conventional antigen-binding molecules that bind to molecules expressed on the surfaces of regulatory T cells and exhausted T cells and also have ADCC activity. Furthermore, the present inventors discovered pharmaceutical compositions that can treat various carcinomas by having the antigen-binding molecule as an active ingredient. In one aspect, the present invention refers to an antigen-binding molecule that inhibits immune response-suppressing activity of a cell having an immune response-suppressing function, comprising: (i) a domain that binds to a molecule expressed on the surface of a cell having an immune response-suppressing function; and (ii) a T cell receptor complex-binding domain, which further comprises an Fc region of an antibody having reduced Fcγ receptor-binding activity. In another aspect, the present invention refers to a pharmaceutical composition comprising the antigen-binding molecule of the present invention. In still another aspect, the present invention refers to a pharmaceutical composition for use in inhibiting an immune response-suppressing activity, comprising the antigen-binding molecule of the present invention as an active ingredient.

Furthermore, the present disclosure provides the following:

[1] an antigen-binding molecule that inhibits immune response-suppressing activity of a cell having an immune response-suppressing function, comprising:

(i) a domain that binds to a molecule expressed on the surface of a cell having an immune response-suppressing function; and

(ii) a T cell receptor complex-binding domain;

[2] the antigen-binding molecule of [1], wherein the cell having immune response-suppressing function is a regulatory T cell or an exhausted T cell;

[3] the antigen-binding molecule of [1], wherein the molecule expressed on the surface of a cell having an immune response-suppressing function is any molecule selected from among CTLA4, PD1, TIM3, LAG3, CD244 (2B4), CD160, GARP, OX40, CD137 (4-1BB), CD25, VISTA, BTLA, TNFR25, CD57, KLRG1, CCR2, CCR5, CCR6, CD39, CD73, CD4, CD18, CD49b, CD1d, CD5, CD21, TIM1, CD19, CD20, CD23, CD24, CD38, CD93, IgM, B220(CD45R), CD317, PD-L1, CD11b, Ly6G, ICAM-1, FAP, PDGFR, Podoplanin, and TIGIT;

[4] the antigen-binding molecule of [3], wherein the molecule expressed on the surface of a cell having an immune response-suppressing function is any molecule selected from among CTLA4, TIM3, LAG3, CD137 (4-1BB), CD25, CCR5, CCR6, CD38, TIGIT, and OX40;

[5] the antigen-binding molecule of any one of [1] to [4], wherein the T cell receptor complex-binding domain is a T cell receptor-binding domain;

[6] the antigen-binding molecule of any one of [1] to [4], wherein the T cell receptor complex-binding domain is a CD3-binding domain;

[7] the antigen-binding molecule of any one of [1] to [6], which further comprises an FcRn-binding domain;

[8] the antigen-binding molecule of [7], wherein the FcRn-binding domain is an Fc region of an antibody;

[9] the antigen-binding molecule of [8], wherein the FcRn-binding domain is an Fc region of an antibody having reduced Fcγ receptor-binding activity;

[10] the antigen-binding molecule of any one of [1] to [9], which is a multispecific antibody;

[11] a pharmaceutical composition comprising the antigen-binding molecule of any one of [1] to [10] as an active ingredient;

[12] a pharmaceutical composition for inhibiting an immune response-suppressing activity, comprising the antigen-binding molecule of any one of [1] to [10] as an active ingredient;

[13] the pharmaceutical composition of [12], wherein the inhibition of an immune response-suppressing activity is inhibition caused by a T cell;

[14] the pharmaceutical composition of [13], wherein the inhibition caused by a T cell is inhibition resulting from cytotoxic activity of the T cell;

[15] the pharmaceutical composition of any one of [12] to [14], wherein the immune response-suppressing activity is an activity by a regulatory T cell or an exhausted T cell;

[16] the pharmaceutical composition of any one of [12] to [14], wherein the immune response-suppressing activity is an activity of a cell expressing any molecule selected from among CTLA4, PD1, TIM3, LAG3, CD244 (2B4), CD160, GARP, OX40, CD137 (4-1BB), CD25, VISTA, BTLA, TNFR25, CD57, KLRG1, CCR2, CCR5, CCR6, CD39, CD73, CD4, CD18, CD49b, CD1d, CD5, CD21, TIM1, CD19, CD20, CD23, CD24, CD38, CD93, IgM, B220(CD45R), CD317, PD-L1, CD11b, Ly6G, ICAM-1, FAP, PDGFR, Podoplanin, and TIGIT;

[17] the pharmaceutical composition of any one of [11] to [16], which is a therapeutic agent for cancer;

[18] the pharmaceutical composition of claim 17, which is a therapeutic agent any cancer selected from among ovarian cancer, gastric cancer, esophageal cancer, pancreatic cancer, renal cell carcinoma, hepatocellular carcinoma, breast cancer, malignant melanoma, non-small-cell lung cancer, cervical cancer, glioblastoma, prostate cancer, neuroblastoma, chronic lymphocytic leukemia, papillary thyroid cancer, colorectal cancer, Hodgkin's lymphoma, and endometriosis;

[19] Also disclosed herein is a method for inducing cytotoxicity, suppressing cell proliferation, activating immunity against a cancer cell or a cancer cell-comprising tumor tissue , or treating or preventing cancer, which comprises the step of administering the antigen-binding molecule of any one of [1] to [10] or the pharmaceutical composition of any one of [11] to [18];

[20] the antigen-binding molecule of any one of [1] to [10] or the pharmaceutical composition of any one of [11] to [18] for use in inducing cytotoxicity, suppressing cell proliferation, activating immunity against a cancer cell or a cancer cell-comprising tumor tissue, or treating or preventing cancer;

[21] use of the antigen-binding molecule of any one of [1] to [10] in the production of the pharmaceutical composition of any one of [11] to [18]; and

[22] a method for producing the pharmaceutical composition of any one of [11] to [18], which comprises the step of using the antigen-binding molecule of any one of [1] to [10].

Furthermore, the present disclosure relates to methods for treating or preventing cancer, or for inhibiting suppression of an immune response, which comprise administering an antigen-binding molecule of the present invention or a pharmaceutical composition of the

present invention to patients in need of treatment. The present disclosure also relates to a kit for use in the methods of the present invention, which comprises an antigen-binding molecule of the

CTLA4/mouse CD3-bound beads and mouse CD3-bound beads by anti-mouse CTLA4/anti-mouse CD3 bispecific antibodies. The graph shows the mean values and standard deviations for each of the measurement results.

Fig. 7-4 presents a schematic diagram showing crosslinking between a mouse CTLA4/mouse CD3-bound bead and a mouse CD3-bound bead by an anti-mouse CTLA4/anti-mouse CD3 bispecific antibody.

Fig. 8 presents a graph showing the *in vivo* antitumor effects obtained by intratumoral (i.t.) administration of an anti-mouse CTLA4 antibody (hUH02hUL01-mFa55, ADCC-enhanced antibody) and an anti-mouse CTLA4/anti-mouse CD3 bispecific antibody (hUH02UL01/2C11-F760, a T cell-redirecting antibody) on mouse colorectal cancer cell line CT26.WT (n = 2 for each group; the plot shows the tumor volume of each individual).

Fig. 9 presents a graph showing the *in vivo* antitumor effects obtained by intratumoral (i.t.) administration and intravenous (i.v.) administration of an anti-mouse CTLA4/anti-mouse CD3 bispecific antibody (hUH02UL01/2C11-F760, a T cell-redirecting antibody) on mouse colorectal cancer cell line CT26.WT (n = 5 for each group; the plot shows the mean tumor volume + standard deviation of each group).

Fig. 10-1 presents graphs showing the results of analyzing CD4-positive cells based on the expression of CD25 and CD45RA, after a seven-day reaction of PBMC derived from a healthy person with a control antibody (control) and an anti-human CTLA4/anti-human CD3 bispecific antibody (TRAB/CTLA4).

Fig. 10-2 presents graphs showing the proportion of regulatory T cells (Treg) in CD4-positive T cells, calculated based on the expression of CD25 and CD45RA, after a seven-day reaction of PBMC derived from a healthy person with a control antibody (control) and an anti-human CTLA4/anti-human CD3 bispecific antibody (TRAB/CTLA4).

Fig. 10-3 presents graphs showing the ratio of effector T cells (Teff) to regulatory T cells (Treg) (Teff/Treg) calculated based on the expression of CD25 and CD45RA, after a seven-day reaction of PBMC derived from a healthy person with a control antibody (control) and an anti-human CTLA4/anti-human CD3 bispecific antibody (TRAB/CTLA4).

Fig. 11-1 presents graphs showing the results of analyzing CD4-positive cells based on the expression of FoxP3 and CD45RA, after a seven-day reaction of PBMC derived from a healthy person with a control antibody (control) and an anti-human CTLA4/anti-human CD3 bispecific antibody (TRAB/CTLA4).

Fig. 11-2 presents graphs showing the proportion of regulatory T cells (Treg) in CD4-positive T cells, calculated based on the expression of FoxP3 and CD45RA, after a seven-day reaction of PBMC derived from a healthy person with a control antibody (control) and an anti-human CTLA4/anti-human CD3 bispecific antibody (TRAB/CTLA4).

Fig. 11-3 presents graphs showing the ratio of effector T cells (Teff) to regulatory T cells (Treg) (Teff/Treg) calculated based on the expression of FoxP3 and CD45RA, after a seven-day reaction of PBMC derived from a healthy person with a control antibody (control) and an anti-human CTLA4/anti-human CD3 bispecific antibody (TRAB/CTLA4).

Fig. 12 presents a diagram showing the relationship between the amino acid residues constituting the Fc regions of IgG1, IgG2, IgG3, and IgG4, and Kabat's EU numbering (herein, it is also called the EU INDEX).

Fig. 13 presents graphs showing the results of analyzing CD4-positive cells based on the expression of CD25 and CD45RA, after a four- or six-day reaction of PBMC derived from a healthy person with an anti-human LAG3/anti-human CD3 bispecific antibody (TRAB/LAG3).

Fig. 14 presents graphs showing the proportion of regulatory T cells (Treg) in CD4-positive T cells, calculated based on the expression of CD25 and CD45RA, after a four- or six-day reaction of PBMC derived from a healthy person with an anti-human LAG3/anti-human CD3 bispecific antibody (TRAB/LAG3).

Fig. 15 presents graphs showing the ratio of effector T cells (Teff) to regulatory T cells (Treg) (Teff/Treg) in CD4-positive T cells, calculated based on the expression of CD25 and CD45RA, after a four- or six-day reaction of PBMC derived from a healthy person with an anti-human LAG3/anti-human CD3 bispecific antibody (TRAB/LAG3).

Fig. 16 presents graphs showing the results of analyzing CD4-positive cells based on the expression of CD25 and CD45RA, after a seven-day reaction of PBMC derived from a healthy person with an anti-human OX40/anti-human CD3 bispecific antibody (TRAB/OX40).

Fig. 17 presents graphs showing the proportion of regulatory T cells (Treg) in CD4-positive T cells, calculated based on the expression of CD25 and CD45RA, after a seven day reaction of PBMC derived from a healthy person with an anti-human OX40/anti-human CD3 bispecific antibody (TRAB/OX40).

Fig. 18 presents graphs showing the ratio of effector T cells (Teff) to regulatory T cells (Treg) (Teff/Treg) in CD4-positive T cells, calculated based on the expression of CD25 and CD45RA, after a seven day reaction of PBMC derived from a healthy person with an anti-human OX40/anti-human CD3 bispecific antibody (TRAB/OX40).

Mode for Carrying Out the Invention

The following definitions are provided to facilitate understanding of the invention described herein.

Antigen-binding molecules

In the present invention, "antigen-binding molecules" are not particularly limited as

CLAIMS

1. An antigen-binding molecule that inhibits immune response-suppressing activity of a cell having an immune response-suppressing function, comprising:
(i) a domain that binds to a molecule expressed on the surface of a cell having an immune response-suppressing function; and
(ii) a T cell receptor complex-binding domain,
which further comprises an Fc region of an antibody having reduced Fcγ receptor-binding activity.

2. The antigen-binding molecule of claim 1, wherein the cell having immune response-suppressing function is a regulatory T cell or an exhausted T cell.

3. The antigen-binding molecule of claim 1, wherein the molecule expressed on the surface of a cell having an immune response-suppressing function is any molecule selected from among CTLA4, PD1, TIM3, LAG3, CD244 (2B4), CD160, GARP, OX40, CD137 (4-1BB), CD25, VISTA, BTLA, TNFR25, CD57, KLRG1, CCR2, CCR5, CCR6, CD39, CD73, CD4, CD18, CD49b, CD1d, CD5, CD21, TIM1, CD19, CD20, CD23, CD24, CD38, CD93, IgM, B220(CD45R), CD317, PD-L1, CD11b, Ly6G, ICAM-1, FAP, PDGFR, Podoplanin, and TIGIT.

4. The antigen-binding molecule of claim 3, wherein the molecule expressed on the surface of a cell having an immune response-suppressing function is any molecule selected from among CTLA4, TIM3, LAG3, CD137 (4-1BB), CD25, CCR5, CCR6, CD38, TIGIT, and OX40.

5. The antigen-binding molecule of claim 4, wherein the molecule expressed on the surface of a cell having an immune response-suppressing function is CTLA4.

6. The antigen-binding molecule of any one of claims 1 to 5, wherein the T cell receptor complex-binding domain is a T cell receptor-binding domain.

7. The antigen-binding molecule of any one of claims 1 to 5, wherein the T cell receptor complex-binding domain is a CD3-binding domain.

8. The antigen-binding molecule of any one of claims 1 to 7, which is a multispecific antibody.

9. A pharmaceutical composition comprising the antigen-binding molecule of any one of claims 1 to 8 as an active ingredient.

10. A pharmaceutical composition for use in inhibiting an immune response-suppressing activity, comprising the antigen-binding molecule of any one of claims 1 to 8 as an active ingredient.

11. The pharmaceutical composition of claim 10, wherein the inhibition of an immune response-suppressing activity is inhibition caused by a T cell.

12. The pharmaceutical composition of claim 11, wherein the inhibition caused by a T cell is inhibition resulting from cytotoxic activity of the T cell.

13. The pharmaceutical composition of any one of claims 10 to 12, wherein the immune response-suppressing activity is an activity by a regulatory T cell or an exhausted T cell.

14. The pharmaceutical composition of any one of claims 10 to 12, wherein the immune response-suppressing activity is an activity of a cell expressing any molecule selected from among CTLA4, PD1, TIM3, LAG3, CD244 (2B4), CD160, GARP, OX40, CD137 (4-1BB), CD25, VISTA, BTLA, TNFR25, CD57, KLRG1, CCR2, CCR5, CCR6, CD39, CD73, CD4, CD18, CD49b, CD1d, CD5, CD21, TIM1, CD19, CD20, CD23, CD24, CD38, CD93, IgM, B220(CD45R), CD317, PD-L1, CD11b, Ly6G, ICAM-1, FAP, PDGFR, Podoplanin, and TIGIT.

15. The pharmaceutical composition of any one of claims 9 to 14 for use in treating cancer.

16. The pharmaceutical composition of claim 15, wherein the cancer is selected from the group consisting of ovarian cancer, gastric cancer, esophageal cancer, pancreatic cancer, renal cell carcinoma, hepatocellular carcinoma, breast cancer, malignant melanoma, non-small-cell lung cancer, cervical cancer, glioblastoma, prostate cancer, neuroblastoma, chronic lymphocytic leukemia, papillary thyroid cancer, colorectal cancer, Hodgkin's lymphoma, and endometriosis.