

CLAIMS

~~1. An immune checkpoint inhibitor, comprising a substance that inhibits binding between fibronectin and an immunosuppressive receptor LILRB4 as an active ingredient.~~

~~2. The immune checkpoint inhibitor according to Claim 1, wherein the fibronectin binds to the immunosuppressive receptor LILRB4 via the amino acid sequence represented by SEQ ID NO: 1 in the fibronectin.~~

~~3. The immune checkpoint inhibitor according to Claim 1 or 2, wherein the substance that inhibits binding between the fibronectin and the immunosuppressive receptor LILRB4 is an anti-fibronectin antibody or a derivative thereof, an anti-immunosuppressive receptor LILRB4 antibody or a derivative thereof, or a fibronectin analog.~~

~~4. The immune checkpoint inhibitor according to Claim 3, wherein the anti-fibronectin antibody or a derivative thereof binds to the amino acid sequence represented by SEQ ID NO: 1 in the fibronectin.~~

~~5. The immune checkpoint inhibitor according to Claim 3, wherein the fibronectin analog is any one of the following peptides (a) to (c):~~

~~—— (a) a peptide containing the amino acid sequence represented by SEQ ID NO: 1;~~

~~—— (b) a peptide containing an amino acid sequence in which one to several amino acids have been deleted, inserted,~~

~~substituted, or added in the amino acid sequence represented by SEQ ID NO: 1, and having a binding capacity to a fibronectin binding site of the immunosuppressive receptor LILRB4; and~~

~~—— (c) a peptide containing an amino acid sequence having 80% or more identity to the amino acid sequence represented by SEQ ID NO: 1, and having a binding capacity to a fibronectin binding site of the immunosuppressive receptor LILRB4.~~

~~6.1. An therapeutic agent for an immune checkpoint related disease, comprising a substance that an anti-leukocyte immunoglobulin-like receptor B4 (LILRB4) antibody or a derivative thereof, wherein the antibody or derivative thereof inhibits binding between fibronectin and an immunosuppressive receptor LILRB4 as an active ingredient.~~

~~7.2. The therapeutic agent according to Claim 61, wherein the antibody or derivative thereof inhibits the binding of the fibronectin binds to the immunosuppressive receptor LILRB4 via the amino acid sequence represented set forth by in SEQ ID NO: 1 in the fibronectin.~~

~~3. The agent according to claim 1 or 2, wherein the antibody or derivative thereof is an immune checkpoint inhibitor.~~

~~4. The agent according to any one of claims 1-3, wherein (i) the antibody is a monoclonal antibody or a polyclonal antibody; and/or (ii) the derivative thereof is selected from F(ab')₂, F(ab)₂, Fab', Fab, Fv, scFv, mutants thereof, fusion proteins or fusion peptides thereof, and combinations thereof.~~

~~8.5. The therapeutic agent according to Claim 6 or 7 any one~~

of claims 1-4, wherein the ~~substance that inhibits binding~~
~~between the fibronectin and the immunosuppressive receptor~~
~~LILRB4 is an anti-fibronectin antibody or a derivative~~
~~thereof, antibody is an anti-immunosuppressive receptor~~human
LILRB4 antibody or a derivative thereof, or a fibronectin
analog.

6. The agent according to any one of claims 1-5, wherein
the antibody or derivative thereof inhibits the binding
between the fibronectin and the LILRB4 in a cell selected from
plasma cells, T cells, macrophages, monocytes, dendritic
cells, eosinophils, basophils, neutrophils, mast cells, and
combination thereof.

7. Use of an agent comprising an anti-LILRB4 antibody, or a
derivative thereof, in the manufacture of a medicament for
inhibiting binding between fibronectin and LILRB4.

9.8. ~~The therapeutic agent according to Claim 8~~ use according
to claim 7, wherein the ~~anti-fibronectin antibody or a~~
derivative thereof inhibits the binding of the fibronectin to
the LILRB4 ~~binds to~~ via the amino acid sequence represented
set forth in by SEQ ID NO: 1 in the fibronectin.

9. The use according to claim 7 or 8, wherein the antibody
or derivative thereof is an immune checkpoint inhibitor.

10. The use according to any one of claims 7-9, wherein (i)
the antibody is a monoclonal antibody or a polyclonal
antibody; and/or (ii) the derivative thereof is selected from
F(ab')₂, F(ab)₂, Fab', Fab, Fv, scFv, mutants thereof, fusion

proteins or fusion peptides thereof, and combinations thereof.

11. The use according to any one of claims 7-10, wherein antibody is an anti-human LILRB4 antibody.

12. The use according to any one of claims 7-11, wherein the antibody or derivative thereof inhibits the binding between the fibronectin and the LILRB4 in a cell selected from plasma cells, T cells, macrophages, monocytes, dendritic cells, eosinophils, basophils, neutrophils, mast cells, and combination thereof.

~~10-13.~~ Use of an agent comprising an anti-LILRB4 antibody, or a derivative thereof, in the manufacture of a medicament for treating an immune checkpoint-related disease
~~The therapeutic agent according to any one of Claims 6 to 10, optionally wherein the immune checkpoint-related disease is selected from the group consisting of an autoimmune disease, a cancer, an inflammatory disease, and an allergic disease and combinations thereof; further optionally wherein the cancer is a solid tumor.~~

~~11-14.~~ The therapeutic agent use according to Claim 11-13, wherein the cancer is due to a metastatic cancer metastasis.

15. The use according to any one of claims 7-14, wherein the antibody or derivative thereof is to be administered to a subject in need thereof parenterally, intravenously, transdermally, intraperitoneally, or intramuscularly.

~~12. A therapeutic agent for an immune checkpoint-related disease, comprising a substance that activates an~~

~~immunosuppressive receptor LILRB4 as an active ingredient.~~

~~13. The therapeutic agent according to Claim 13, wherein the substance that activates the immunosuppressive receptor LILRB4 is an anti-fibronectin antibody or a derivative thereof, an anti-immunosuppressive receptor LILRB4 antibody or a derivative thereof, or fibronectin or a fibronectin analog.~~

~~14. The therapeutic agent according to Claim 14, wherein the fibronectin analog is any one of the following peptides (a) to (c):~~

~~—— (a) a peptide containing the amino acid sequence represented by SEQ ID NO: 1;~~

~~—— (b) a peptide containing an amino acid sequence in which one to several amino acids have been deleted, inserted, substituted, or added in the amino acid sequence represented by SEQ ID NO: 1, and having a binding capacity to a fibronectin binding site of the immunosuppressive receptor LILRB4; and~~

~~—— (c) a peptide containing an amino acid sequence having 80% or more identity to the amino acid sequence represented by SEQ ID NO: 1, and having a binding capacity to a fibronectin binding site of the immunosuppressive receptor LILRB4.~~

~~15. The therapeutic agent according to any one of Claims 13 to 15, wherein the immune checkpoint related disease is a bone disease.~~

~~16. An immunosuppressant, comprising a substance that activates an immunosuppressive receptor LILRB4 as an active~~

ingredient.

~~17. The immunosuppressant according to Claim 17, wherein the substance that activates the immunosuppressive receptor LILRB4 is an anti-fibronectin antibody or a derivative thereof, an anti-immunosuppressive receptor LILRB4 antibody or a derivative thereof, or fibronectin or a fibronectin analog.~~

~~18. The immunosuppressant according to Claim 18, wherein the fibronectin analog is any one of the following peptides (a) to (c):~~

~~—— (a) a peptide containing the amino acid sequence represented by SEQ ID NO: 1;~~

~~—— (b) a peptide containing an amino acid sequence in which one to several amino acids have been deleted, inserted, substituted, or added in the amino acid sequence represented by SEQ ID NO: 1, and having a binding capacity to a fibronectin binding site of the immunosuppressive receptor LILRB4; and~~

~~—— (c) a peptide containing an amino acid sequence having 80% or more identity to the amino acid sequence represented by SEQ ID NO: 1, and having a binding capacity to a fibronectin binding site of the immunosuppressive receptor LILRB4.~~

~~19. An anti fibronectin antibody or a derivative thereof, which binds to the amino acid sequence represented by SEQ ID NO: 1.~~

~~20. A fibronectin analog, in which any one of the following peptides (a) to (c) and an Fc region of immunoglobulin G are~~

~~fused with each other:~~

~~—— (a) a peptide containing the amino acid sequence represented by SEQ ID NO: 1;~~

~~—— (b) a peptide containing an amino acid sequence in which one to several amino acids have been deleted, inserted, substituted, or added in the amino acid sequence represented by SEQ ID NO: 1, and having a binding capacity to a fibronectin binding site of the immunosuppressive receptor LILRB4; and~~

~~—— (c) a peptide containing an amino acid sequence having 80% or more identity to the amino acid sequence represented by SEQ ID NO: 1, and having a binding capacity to a fibronectin binding site of the immunosuppressive receptor LILRB4.~~

~~21. A kit for detecting fibronectin containing the amino acid sequence represented by SEQ ID NO: 1 or a partial protein thereof contained in a biological sample, comprising the anti-fibronectin antibody or a derivative thereof according to Claim 20.~~

~~22. A method for detecting fibronectin or a partial protein thereof in a biological sample using the kit according to Claim 22.~~