[Claim 1]

An antibody having properties described in the following (I) to (III) or a functional fragment thereof:

(I) binding to the ROBO4 protein with a K_D value of 1×10^{-8} M or lower;
(II) suppressing or inhibiting vascular endothelial cell migration in the absence of a cross-linking antibody in vitro; and
(III) suppressing or inhibiting angiogenesis in vivo,
wherein the antibody consists of a heavy chain comprising CDRH1 consisting of the amino acid sequence represented by SEQ ID NO: 44 (Figure 25), CDRH2 consisting of the amino acid sequence represented by SEQ ID NO: 46 (Figure 26) or the amino acid sequence represented by SEQ ID NO: 68 (Figure 44), and CDRH3 consisting of the amino acid sequence represented by SEQ ID NO: 48 (Figure 27), and a light chain comprising CDRL1 consisting of the amino acid sequence represented by SEQ ID NO: 50 (Figure 28) or the amino acid sequence represented by SEQ ID NO: 70 (Figure 46), CDRL2 consisting of the amino acid sequence represented by SEQ ID NO: 52 (Figure 29), and CDRL3 consisting of the amino acid sequence represented by SEQ ID NO: 54 (Figure 30).

[Claim 2]

The antibody or the functional fragment thereof according to claim 1, wherein the ROBO4 protein is the human ROBO4 protein.

[Claim 3]

The antibody or the functional fragment thereof according to claim 1, wherein the ROBO4 protein is a protein consisting of an amino acid sequence of amino acid Nos. 1 to 1007 of SEQ ID NO: 2.

[Claim 4]

The antibody or the functional fragment thereof according to claim 1, wherein the ROBO4 protein is a protein consisting of an amino acid sequence of amino acid Nos. 46 to 1007 of SEQ ID NO: 2.

[Claim 5]

The antibody or the functional fragment thereof according to claim 3 or 4, wherein the antibody or the functional fragment thereof binds to a site consisting of an amino acid sequence of amino acid Nos. 132 to 209 of SEQ ID NO: 2.

[Claim 6]

The antibody or the functional fragment thereof according to claim 1, wherein the antibody or the functional fragment thereof is a monoclonal antibody or a functional fragment thereof.

[Claim 7]

The antibody or the functional fragment thereof according to any one of claims 1 to 6, wherein the antibody comprises a heavy chain variable region consisting of the amino acid sequence represented by SEQ ID NO: 31 (Figure 16), and a light chain variable region consisting of the amino acid sequence represented by SEQ ID NO: 33 (Figure 18).

[Claim 8]

The antibody or the functional fragment thereof according to any one of claims 1 to 6, wherein the antibody comprises any one heavy chain variable region selected from the following a) to d) and a light chain variable region selected from e) and f):

a) a heavy chain (hMAb1-H1-type) variable region consisting of an amino acid sequence represented by amino acid Nos. 20 to 137 of SEQ ID NO: 56 (Figure 32),
b) a heavy chain (hMAb1-H2-type) variable region consisting of an amino acid sequence represented by amino acid Nos. 20 to 137 of SEQ ID NO: 58 (Figure 34),
c) a heavy chain (hMAb1-H3-type) variable region consisting of an amino acid sequence represented by amino acid Nos. 20 to 137 of SEQ ID NO: 60 (Figure 36), and
d) a heavy chain (hMAb1-H4-type) variable region consisting of an amino acid sequence represented by amino acid Nos. 20 to 137 of SEQ ID NO: 62 (Figure 38); and
e) a light chain (hMAb1-L1-type) variable region consisting of an amino acid sequence represented by amino acid Nos. 21 to 134 of SEQ ID NO: 64 (Figure 40), and
f) a light chain (hMAb1-L2-type) variable region consisting of an amino acid sequence represented by amino acid Nos. 21 to 134 of SEQ ID NO: 66 (Figure 42).

[Claim 9]

The antibody or the functional fragment thereof according to any one of claims 1 to 6, wherein the antibody comprises any one of the following combinations 1) to 6) of a heavy chain variable region and a light chain variable region:

1) a heavy chain variable region consisting of an amino acid sequence represented by amino acid Nos. 20 to 137 of SEQ ID NO: 58 (Figure 34) and a light chain variable region consisting of an amino acid sequence represented by amino acid Nos. 21 to 134 of SEQ ID NO: 64 (Figure 40),

2) a heavy chain variable region consisting of an amino acid sequence represented by amino acid Nos. 20 to 137 of SEQ ID NO: 58 (Figure 34) and a light chain variable region consisting of an amino acid sequence represented by amino acid Nos. 21 to 134 of SEQ ID NO: 66 (Figure 42),

3) a heavy chain variable region consisting of an amino acid sequence represented by amino acid Nos. 20 to 137 of SEQ ID NO: 62 (Figure 38) and a light chain variable region consisting of an amino acid sequence represented by amino acid Nos. 21 to 134 of SEQ ID NO: 66 (Figure 42),

4) a heavy chain variable region consisting of an amino acid sequence represented by amino acid Nos. 20 to 137 of SEQ ID NO: 62 (Figure 38) and a light chain variable region consisting of an amino acid sequence represented by amino acid Nos. 21 to 134 of SEQ ID NO: 64 (Figure 40),

5) a heavy chain variable region consisting of an amino acid sequence represented by amino acid Nos. 20 to 137 of SEQ ID NO: 56 (Figure 32) and a light chain variable region consisting of an amino acid sequence represented by amino acid Nos. 21 to 134 of SEQ ID NO: 64 (Figure 40), and

6) a heavy chain variable region consisting of an amino acid sequence represented by amino acid Nos. 20 to 137 of SEQ ID NO: 60 (Figure 36) and a light chain variable region consisting of an amino acid sequence represented by amino acid Nos. 21 to 134 of SEQ ID NO: 64 (Figure 40).

[Claim 10]

The antibody or the functional fragment thereof according to any one of claims 1 to 9, wherein the antibody or the functional fragment thereof is a chimeric antibody or a functional fragment thereof.

[Claim 11]

The antibody or the functional fragment thereof according to any one of claims 1 to 9, wherein the antibody or the functional fragment thereof is a humanized antibody or a functional fragment thereof.

[Claim 12]

The antibody or the functional fragment thereof according to any one of claims 1 to 11, wherein the antibody comprises a human IgG1 or human IgG2 heavy chain constant region.

[Claim 13]

The antibody or the functional fragment thereof according to any one of claims 1 to 6, wherein the antibody or the functional fragment thereof binds to a site on an antigen recognized by the antibody according to claims 8 or 9.

[Claim 14]

The antibody or the functional fragment thereof according to any one of claims 1 to 6, wherein the antibody or the functional fragment thereof competes with any one antibody according to claims 8 or 9 for the binding to ROBO4 protein.

[Claim 15]

The antibody according to any one of claims 1 to 6, wherein the antibody comprises any one of the following combinations 1) to 6) of a heavy chain and a light chain:

1) a heavy chain consisting of an amino acid sequence represented by amino acid Nos. 20 to 463 of SEQ ID NO: 58 (Figure 34) and a light chain consisting of an amino acid sequence represented by amino acid Nos. 21 to 239 of SEQ ID NO: 64 (Figure 40) (H-1140),

2) a heavy chain consisting of an amino acid sequence represented by amino acid Nos. 20 to 463 of SEQ ID NO: 58 (Figure 34) and a light chain consisting of an amino acid sequence represented by amino acid Nos. 21 to 239 of SEQ ID NO: 66 (Figure 42) (H-1143),

3) a heavy chain consisting of an amino acid sequence represented by amino acid Nos. 20 to 463 of SEQ ID NO: 62 (Figure 38) and a light chain consisting of an amino acid sequence represented by amino acid Nos. 21 to 239 of SEQ ID NO: 66 (Figure 42) (H-2143).

4) a heavy chain consisting of an amino acid sequence represented by amino acid Nos. 20 to 463 of SEQ ID NO: 62 (Figure 38) and a light chain consisting of an amino acid sequence represented by amino acid Nos. 21 to 239 of SEQ ID NO: 64 (Figure 40) (H-2140),

5) a heavy chain consisting of an amino acid sequence represented by amino acid Nos. 20 to 463 of SEQ ID NO: 56 (Figure 32) and a light chain consisting of an amino acid sequence represented by amino acid Nos. 21 to 239 of SEQ ID NO: 64 (Figure 40) (H-1040), and

6) a heavy chain consisting of an amino acid sequence represented by amino acid Nos. 20 to 463 of SEQ ID NO: 60 (Figure 36) and a light chain consisting of an amino acid sequence represented by amino acid Nos. 21 to 239 of SEQ ID NO: 64 (Figure 40) (H-2040).

[Claim 16]

An antibody comprising a light chain and modified form of a heavy chain as defined in claim 15, wherein said modified form lacks one to ten carboxyl-terminal amino acid(s) of said heavy chain.

[Claim 17]

The antibody according to any one of claims 1 to 6, wherein the antibody is 95% or more identical in the amino acid sequence to any one antibody according to claim 15; has a K_D value of 1×10^{-8} M or lower for a human ROBO4; suppresses or inhibits vascular endothelial cell migration in the absence of a cross-linking antibody in vitro; and suppresses or inhibits angiogenesis in vivo.

[Claim 18]

The antibody or the functional fragment thereof according to claim 13, wherein the antibody or the functional fragment thereof is a human antibody or a functional fragment thereof.

[Claim 19]

A nucleotide sequence selected from the group consisting of the following (I) to (III):

(I) a nucleotide sequence comprising a nucleotide sequence encoding the partial or whole amino acid sequence of the heavy chain or light chain of an antibody according to any one of claims 1 to 18,

(II) a nucleotide sequence consisting of a nucleotide sequence comprising a nucleotide sequence encoding the partial or whole amino acid sequence of the heavy chain or light chain of an antibody according to any one of claims 1 to 18, and

(III) a nucleotide sequence consisting of a nucleotide sequence encoding the partial or whole amino acid sequence of the heavy chain or light chain of an antibody according to any one of claims 1 to 18.

[Claim 20]

A recombinant vector containing an insert of a nucleotide sequence according to claim 19.

[Claim 21]

A pharmaceutical composition comprising an antibody or a functional fragment thereof according to any one of claims 1 to 18 as an active ingredient.

[Claim 22]

The pharmaceutical composition according to claim 21, wherein the pharmaceutical composition is for use in treating or preventing an angiogenic disease.

[Claim 23]

The pharmaceutical composition for the use according to claim 22, wherein the angiogenic disease is exudative age-related macular degeneration, diabetic retinopathy, macular edema, benign or malignant tumor, atherosclerosis, retrolental fibroplasia, angioma, chronic inflammation, ocular neovascular disease, proliferative retinopathy, neovascular glaucoma, immune rejection of a corneal tissue transplant or other tissue transplants, rheumatoid arthritis, psoriasis, acute inflammation, sepsis, or obesity.

[Claim 24]

The pharmaceutical composition for the use according to claim 22, wherein the angiogenic disease is exudative age-related macular degeneration, diabetic retinopathy, macular

edema, retrolental fibroplasia, ocular neovascular disease, proliferative retinopathy, neovascular glaucoma, or immune rejection of a corneal tissue transplant.

[Claim 25]

An angiogenesis inhibitor comprising an antibody or a functional fragment thereof according to any one of claims 1 to 18 as an active ingredient.

[Claim 26]

The pharmaceutical composition according to any one of claims 21 to 24, wherein said composition is to be used in combination with a further therapeutic or prophylactic agent.