derived from yeast, and no significant difference in activity is observed between the two (NPL8). Treatment of pulmonary alveolar proteinosis and Crohn's disease is attempted using the preparations, and a therapeutic effect is reported, particularly for pulmonary alveolar proteinosis (NPL9 and NPL10).

[0011] Although it is reported that neutralization by autoantibodies is reduced by amino acid modification of the GM-CSF molecule, the effect remains slight (NPL11). Research is reported in which a receptor-binding peptide is connected with a linker as a GM-CSF mimetic, which has a property of transmitting signals through a GM-CSF receptor, like the GM-CSF, but is completely different from the GM-CSF as a molecule (PTL1).

CITATION LIST

PATENT LITERATURE

[0012] PTL1: WO2018/227142

PTL2: WO2017/021540

NON-PATENT LITERATURE

[0013] NPL1: Proc. Natl. Acad. Sci. USA, 91, 5592-5596 (1994)

NPL2: Cell, 134, 496-507 (2008)

NPL3: Cytokine, 74, 247-258 (2015)

NPL4: J. Exp. Med., 190, 875-880 (1999)

NPL5: Blood, 113, 2547-2556 (2009)

NPL6: Gastroenterology, 136, 1261-1271 (2009)

NPL7: Inflamm. Bowel Dis., 19, 1671-1680 (2013)

NPL8: Eur J Haematol., 55, 348-356 (1995)

NPL9: N Engl J Med., 381, 923-932 (2019)

NPL10: N Engl J Med., 352, 2193-2201 (2005)

NPL11: Protein Eng Des Sel., 28, 461-466 (2015)

NPL12: Blood, 103, 1089-1098 (2004)

NPL13: EbioMedicine, 30, 730-743 (2015)

SUMMARY

TECHNICAL PROBLEM

[0014] A previously studied GM-CSF receptor-binding peptide has a problem of insufficient efficacy, and a possible reason for this is that the GM-CSF receptor-binding peptide is derived from a GM-CSF sequence and is therefore neutralized by a patient autoantibody. Considering that autoantibodies to the GM-CSF are produced for various epitopes of the GM-CSF (NPL12), it is considered difficult to solve the neutralization of the GM-CSF receptor peptide by patient autoantibodies by molecular modification of an administered peptide.

[0015] On the other hand, it is shown that agonists can be obtained by using a bispecific antibody not only for a receptor consisting of homodimers, such as an erythropoietin receptor or a growth hormone receptor, but also for a receptor consisting of heterodimers (multimers), such as an interleukin 2 (IL-2) receptor or a fibroblast growth factor (FGF) receptor and a β-Klotho protein complex (NPL13 and NPL2). However, a GM-CSF receptor agonist is not reported so far. As described above, an activation mechanism of the GM-CSF receptor is very complex, and therefore it is not considered easy to prepare a substance having an agonist activity. In order to exert the agonist activity on the GM-CSF receptor, it is considered that it is necessary to mimic changes in distance and angle between CD116 and CD131 caused by binding with a GM-CSF and formation of a complex.

[0016] The present disclosure is made in view of such circumstances, and an object thereof is to provide a bispecific antibody having an agonist activity to a GM-CSF receptor, a bispecific antibody fragment thereof, a DNA encoding the bispecific antibody or the bispecific antibody fragment thereof, a vector containing the DNA, a hybridoma and transformant producing the bispecific antibody or the bispecific antibody fragment thereof, a method for producing the bispecific antibody or the bispecific antibody fragment thereof, a therapeutic and diagnostic agent containing the bispecific antibody or the bispecific antibody fragment thereof, a therapeutic and diagnostic method using the bispecific antibody or the bispecific antibody fragment thereof, and a detection or measurement reagent containing the bispecific antibody or the bispecific antibody fragment thereof.

SOLUTION TO PROBLEM

[0017] The present inventors have found that, since a GM-CSF receptor is composed of CD116 and CD131, a bispecific antibody having an agonist activity to the GM-CSF receptor can be prepared by preparing a bispecific antibody containing antigen-binding domains binding to CD116 and CD131, which are constituent molecules of the GM-CSF receptor,

thereby completing the present disclosure.

[0018] That is, the present disclosure relates to the following.

1. A bispecific antibody or a bispecific antibody fragment thereof containing:

a first antigen-binding domain; and

a second antigen-binding domain, in which

one of the first antigen-binding domain and the second antigen-binding domain is an antigen-binding domain binding to CD116, and the other one is an antigen-binding domain binding to CD131.

2. The bispecific antibody or the bispecific antibody fragment thereof according to above 1, which has an agonist activity to a granulocyte macrophage-colony stimulating factor (hereinafter abbreviated as GM-CSF) receptor.

3. The bispecific antibody or the bispecific antibody fragment thereof according to above 1 or 2, in which the first antigen-binding domain and the second antigen-binding domain each contain a heavy chain variable region (hereinafter abbreviated as VH) and a light chain variable region (hereinafter abbreviated as VL).

4. The bispecific antibody or the bispecific antibody fragment thereof according to any one of above 1 to 3, which binds to CD116 and CD131 in a monovalent or divalent manner, separately.

5. The bispecific antibody or the bispecific antibody fragment thereof according to any one of above 1 to 4, in which the antigen-binding domain binding to CD131 is any one selected from the following (1a) to (1e):

(1a) an antigen-binding domain containing a VH containing complementarity determining regions (hereinafter abbreviated as CDRs) 1 to 3 containing the amino acid sequences represented by SEQ ID NOs: 61 to 63, respectively, and a VL containing CDRs 1 to 3 containing the amino acid sequences represented by SEQ ID NOs: 64 to 66, respectively,

(1b) an antigen-binding domain containing a VH containing CDRs 1 to 3 containing the amino acid sequences represented by SEQ ID NOs: 67 to 69, respectively, and a VL containing CDRs 1 to 3 containing the amino acid sequences represented by SEQ ID NOs: 70 to 72, respectively,

(1c) an antigen-binding domain containing a VH containing CDRs 1 to 3 containing the amino acid sequences represented by SEQ ID NOs: 73 to 75, respectively, and a VL containing CDRs 1 to 3 containing the amino acid sequences represented by SEQ ID NOs: 76 to 78, respectively,

A10. The bispecific antibody or the bispecific antibody fragment thereof according to any one of above 1 to 18 and A1 to A5, for use in treatment and/or diagnosis of a disease associated with a GM-CSF.

A11. The bispecific antibody or the bispecific antibody fragment thereof according to above A10, in which the disease associated with a GM-CSF is a disease associated with an autoantibody to a GM-CSF.

A12. Use of the bispecific antibody or the bispecific antibody fragment thereof according to any one of above 1 to 18 and A1 to A5 for the manufacture of a therapeutic and/or diagnostic agent for a diseases associated with a GM-CSF.

A13. The use according to above A12, in which the disease associated with a GM-CSF is a disease associated with an autoantibody to a GM-CSF.

A14. A reagent for detecting or measuring at least one of CD116 and CD131, containing the bispecific antibody or the bispecific antibody fragment thereof according to any one of above 1 to 18 and A1 to A5.

23. A method for purifying a composition containing an antibody, the method including: purifying an antibody containing an Fc region by Protein A column chromatography, in which the antibody is an antibody with an H435F mutation introduced in the Fc region.

24. The bispecific antibody or the bispecific antibody fragment thereof according to any one of above 1 to 18, which binds to an epitope containing W at position 163 and R at position 221 in CD131 (SEQ ID NO: 211) and an epitope containing N at position 156, K at position 158, and T at position 187 in CD116 (SEQ ID NO: 210).

[0018a] In one aspect, the present disclosure refers to a bispecific antibody or a bispecific antibody fragment thereof comprising: a first antigen-binding domain; and a second antigen-binding domain, wherein the first antigen-binding domain is the antigen-binding domain binding to CD131, and the second antigen-binding domain is the antigen-binding domain binding to CD116.

[0018b] In one aspect, the present disclosure refers to a DNA encoding the bispecific antibody or the bispecific antibody fragment thereof as disclosed herein.

[0018c] In one aspect, the present disclosure refers to a recombinant vector comprising the DNA as disclosed herein.

[0018d] In one aspect, the present disclosure refers to a transformant obtained by introducing the recombinant vector as disclosed herein into a host cell.

[0018e] In one aspect, the present disclosure refers to the bispecific antibody or the bispecific antibody fragment thereof as disclosed herein for use in treating and/or diagnosing a disease associated with a GM-CSF.

[0018f] In one aspect, the present disclosure refers to a method for producing the bispecific antibody or the bispecific antibody fragment thereof as disclosed herein, the method including: culturing the transformant as disclosed herein in a medium; producing and accumulating the bispecific antibody or the bispecific antibody fragment thereof as disclosed herein in a culture; and collecting the bispecific antibody or the bispecific antibody fragment thereof from the culture.

[0018g] In one aspect, the present disclosure refers to use of the bispecific antibody or the bispecific antibody fragment thereof as disclosed herein in the manufacture of a medicament for treating and/or diagnosing a disease associated with a GM-CSF.

ADVANTAGEOUS EFFECTS OF DISCLOSURE

[0019] According to the present disclosure, there is provided a novel bispecific antibody binding to CD116 and CD131, a novel bispecific antibody having an agonist activity to a GM-CSF receptor, a bispecific antibody fragment thereof, a DNA encoding the bispecific antibody or the bispecific antibody fragment thereof, a vector containing the DNA, a hybridoma or transformant producing the bispecific antibody or the bispecific antibody fragment thereof, a method for producing the bispecific antibody or the bispecific antibody fragment thereof, a therapeutic and diagnostic agent containing the bispecific antibody or the bispecific antibody fragment thereof, a therapeutic and diagnostic method using the bispecific antibody or the bispecific antibody fragment thereof, and a detection or measurement reagent containing the