combination thereof with respect to the amino acid sequence of the aforementioned antibodies indicated by their MF designation, wherein said insertions, deletions, or substitutions or a combination thereof are not in the CDR1, CDR2 or CDR3 of the variable heavy chain region, and

wherein the antibody or variant thereof comprises a light chain variable region CDR1 comprising sequence QSISSY, CDR2 comprising sequence AAS and CDR3 comprising sequence QQSYSTPPT.

32. The antibody or variant thereof of any one of claims 16-28 that comprises a variable domain that can bind to an extracellular part of PD-L1 and a variable domain that can bind to an extracellular part of PD-1,

wherein said variable domain that can bind to an extracellular part of PD-L1 comprises a heavy chain variable region that comprises the amino acid sequence of MF7703 having at most 15, preferably 0, 1, 2, 3, 4, 5, 6, 7, 8, 9 or 10 and preferably having 0, 1, 2, 3, 4 or 5 amino acid insertions, deletions, substitutions or a combination thereof with respect to the amino acid sequence of the aforementioned antibodies indicated by their MF designation, wherein said insertions, deletions, or substitutions or a combination thereof are not in the CDR1, CDR2 or CDR3 of the variable heavy chain region;

wherein the variable domain that can bind to an extracellular part of PD-1 comprises a heavy chain variable region that comprises the amino acid sequence of MF6974 having at most 15, preferably 0, 1, 2, 3, 4, 5, 6, 7, 8, 9 or 10 and preferably having 0, 1, 2, 3, 4 or 5 amino acid insertions, deletions, substitutions or a combination thereof with respect to the amino acid sequence of the aforementioned antibodies indicated by their MF designation, wherein said insertions, deletions, or substitutions or

a combination thereof are not in the CDR1, CDR2 or CDR3 of the variable heavy chain region, and

wherein the antibody or variant thereof comprises a light chain variable region CDR1 comprising sequence QSISSY, CDR2 comprising sequence AAS and CDR3
5 comprising sequence QQSYSTPPT.

33. The antibody or variant thereof of any one of claims 16-28 that comprises a variable domain that can bind to an extracellular part of PD-L1 and a variable domain that can bind to an extracellular part of PD-1,

10 wherein said variable domain that can bind to an extracellular part of PD-L1 comprises a heavy chain variable region that comprises the amino acid sequence of MF7703 having at most 15, preferably 0, 1, 2, 3, 4, 5, 6, 7, 8, 9 or 10 and preferably having 0, 1, 2, 3, 4 or 5 amino acid insertions, deletions, substitutions or a combination thereof with respect to the amino acid sequence of the aforementioned antibodies
15 indicated by their MF designation, wherein said insertions, deletions, or substitutions or a combination thereof are not in the CDR1, CDR2 or CDR3 of the variable heavy chain region;

wherein the variable domain that can bind to an extracellular part of PD-1 comprises a heavy chain variable region that comprises the amino acid sequence of
20 MF7686 having at most 15, preferably 0, 1, 2, 3, 4, 5, 6, 7, 8, 9 or 10 and preferably having 0, 1, 2, 3, 4 or 5 amino acid insertions, deletions, substitutions or a combination thereof with respect to the amino acid sequence of the aforementioned antibodies indicated by their MF designation, wherein said insertions, deletions, or substitutions or a combination thereof are not in the CDR1, CDR2 or CDR3 of the variable heavy chain
25 region, and

wherein the antibody or variant thereof comprises a light chain variable region CDR1 comprising sequence QSISSY, CDR2 comprising sequence AAS and CDR3 comprising sequence QQSYSTPPT.

30 34. The antibody or variant thereof of any one of claims 16-28 that comprises a variable domain that can bind to an extracellular part of PD-L1 and a variable domain that can bind to an extracellular part of PD-1,

wherein said variable domain that can bind to an extracellular part of PD-L1
35 comprises a heavy chain variable region that comprises the amino acid sequence of MF7703 having at most 15, preferably 0, 1, 2, 3, 4, 5, 6, 7, 8, 9 or 10 and preferably

having 0, 1, 2, 3, 4 or 5 amino acid insertions, deletions, substitutions or a combination thereof with respect to the amino acid sequence of the aforementioned antibodies indicated by their MF designation, wherein said insertions, deletions, or substitutions or a combination thereof are not in the CDR1, CDR2 or CDR3 of the variable heavy chain region;

wherein the variable domain that can bind to an extracellular part of PD-1 comprises a heavy chain variable region that comprises the amino acid sequence of MF6076 having at most 15, preferably 0, 1, 2, 3, 4, 5, 6, 7, 8, 9 or 10 and preferably having 0, 1, 2, 3, 4 or 5 amino acid insertions, deletions, substitutions or a combination thereof with respect to the amino acid sequence of the aforementioned antibodies indicated by their MF designation, wherein said insertions, deletions, or substitutions or a combination thereof are not in the CDR1, CDR2 or CDR3 of the variable heavy chain region, and

wherein the antibody or variant thereof comprises a light chain variable region CDR1 comprising sequence QSISSY, CDR2 comprising sequence AAS and CDR3 comprising sequence QQSYSTPPT.

35. The antibody or variant thereof of any one of claims 16-34 which comprises a light chain variable region having a sequence that is at least 80% identical to the amino acid sequence as depicted in Figure 1B, comprising light chain variable region CDR1 comprising sequence QSISSY, CDR2 comprising sequence AAS and CDR3 comprising sequence QQSYSTPPT.

36. The antibody or variant thereof of any one of claims 1-35, wherein the antigen binding sites of said antibody or variant thereof consist of one immunoglobulin variable domain that can bind an extracellular part of PD-1 and one immunoglobulin variable domain that can bind an extracellular part of PD-L1 or PD-L2.

37. The antibody of any one of claims 1-36, wherein said antibody is a full length bispecific antibody.

38. The antibody of any one of claims 1-37, wherein said antibody is an IgG.

39. A method of inhibiting a biological activity in a first or second cell mediated by the binding of a member of the CD28 family (first membrane protein) and

on a first cell to a member of the B7 family (second membrane protein) on a second cell, wherein said first and second membrane protein are binding partners (i.e. a ligand and receptor pair), the method comprising

- providing a system comprising said first and second cell with an antibody
5 or a variant of said antibody that maintains the binding specificity of the antibody comprising a variable domain that can bind to an extracellular part of said first membrane protein and a variable domain that can bind to an extracellular part of said second membrane protein; and

- incubating said system under conditions that are permissive for the first
10 or second cell to express said biological activity mediated by the binding of said first membrane protein to said second membrane protein in the absence of said antibody or variant thereof;

- wherein the binding of the variable domain that can bind to an
15 extracellular part of said first membrane protein blocks the binding of said first membrane protein to said second membrane protein and/or the binding of the variable domain that can bind to an extracellular part of said second membrane protein blocks the binding of said first membrane protein to said second membrane protein, wherein said antibody or variant thereof is an antibody or variant thereof of any one of claims 1-38.

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40. The method of claim 39, wherein the binding of the antibody or variant thereof reduces an inhibitory activity of the binding of the receptor-ligand pair in said first cell.

41. A method for producing an antibody or variant thereof of any one of claims 1-38
25 from a single cell, wherein said antibody or variant thereof comprises two CH3 domains that are capable of forming an interface, said method comprising providing:

- a cell having a) a first nucleic acid molecule encoding a IgG heavy chain that specifically recognizes an extracellular part of a protein of the CD28 family, preferably PD-1, and that contains a 1st CH3 domain, and b) a second nucleic acid sequence
30 encoding a IgG heavy chain that specifically recognizes an extracellular part of a protein of the B7 family, preferably PD-L1, and that contains a 2nd CH3 domain, wherein said nucleic acid sequences are provided with mutations for preferential pairing of said 1st and 2nd CH3 domains, said method further comprising the step of culturing said cell and allowing for expression of said nucleic acid sequences and harvesting said antibody
35 or variant thereof from the culture.

42. A method according to claim 41, wherein said cell has a third nucleic acid sequence encoding a common light chain, preferably the rearranged germline human kappa light chain IgV κ 1-39*01/IGJ κ 1*01.

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43. A method according to claim 41 or 42, wherein said first CH3 domain comprises the amino acid substitutions L351K and T366K (numbering according to the EU numbering) and wherein said second CH3 domain comprises the amino acid substitutions L351D and L368E (numbering according to the EU numbering), said
10 method further comprising the step of culturing said cell and allowing for expression of said nucleic acid sequences and harvesting said antibody or variant thereof from the culture.

44. An antibody or variant thereof of any one of claims 1-38 for use as a medicament.

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45. An antibody or variant thereof of any one of claims 1-38 for use in a method for the treatment of cancer or an infection with a pathogen, preferably a virus or parasite.

46. A composition or kit of parts comprising at least one antibody or variant thereof
20 according to any one of claims 1-38.

47. A pharmaceutical composition comprising at least one antibody or variant thereof of any one of claims 1-38 and a pharmaceutically acceptable carrier, diluent or excipient.

25 48. A nucleic acid molecule encoding an antibody or variant of any one of claims 1-38.

49. A vector comprising a nucleic acid molecule according to claim 48.

50. An isolated or recombinant cell, or a non-human animal, comprising a nucleic
30 acid molecule according to claim 48 or a vector according to claim 49.

51. Use of an antibody or variant of any one of claims 1-38, a composition according to claim 46 or 47, a nucleic acid molecule according to claim 48, or a vector according to

claim 49 in the manufacture of a medicament for treating a cancer or an infection with a pathogen.