elderly and/or diabetic patients where new vessel growth may be required in ischemic brains, hearts or limbs.

Typically for ocular diseases via intravitreal application smaller antibody fragments like Fab or Fab(2) are often used as they have a low serum half-life and the risk of systemic toxicities is lower. However this smaller fragments typically have also lower intravitreal half-lifes (e.g. due to the faster diffusion into serum) and have to be dosed typically more often.

Kim et al, Molecular Vision, 15 (2009) 2803-2812 relates to full length antibodies administered intravitreally in the eye, wherein an IgG with FcRn binding was eliminated into the blood in wild-type mice, whereas an IgY with no FcRn binding was not eliminated into the blood system. Furthermore the IgG with FcRn binding was not eliminated into the blood system in FcRn knockdown-mice.

There is a need in the art for better means for treating and preventing various ocular vascular diseases such as ischemic retinopathies.

Summary

The disclosure relates to a method for the reduction of the viscosity of an antibody wherein the antibody comprises a constant heavy chain region of human IgG1 or human IgG4 subclass (derived from human origin); and wherein the method comprises the modification of the antibody constant heavy chain region of human IgG1 or human IgG4 subclass with the mutations I253A, H310A, and H435A (numbering according to EU Index of Kabat).

One aspect of the disclosure is a method for the reduction of the viscosity of an antibody wherein the antibody comprises a constant heavy chain region of human IgG1 ~~or human IgG4 subclass~~ (derived from human origin); and wherein the antibody is a bispecific antibody comprising a first antigen-binding site that specifically binds to human VEGF and a second antigen-binding site that specifically binds to human ANG-2, wherein

i) said first antigen-binding site specifically binding to VEGF comprises in the heavy chain variable domain a CDR3H region of SEQ ID NO: 1, a CDR2H region of SEQ ID NO: 2, and a CDR1H region of SEQ ID NO:3, and in the light chain variable domain a CDR3L region of SEQ ID NO: 4, a CDR2L region of SEQ ID NO:5, and a CDR1L region of SEQ ID NO:6; and

ii) said second antigen-binding site specifically binding to ANG-2 comprises in the heavy chain variable domain a CDR3H region of SEQ ID NO: 9, a CDR2H region of, SEQ ID NO: 10, and a CDR1H region of SEQ ID NO: 11, and in the light chain variable domain a CDR3L region of SEQ ID NO: 12, a CDR2L region of SEQ ID NO: 13, and a CDR1L region of SEQ ID NO: 14, and wherein

iii) the bispecific antibody comprises a constant heavy chain region of human IgG1 ~~or human IgG4 subclass~~ (derived from human origin); and~~)~~ comprising the mutations I253A, H310A, and H435A (numbering according to EU Index of Kabat)

wherein the method comprises

the modification of the antibody constant heavy chain region of human IgG1 with the mutations I253A, H310A, and H435A (numbering according to EU Index of Kabat).

In one embodiment of the disclosure said method is characterized in that the antibody is a bispecific antibody comprising a first antigen-binding site that specifically binds to human VEGF and a second antigen-binding site that specifically binds to human ANG-2, wherein

i) said first antigen-binding site specifically binding to VEGF comprises in the heavy chain variable domain a CDR3H region of SEQ ID NO: 1, a CDR2H region of SEQ ID NO: 2, and a CDR1H region of SEQ ID NO:3, and in the light chain variable domain a CDR3L region of SEQ ID NO: 4, a CDR2L region of SEQ ID NO:5, and a CDR1L region of SEQ ID NO:6; and

ii) said second antigen-binding site specifically binding to ANG-2 comprises in the heavy chain variable domain a CDR3H region of SEQ ID NO: 9, a CDR2H region of, SEQ ID NO: 10, and a CDR1H region of SEQ ID NO: 11, and in the light chain variable domain a CDR3L region of SEQ ID NO: 12, a CDR2L region of SEQ ID NO: 13, and a CDR1L region of SEQ ID NO: 14, and wherein

iii) the bispecific antibody comprises a constant heavy chain region of human IgG1 or human IgG4 subclass (derived from human origin); and comprising the mutations I253A, H310A, and H435A (numbering according to EU Index of Kabat).

In one embodiment of the disclosure such method is characterized in that said bispecific antibody described above comprises a constant heavy chain region of human IgG1 subclass (derived from human origin); and comprising the mutations I253A, H310A, and H435A (numbering according to EU Index of Kabat) and further comprising the mutations L234A , L235A and P329G (numbering according to EU Index of Kabat).

One embodiment of the disclosure is an antibody obtained by such method.

The disclosure also relates to the use of the mutations I253A, H310A, and H435A (numbering according to EU Index of Kabat) for the reduction of the viscosity of an antibody wherein the antibody comprises a constant heavy chain region of human IgG1 or human IgG4 subclass (derived from human origin).

One aspect of the disclosure is the use of the mutations I253A, H310A, and H435A (numbering according to EU Index of Kabat) for the reduction of the viscosity of an antibody wherein the antibody comprises a constant heavy chain region of human IgG1 ~~or human IgG4 subclass~~(derived from human origin); and wherein the antibody is a bispecific antibody comprising a first antigen-binding site that specifically binds to human VEGF and a second antigen-binding site that specifically binds to human ANG-2, wherein

i) said first antigen-binding site specifically binding to VEGF comprises in the heavy chain variable domain a CDR3H region of SEQ ID NO: 1, a CDR2H region of SEQ ID NO: 2, and a CDR1H region of SEQ ID NO:3, and in the light chain variable domain a CDR3L region of SEQ ID NO: 4, a CDR2L region of SEQ ID NO:5, and a CDR1L region of SEQ ID NO:6; and

ii) said second antigen-binding site specifically binding to ANG-2 comprises in the heavy chain variable domain a CDR3H region of SEQ ID NO: 9, a CDR2H region of, SEQ ID NO: 10, and a CDR1H region of SEQ ID NO: 11, and in the light chain variable domain a CDR3L region of SEQ ID NO: 12, a CDR2L region of SEQ ID NO: 13, and a CDR1L region of SEQ ID NO: 14, and wherein

iii) the bispecific antibody comprises a constant heavy chain region of human IgG1 (derived from human origin); and comprising the mutations I253A, H310A, and H435A (numbering according to EU Index of Kabat).

In one embodiment of the disclosure said use is characterized in that the antibody is a bispecific antibody comprising a first antigen-binding site that specifically binds to human VEGF and a second antigen-binding site that specifically binds to human ANG-2,
wherein

i) said first antigen-binding site specifically binding to VEGF comprises in the heavy chain variable domain a CDR3H region of SEQ ID NO: 1, a CDR2H region of SEQ ID NO: 2, and a CDR1H region of SEQ ID NO:3, and in the light chain variable domain a CDR3L region of SEQ ID NO: 4, a CDR2L region of SEQ ID NO:5, and a CDR1L region of SEQ ID NO:6; and

ii) said second antigen-binding site specifically binding to ANG-2 comprises in the heavy chain variable domain a CDR3H region of SEQ ID NO: 9, a CDR2H region of, SEQ ID NO: 10, and a CDR1H region of SEQ ID NO: 11, and in the light chain variable domain a CDR3L region of SEQ ID NO: 12, a CDR2L region of SEQ ID NO: 13, and a CDR1L region of SEQ ID NO: 14, and wherein

iii) the bispecific antibody comprises a constant heavy chain region of human IgG1 or human IgG4 subclass (derived from human origin); and comprising the mutations I253A, H310A, and H435A (numbering according to EU Index of Kabat).

In one embodiment of the disclosure said specific use is characterized in that the bispecific antibody comprises a constant heavy chain region of human IgG1 subclass (derived from human origin); and comprising the mutations I253A, H310A, and H435A (numbering according to EU Index of Kabat) and further comprising the mutations L234A , L235A and P329G (numbering according to EU Index of Kabat).

One aspect of the disclosure is directed to a bispecific, bivalent antibody comprising a first antigen-binding site that specifically binds to human VEGF and a second antigen-binding site that specifically binds to human ANG-2, wherein

i) said first antigen-binding site specifically binding to VEGF comprises in the heavy chain variable domain a CDR3H region of SEQ ID NO: 1, a CDR2H region of SEQ ID NO: 2, and a CDR1H region of SEQ ID NO:3, and in the light chain variable domain a CDR3L region of SEQ ID NO: 4, a CDR2L region of SEQ ID NO:5, and a CDR1L region of SEQ ID NO:6; and

ii) said second antigen-binding site specifically binding to ANG-2 comprises in the heavy chain variable domain a CDR3H region of SEQ ID NO: 9, a CDR2H region of, SEQ ID NO: 10, and a CDR1H region of SEQ ID NO: 11, and in the light chain variable domain a CDR3L region of SEQ ID NO: 12, a CDR2L region of SEQ ID NO: 13, and a CDR1L region of SEQ ID NO: 14,

and wherein

iii) the bispecific antibody comprises a constant heavy chain region of human IgG1 or human IgG4 subclass (derived from human origin); and comprising the mutations I253A, H310A, and H435A (numbering according to EU Index of Kabat).

In one embodiment said bispecific antibody is characterized in that

i) said first antigen-binding site specifically binding to VEGF comprises as heavy chain variable domain VH an amino acid sequence of SEQ ID NO: 7, and as light chain variable domain VL an amino acid sequence of SEQ ID NO: 8, and

ii) said second antigen-binding site specifically binding to ANG-2 comprises as heavy chain variable domain VH an amino acid sequence of SEQ ID NO: 15, and as light chain variable domain VL an amino acid sequence of SEQ ID NO: 16.

In one embodiment said bispecific antibody is characterized in that the constant heavy chain region under iii) is of human IgG1 subclass. In one embodiment said bispecific antibody of IgG1 subclass is characterized in that the constant heavy chain region of IgG1 subclass further comprises the mutations L234A , L235A and P329G (numbering according to EU Index of Kabat)

In one embodiment said bispecific antibody is characterized in that the constant heavy chain region under iii) is of human IgG4 subclass. In one embodiment said bispecific antibody of IgG4 subclass is characterized in that the constant heavy chain region of IgG4 subclass further comprises the mutations S228P and L235E (numbering according to EU Index of Kabat). In one embodiment said bispecific antibody of IgG4 subclass is characterized in that the constant heavy chain region of IgG4 subclass further comprises the mutations S228P , L235E and P329G (numbering according to EU Index of Kabat)

Still further ambodiments of the disclosure are a pharmaceutical composition comprising said bispecific antibody, said pharmaceutical composition for use in the treatment of ocular vascular diseases, the use of said bispecific antibody for the manufacture of a medicament for the treatment of ocular vascular diseases, a method of treatment of patient suffering from ocular vascular diseases by administering said bispecific antibody to a patient in the need of such treatment. One aspect of the disclosure is the bispecific antibody as defined herein for use in the treatment of ocular vascular diseases. In one embodiment

the bispecific antibody or the pharmaceutical composition comprising said bispecific antibody is administered via intravitreal application.

A further embodiment of the disclosure is a nucleic acid molecule encoding a heavy and/or light chain of a bispecific antibody according to the disclosure. One aspect of the disclosure is a nucleic acid encoding a bispecific antibody as defined herein.

The disclosure further provides, in one aspect, expression vectors containing said nucleic acid according to the disclosure capable of expressing said nucleic acid in a prokaryotic or eukaryotic host cell. The host cells may contain such vectors for the recombinant production of a bispecific antibody according to the disclosure.

One aspect of the disclolsure further comprises a prokaryotic or eukaryotic host cell comprising a vector according to the disclosure.

The disclosure further comprises a method for the production of a bispecific antibody according to the disclosure, characterized by expressing a nucleic acid according to the disclosure in a prokaryotic or eukaryotic host cell and recovering said bispecific antibody from said cell or the cell culture supernatant. One aspect is a method for the preparation of a bispecific antibody according to the disclosure comprising the steps of

a) transforming a host cell with vectors comprising nucleic acid molecules encoding said antibody;

b) culturing the host cell under conditions that allow synthesis of said antibody molecule; and

c) recovering said antibody molecule from said culture

~~One aspect of t~~The disclosure further comprises the bispecific antibody obtained by such method for the production of a bispecific antibody.

Accordingly one aspect of the disclosure is a bispecific, bivalent antibody comprising a first antigen-binding site that specifically binds to human VEGF and a second antigen-binding site that specifically binds to human ANG-2, characterized in comprising the amino acid sequences of SEQ ID NO: 21, of SEQ ID NO: 22, of SEQ ID NO: 23, and of SEQ ID NO: 24.

Accordingly one aspect of the disclosure is a bispecific, bivalent antibody comprising a first antigen-binding site that specifically binds to human VEGF and

In one embodiment the bispecific, bivalent antibody is characterized in comprising

a first antigen-binding site that specifically binds to human VEGF and a second antigen-binding site that specifically binds to human ANG-2, characterized in that

i) said first antigen-binding site comprises as heavy chain variable domain (VH) the SEQ ID NO: 7, and as light chain variable domain (VL) the SEQ ID NO: 8; and

ii) said second antigen-binding site comprises as heavy chain variable domain (VH) the SEQ ID NO: 15, and as light chain variable domain (VL) the SEQ ID NO: 16; and

iii) the bispecific antibody comprises a constant heavy chain region of IgG1 or IgG4 subclass (derived from human origin); and comprising the mutations I253A, H310A, and H435A (numbering according to EU Index of Kabat)

and having one or more of the following properties (determined in assays as described in Example 6

- shows a lower serum concentration compared to corresponding bispecific antibody without the mutations described under iii) (96 hours after intravitreal application in mice, which are mouse FcRn deficient, but hemizygous transgenic for human FcRn);

- shows a similar (factor 0.8 to 1.2) concentration in whole right eye lysates compared to corresponding bispecific antibody without the mutations described under iii) (in mice, which are mouse FcRn deficient, but hemizygous transgenic for human FcRn, 96 hours after intravitreal application in the right eye).

In one embodiment the bispecific antibody is characterized in comprising
a first antigen-binding site that specifically binds to human VEGF and a second antigen-binding site that specifically binds to human ANG-2, characterized in that

i) said first antigen-binding site comprises as heavy chain variable domain (VH) the SEQ ID NO: 7 with 1, 2 or 3 amino acid residue substitutions,

and as light chain variable domain (VL) the SEQ ID NO: 8 with 1, 2 or 3 amino acid residue substitutions; and

ii) said second antigen-binding site comprises as heavy chain variable domain (VH) the SEQ ID NO: 15 with 1, 2 or 3 amino acid residue substitutions, and as light chain variable domain (VL) the SEQ ID NO: with 1, 2 or 3 amino acid residue substitutions; and

iii) the bispecific antibody comprises a constant heavy chain region of IgG1 or IgG4 subclass (derived from human origin)~~;~~ and~~)~~ comprising the mutations I253A, H310A, and H435A (numbering according to EU Index of Kabat)

and having one or more of the following properties (determined in assays as described in Example 6

- shows a lower serum concentration compared to corresponding bispecific antibody without the mutations described under iii) (96 hours after intravitreal application in mice, which are mouse FcRn deficient, but hemizygous transgenic for human FcRn);

- shows a similar (factor 0.8 to 1.2) concentration in whole right eye lysates compared to corresponding bispecific antibody without the mutations described under iii) (in mice, which are mouse FcRn deficient, but hemizygous transgenic for human FcRn, 96 hours after intravitreal application in the right eye).

As used herein, "antibody" refers to a binding protein that comprises antigen-binding sites. The terms “binding site” or “antigen-binding site” as used herein denotes the region(s) of an antibody molecule to which a ligand actually binds. The term “antigen-binding site” comprises an antibody heavy chain variable domains (VH) and an antibody light chain variable domains (VL) (pair of VH/VL).).

Antibody specificity refers to selective recognition of the antibody for a particular epitope of an antigen. Natural antibodies, for example, are monospecific.

“Bispecific antibodies” according to the invention are antibodies which have two different antigen-binding specificities. Antibodies of the present invention are

SEQ ID NO:	49	heavy chain constant region derived from human IgG1
SEQ ID NO:	50	heavy chain constant region derived from human IgG4

In the following, embodiments of the invention are listed:

1. A bispecific antibody comprising a first antigen-binding site that specifically binds to human VEGF and a second antigen-binding site that specifically binds to human ANG-2,
wherein

i) said first antigen-binding site specifically binding to VEGF comprises in the heavy chain variable domain a CDR3H region of SEQ ID NO: 1, a CDR2H region of SEQ ID NO: 2, and a CDR1H region of SEQ ID NO:3, and in the light chain variable domain a CDR3L region of SEQ ID NO: 4, a CDR2L region of SEQ ID NO:5, and a CDR1L region of SEQ ID NO:6; and

ii) said second antigen-binding site specifically binding to ANG-2 comprises in the heavy chain variable domain a CDR3H region of SEQ ID NO: 9, a CDR2H region of, SEQ ID NO: 10, and a CDR1H region of SEQ ID NO: 11, and in the light chain variable domain a CDR3L region of SEQ ID NO: 12, a CDR2L region of SEQ ID NO: 13, and a CDR1L region of SEQ ID NO: 14, and wherein

iii) the bispecific antibody comprises a constant heavy chain region of human IgG1 or human IgG4 subclass (derived from human origin); and comprising the mutations I253A, H310A, and H435A (numbering according to EU Index of Kabat)

2. The bispecific antibody according to embodiment 1, wherein

i) said first antigen-binding site specifically binding to VEGF comprises as heavy chain variable domain VH an amino acid sequence of SEQ ID NO: 7, and as light chain variable domain VL an amino acid sequence of SEQ ID NO: 8, and

ii) said second antigen-binding site specifically binding to ANG-2 comprises as heavy chain variable domain VH an amino acid sequence

Patent Claims

1. A method for the reduction of the viscosity of an antibody wherein the antibody comprises a constant heavy chain region of human IgG1 ~~or human IgG4 subclass~~ (derived from human origin); and~~)~~ wherein the antibody is a bispecific antibody comprising a first antigen-binding site that specifically binds to human VEGF and a second antigen-binding site that specifically binds to human ANG-2,

wherein

i) said first antigen-binding site specifically binding to VEGF comprises in the heavy chain variable domain a CDR3H region of SEQ ID NO: 1, a CDR2H region of SEQ ID NO: 2, and a CDR1H region of SEQ ID NO:3, and in the light chain variable domain a CDR3L region of SEQ ID NO: 4, a CDR2L region of SEQ ID NO:5, and a CDR1L region of SEQ ID NO:6; and

ii) said second antigen-binding site specifically binding to ANG-2 comprises in the heavy chain variable domain a CDR3H region of SEQ ID NO: 9, a CDR2H region of, SEQ ID NO: 10, and a CDR1H region of SEQ ID NO: 11, and in the light chain variable domain a CDR3L region of SEQ ID NO: 12, a CDR2L region of SEQ ID NO: 13, and a CDR1L region of SEQ ID NO: 14, and wherein

iii) the bispecific antibody comprises a constant heavy chain region of human IgG1 ~~or human IgG4 subclass~~ (derived from human origin); and~~)~~ comprising the mutations I253A, H310A, and H435A (numbering according to EU Index of Kabat)

wherein the method comprises
the modification of the antibody constant heavy chain region of human IgG1 with the mutations I253A, H310A, and H435A (numbering according to EU Index of Kabat).

2. The method of claim 1, wherein the bispecific antibody comprises a constant heavy chain region of human IgG1 subclass (derived from human origin); and comprising the mutations I253A, H310A, and H435A (numbering according to EU Index of Kabat) and further comprising the mutations L234A , L235A and P329G (numbering according to EU Index of Kabat).

3. Use of the mutations I253A, H310A, and H435A (numbering according to EU Index of Kabat) for the reduction of the viscosity of an antibody wherein the antibody comprises a constant heavy chain region of human IgG1 ~~or human IgG4 subclass~~(derived from human origin); and

wherein the antibody is a bispecific antibody comprising a first antigen-binding site that specifically binds to human VEGF and a second antigen-binding site that specifically binds to human ANG-2, wherein

i) said first antigen-binding site specifically binding to VEGF comprises in the heavy chain variable domain a CDR3H region of SEQ ID NO: 1, a CDR2H region of SEQ ID NO: 2, and a CDR1H region of SEQ ID NO:3, and in the light chain variable domain a CDR3L region of SEQ ID NO: 4, a CDR2L region of SEQ ID NO:5, and a CDR1L region of SEQ ID NO:6; and

ii) said second antigen-binding site specifically binding to ANG-2 comprises in the heavy chain variable domain a CDR3H region of SEQ ID NO: 9, a CDR2H region of, SEQ ID NO: 10, and a CDR1H region of SEQ ID NO: 11, and in the light chain variable domain a CDR3L region of SEQ ID NO: 12, a CDR2L region of SEQ ID NO: 13, and a CDR1L region of SEQ ID NO: 14, and wherein

iii) the bispecific antibody comprises a constant heavy chain region of human IgG1 (derived from human origin)~~;~~ and~~)~~ comprising the mutations I253A, H310A, and H435A (numbering according to EU Index of Kabat).

4. The use of claim 3, wherein the bispecific antibody comprises a constant heavy chain region of human IgG1 subclass (derived from human origin)~~;~~ and~~)~~ comprising the mutations I253A, H310A, and H435A (numbering according to EU Index of Kabat) and further comprising the mutations L234A , L235A and P329G (numbering according to EU Index of Kabat).

5. A bispecific antibody comprising a first antigen-binding site that specifically binds to human VEGF and a second antigen-binding site that specifically binds to human ANG-2,

wherein

i) said first antigen-binding site specifically binding to VEGF comprises in the heavy chain variable domain a CDR3H region of SEQ ID NO: 1, a CDR2H region of SEQ ID NO: 2, and a CDR1H region of SEQ ID NO:3, and in the light chain variable domain a CDR3L region of SEQ ID NO: 4, a CDR2L region of SEQ ID NO:5, and a CDR1L region of SEQ ID NO:6; and

ii) said second antigen-binding site specifically binding to ANG-2 comprises in the heavy chain variable domain a CDR3H region of SEQ ID NO: 9, a CDR2H region of, SEQ ID NO: 10, and a CDR1H region of SEQ ID NO: 11, and in the light chain variable domain a CDR3L region of SEQ ID NO: 12, a CDR2L region of SEQ ID NO: 13, and a CDR1L region of SEQ ID NO: 14, and wherein

iii) the bispecific antibody comprises a constant heavy chain region of human IgG1 (derived from human origin); and~~)~~ comprising the mutations I253A, H310A, and H435A (numbering according to EU Index of Kabat)

6. The bispecific antibody according to claim 5, wherein

i) said first antigen-binding site specifically binding to VEGF comprises as heavy chain variable domain VH an amino acid sequence of SEQ ID NO: 7, and as light chain variable domain VL an amino acid sequence of SEQ ID NO: 8, and

ii) said second antigen-binding site specifically binding to ANG-2 comprises as heavy chain variable domain VH an amino acid sequence of SEQ ID NO: 15, and as light chain variable domain VL an amino acid sequence of SEQ ID NO: 16.

~~7. The bispecific antibody according to any one of claims 5 to 6, wherein the constant heavy chain region under iii) is of IgG1 subclass.~~

~~8~~7. The bispecific antibody according to any one of claim ~~7~~5 or 6, wherein the constant heavy chain region of IgG1 subclass further comprises the mutations L234A , L235A and P329G (numbering according to EU Index of Kabat)

~~9. The bispecific antibody according to any one of claims 5 to 6, wherein the constant heavy chain region under iii) is of IgG4 subclass~~

~~10~~8. A pharmaceutical composition comprising an antibody according to any one of claims 5 to ~~9~~7.

~~11~~9. The bispecific antibody according to any one of claims 5 to ~~9~~ 7 for use in the treatment of ocular vascular diseases.

~~12~~10. The bispecific antibody according to claim ~~11~~9, wherein the antibody is administered via intravitreal application.

~~13~~11. A nucleic acid encoding a bispecific antibody according to any one of claims 5 to ~~9~~7.

~~14~~12. Expression vector containing said nucleic acid according claim ~~13~~ 11 capable of expressing said nucleic acid in a prokaryotic or eukaryotic host cell.

~~15~~13. A prokaryotic or eukaryotic host cell comprising a vector according to claim ~~14~~12.

~~16~~14. A method for the preparation of a bispecific antibody according to any one of claims 5 to ~~9~~7

comprising the steps of

a) transforming a host cell with vectors comprising nucleic acid molecules encoding said antibody;

b) culturing the host cell under conditions that allow synthesis of said antibody molecule; and

c) recovering said antibody molecule from said culture.

~~17. A bispecific antibody obtained by the method of claim 16.~~

~~18~~15. A bispecific, bivalent antibody comprising a first antigen-binding site that specifically binds to human VEGF and a second antigen-binding site that specifically binds to human ANG-2, characterized in comprising the amino acid sequences of SEQ ID NO: 25, of SEQ ID NO: 26, of SEQ ID NO: 27, and of SEQ ID NO: 28.

~~19~~16. A bispecific, bivalent antibody comprising a first antigen-binding site that specifically binds to human VEGF and a second antigen-binding site that specifically binds to human ANG-2, characterized in comprising the amino acid sequences of SEQ ID NO: 21, of SEQ ID NO: 22., of SEQ ID NO: 23., and of SEQ ID NO: 24.

~~20~~17. The bispecific antibody according to any one of claims ~~claims 18~~ 15 ~~to~~ or ~~19~~ 16 for use in the treatment of ocular vascular diseases.

~~21~~18. The bispecific antibody according to claim ~~20~~17, wherein the antibody is administered via intravitreal application.

~~22~~19. Use of the bispecific antibody according to any one of claims 5 to ~~9~~7, 15 or 16~~and claims 18 to 19~~ in the manufacture of a medicament for the treatment of ocular vascular diseases.

~~23~~20. Use of claim ~~22~~19, wherein the antibody is administered via intravitreal application.