

into the biparatopic VH and VL pair. One exemplary Fab fragment specifically binding to VEGF and IL-6 is disclosed in WO2012/163520.

Yet there is a need for improved therapeutic antibodies that bind to VEGF and ANG2, e.g. by improving efficacy vs. standard-of-care and by improving duration of action and in turn, reducing frequency of intravitreal injections, leading to less administration burden for the patient.

SUMMARY ~~OF THE INVENTION~~

The present ~~invention~~disclosure relates to bispecific anti-VEGF-A/anti-ANG2 antibodies and methods of using the same.

~~In one aspect the invention~~The disclosure provides antibody that binds to human VEGF-A and to human ANG2, comprising a VEGF-A paratope and an ANG2 paratope within one cognate pair of a variable light chain domain (VL domain) and a variable heavy chain domain (VH domain), wherein the VEGF-A paratope comprises amino acid residues from CDR-H2, CDR-L1 and CDR-L3 of the antibody, wherein the ANG2 paratope comprises amino acid residues from the CDR-H1, CDR-H3 and CDR-L2 of the antibody.

~~In one aspect the invention~~The disclosure provides an antibody that binds to human VEGF-A and to human ANG2, comprising a VEGF-A paratope and an ANG2 paratope within one cognate pair of a variable light chain domain (VL domain) and a variable heavy chain domain (VH domain), wherein the pair of the variable light chain domain and the variable heavy chain domain simultaneously binds to human VEGF-A and human ANG2.

~~In one aspect the invention~~The disclosure provides an antibody that binds to human VEGF-A and to human ANG2, comprising a VEGF-A paratope and an ANG2 paratope within one cognate pair of a variable light chain domain (VL domain) and a variable heavy chain domain (VH domain), wherein the antibody binds to the same epitope on human VEGF-A and to the same epitope on human ANG2 as an antibody with a variable heavy chain domain of SEQ ID NO: 19 and a variable light chain domain of SEQ ID NO: 20.

~~In one aspect the invention~~The disclosure provides an antibody that binds to human VEGF-A and to human ANG2, wherein an antibody Fab fragment of the antibody

binds (i) to human VEGF-A121 with a K_D of less than 50 pM as measured by KinExA, and (ii) to human ANG2 with a K_D of less than 50 pM as measured by KinExA.

~~In one aspect the invention~~The disclosure provides an antibody that binds to human VEGF-A and to human ANG2, wherein an antibody Fab fragment of the antibody exhibits an aggregation onset temperature of 70 °C or more as measured by static light scattering (SLS), in one ~~embodiment~~example as measured by SLS as described in the chapter “Thermal stability” in the Materials & general methods section.

~~In one aspect the invention~~The disclosure provides an antibody that binds to human VEGF-A and to human ANG2, wherein an antibody Fab fragment of the antibody exhibits a melting temperature of more than 80 °C as measured by static light scattering (SLS), in one ~~embodiment~~example as measured by SLS as described in the chapter “Thermal stability” in the Materials & general methods section.

~~In one aspect the invention~~The disclosure provides an antibody that binds to human VEGF-A and to human ANG2, wherein a 20mM His/HisHCl, pH 6.0 solution comprising 180 mg/ml of the antibody Fab fragment has a viscosity of less than 20 cP at 20 °C as detected by dynamic light scattering with a latex-bead DLS method as described in Example 8.

In one aspect the ~~invention~~disclosure provides an antibody that binds to human VEGF-A and to human ANG2, wherein the antibody comprises a VH domain comprising (a) CDR-H1 comprising the amino acid sequence of SEQ ID NO:3, (b) CDR-H2 comprising the amino acid sequence of SEQ ID NO:21, and (c) CDR-H3 comprising the amino acid sequence of SEQ ID NO:14, and a VL domain comprising (d) CDR-L1 comprising the amino acid sequence of SEQ ID NO:22, (e) CDR-L2 comprising the amino acid sequence of SEQ ID NO:23, and (f) CDR-L3 comprising the amino acid sequence of SEQ ID NO:8.

In one ~~aspect-example~~ the ~~invention~~disclosure provides an antibody that binds to human VEGF-A and to human ANG2, wherein the amino acid sequence of SEQ ID NO:21, and (c) CDR-H3 comprising the amino acid sequence of SEQ ID NO:14, (d) a human heavy chain framework with (i) FR1 comprising amino acid residues H3, D26, F27, E29, and Y30, (ii) FR3 comprising amino acid residues R66 and R94; and a VL domain comprising (e) CDR-L1 comprising the amino acid sequence of SEQ ID NO:22, (f) CDR-L2 comprising the amino acid sequence of SEQ ID NO:23, (g) CDR-L3 comprising the amino acid sequence of SEQ ID NO:8, and (h) a human

light chain framework with (i) FR1 comprising amino acid residues I2 and Y3, (ii) FR2 comprising amino acid residues L46 and F49, (iii) FR3 comprising amino acid residue E57, wherein the numbering of the VH and VL domains is according to the Kabat numbering system.

In another aspect, the present disclosure provides an antibody that binds to human VEGF-A and to human ANG2, wherein the antibody comprises a VH domain comprising (a) CDR-H1 comprising the amino acid sequence of SEQ ID NO:3, (b) CDR-H2 comprising the amino acid sequence of SEQ ID NO:21, and (c) CDR-H3 comprising the amino acid sequence of SEQ ID NO:14, (d) a human heavy chain framework with (i) FR1 comprising amino acid residues H3, D26, F27, E29, and Y30, (ii) FR3 comprising amino acid residues R66 and R94; and a VL domain comprising (e) CDR-L1 comprising the amino acid sequence of SEQ ID NO:22, (f) CDR-L2 comprising the amino acid sequence of SEQ ID NO:23, (g) CDR-L3 comprising the amino acid sequence of SEQ ID NO:8, and (h) a human light chain framework with (i) FR1 comprising amino acid residues I2 and Y3, (ii) FR2 comprising amino acid residues L46 and F49, (iii) FR3 comprising amino acid residue E57, wherein the numbering of the VH and VL domains is according to the Kabat numbering system.

~~In one aspect the invention~~The disclosure provides an antibody that binds to human VEGF-A and to human ANG2 comprising a VH domain comprising amino acid residues H3, D26, F27, E29, Y30, D35b, D35c, D55, H56, K57, Y58, T61, K62, F63, I64, G65, R66, R94, D95, V96, F98, and F99, and a VL domain comprising amino acid residues I2, Y3, Y27, W27a, E32, L46, F49, D50, F53, K54, V55, Y56, E57, Y91, R92, Y93, H94, and P95, wherein the numbering of the VH and VL domains is according to the Kabat numbering system. In one ~~embodiment~~example the antibody comprises a VEGF-A paratope comprising the following amino acid residues in the VH domain D35c, D55, H56, K57, Y58, T61, K62, F63, I64, G65, R66, and D95, and the following amino acid residues in the VL domain I2, Y3, Y27, W27a, E32, R92, Y93, H94, and P95; and an ANG2 paratope comprising the following amino acid residues in the VH domain H3, D26, F27, E29, Y30, D35b, R94, V96, F98, and F99, and the following amino acid residues in the VL domain E32, L46, F49, D50, F53, K54, V55, Y56, E57, and Y91.

~~In one aspect the invention~~The disclosure provides an antibody that binds to human VEGF-A and to human ANG2 comprising (a) a VH domain comprising an amino acid sequence having at least 90% sequence identity to the amino acid sequence of SEQ ID NO:19; and (b) a VL domain comprising an amino acid sequence having at least 90% sequence identity to the amino acid sequence of SEQ ID NO:20.

~~In one aspect the invention~~The disclosure provides an antibody that binds to human VEGF-A and to human ANG2 comprising a VH domain comprising (a) CDR-H1 comprising the amino acid sequence of SEQ ID NO:3, (b) CDR-H2 comprising the amino acid sequence of SEQ ID NO:21, and (c) CDR-H3 comprising the amino acid sequence of SEQ ID NO:14, and a VL domain comprising (d) CDR-L1 comprising the amino acid sequence of SEQ ID NO:22, (e) CDR-L2 comprising the amino acid sequence of SEQ ID NO:23, and (f) CDR-L3 comprising the amino acid sequence of SEQ ID NO:8, comprising (a) a VH domain comprising an amino acid sequence having at least 90% sequence identity to the amino acid sequence of SEQ ID NO:19; and (b) a VL domain comprising an amino acid sequence having at least 90% sequence identity to the amino acid sequence of SEQ ID NO:20.

~~In one aspect the invention~~The disclosure provides an antibody that binds to human VEGF-A and to human ANG2 comprising a VH domain comprising (a) CDR-H1 comprising the amino acid sequence of SEQ ID NO:3, (b) CDR-H2 comprising the amino acid sequence of SEQ ID NO:21, and (c) CDR-H3 comprising the amino acid sequence of SEQ ID NO:14, and a VL domain comprising (d) CDR-L1 comprising the amino acid sequence of SEQ ID NO:22, (e) CDR-L2 comprising the amino acid sequence of SEQ ID NO:23, and (f) CDR-L3 comprising the amino acid sequence of SEQ ID NO:8, comprising (a) a VH domain comprising an amino acid sequence having at least 90% sequence identity to the amino acid sequence of SEQ ID NO:19, wherein the VH domain comprises amino acid residues H3, D26, F27, E29, Y30, R66 and R94; and (b) a VL domain comprising an amino acid sequence having at least 90% sequence identity to the amino acid sequence of SEQ ID NO:20, wherein the VL domain comprises amino acid residues I2, Y3, L46, F49, and E57, wherein the numbering of the VH and VL domains is according to the Kabat numbering system.

~~In one aspect the invention~~The disclosure provides an antibody that binds to human VEGF-A and to human ANG2 comprising a VH domain comprising (a) CDR-H1 comprising the amino acid sequence of SEQ ID NO:3, (b) CDR-H2 comprising the amino acid sequence of SEQ ID NO:21, and (c) CDR-H3 comprising the amino acid sequence of SEQ ID NO:14, (d) a human heavy chain framework with (i) FR1 comprising amino acid residues H3, D26, F27, E29, and Y30, (ii) FR3 comprising amino acid residues R66 and R94; and a VL domain comprising (e) CDR-L1 comprising the amino acid sequence of SEQ ID NO:22, (f) CDR-L2 comprising the amino acid sequence of SEQ ID NO:23, (g) CDR-L3 comprising the amino acid sequence of SEQ ID NO:8, and (h) a human light chain framework with (i) FR1 comprising amino acid residues I2 and Y3, (ii) FR2 comprising amino acid residues L46 and F49, (iii) FR3 comprising amino acid residue E57, wherein the numbering of the VH and VL domains is according to the Kabat numbering system, comprising (a) a VH domain comprising an amino acid sequence having at least 90% sequence identity to the amino acid sequence of SEQ ID NO:19; and (b) a VL domain comprising an amino acid sequence having at least 90% sequence identity to the amino acid sequence of SEQ ID NO:20.

~~In one aspect the invention~~The disclosure provides an antibody that binds to human VEGF-A and to human ANG2 comprising (a) a VH domain comprising an amino acid sequence of SEQ ID NO:19 with up to 15 amino acid substitutions, wherein the amino acid substitutions are located at one or more of positions 1, 2, 4 to 25, 28, 35d

to 54, 59, 60, 67 to 93, 97, 101 to 113 of SEQ ID NO:19; and (b) a variable light chain domain comprising an amino acid sequence of SEQ ID NO:20 with up to 15 amino acid substitutions, wherein the amino acid substitutions are located at positions 1, 4 to 26, 27b to 27d, 33 to 45, 47, 48, 51, 52, 58 to 90, 96 to 107 of SEQ ID NO:20, wherein the numbering of the VH and VL domains is according to the Kabat numbering system.

~~In one aspect the invention~~The disclosure provides an antibody that binds to human VEGF-A and to human ANG2 comprising (a) CDR-H1 comprising the amino acid sequence of SEQ ID NO:3, (b) CDR-H2 comprising the amino acid sequence of SEQ ID NO:21, and (c) CDR-H3 comprising the amino acid sequence of SEQ ID NO:14, and a VL domain (d) CDR-L1 comprising the amino acid sequence of SEQ ID NO:22, (e) CDR-L2 comprising the amino acid sequence of SEQ ID NO:23, and (f) CDR-L3 comprising the amino acid sequence of SEQ ID NO:8, comprising (a) a VH domain comprising an amino acid sequence of SEQ ID NO:19 with up to 15 amino acid substitutions; and (b) a variable light chain domain comprising an amino acid sequence of SEQ ID NO:20 with up to 15 amino acid substitutions.

~~In one aspect the invention~~The disclosure provides an antibody that binds to human VEGF-A and to human ANG2 comprising (a) CDR-H1 comprising the amino acid sequence of SEQ ID NO:3, (b) CDR-H2 comprising the amino acid sequence of SEQ ID NO:21, and (c) CDR-H3 comprising the amino acid sequence of SEQ ID NO:14, (d) a human heavy chain framework with (i) FR1 comprising amino acid residues H3, D26, F27, E29, and Y30, (ii) FR3 comprising amino acid residues R66 and R94; and a VL domain comprising (e) CDR-L1 comprising the amino acid sequence of SEQ ID NO:22, (f) CDR-L2 comprising the amino acid sequence of SEQ ID NO:23, (g) CDR-L3 comprising the amino acid sequence of SEQ ID NO:8, and (h) a human light chain framework with (i) FR1 comprising amino acid residues I2 and Y3, (ii) FR2 comprising amino acid residues L46 and F49, (iii) FR3 comprising amino acid residue E57, wherein the numbering of the VH and VL domains is according to the Kabat numbering system, and comprising (a) a VH domain comprising an amino acid sequence of SEQ ID NO:19 with up to 15 amino acid substitutions; and (b) a variable light chain domain comprising an amino acid sequence of SEQ ID NO:20 with up to 15 amino acid substitutions.

In ~~one another~~ aspect the ~~invention~~disclosure provides an antibody that binds to human VEGF-A and to human ANG2, comprising a VH sequence of SEQ ID NO:19 and a VL sequence of SEQ ID NO:20.

~~In one aspect the invention~~The disclosure provides an antibody that binds to human VEGF-A and to human ANG2 comprising a heavy chain amino acid sequence of SEQ ID NO:24 and a light chain amino acid sequence of SEQ ID NO:25.

5 ~~In one aspect the invention~~The disclosure provides an antibody that binds to human VEGF-A and to human ANG2 comprising (a) CDR-H1 comprising the amino acid sequence of SEQ ID NO:3, (b) CDR-H2 comprising the amino acid sequence of SEQ ID NO:21, and (c) CDR-H3 comprising the amino acid sequence of SEQ ID NO:14, and a VL domain comprising (d) CDR-L1 comprising the amino acid
10 sequence of SEQ ID NO:22, (e) CDR-L2 comprising the amino acid sequence of SEQ ID NO:23, and (f) CDR-L3 comprising the amino acid sequence of SEQ ID NO:8, wherein an antibody Fab fragment of the antibody binds (i) to human VEGF-A121 with a K_D of less than 50 pM as measured by KinExA, and (ii) to human ANG2 with a K_D of less than 50 pM as measured by KinExA.

15 ~~In one aspect the invention~~The disclosure provides an antibody that binds to human VEGF-A and to human ANG2 comprising a VH domain comprising (a) CDR-H1 comprising the amino acid sequence of SEQ ID NO:3, (b) CDR-H2 comprising the amino acid sequence of SEQ ID NO:21, and (c) CDR-H3 comprising the amino acid sequence of SEQ ID NO:14, (d) a human heavy chain framework with (i) FR1 comprising amino acid residues H3, D26, F27, E29, and Y30, (ii) FR3
20 comprising amino acid residues R66 and R94; and a VL domain comprising (e) CDR-L1 comprising the amino acid sequence of SEQ ID NO:22, (f) CDR-L2 comprising the amino acid sequence of SEQ ID NO:23, (g) CDR-L3 comprising the amino acid sequence of SEQ ID NO:8, and (h) a human light chain framework with (i) FR1 comprising amino acid residues I2 and Y3, (ii) FR2 comprising amino acid residues L46 and F49, (iii) FR3 comprising amino acid residue E57, wherein the numbering of the VH and VL domains is according to the Kabat numbering system, wherein the antibody comprises (a) a VH domain comprising an amino acid sequence having at least 90% sequence identity to the amino acid sequence of SEQ ID NO:19;
25 and (b) a VL domain comprising an amino acid sequence having at least 90% sequence identity to the amino acid sequence of SEQ ID NO:20; and wherein an antibody Fab fragment of the antibody binds (i) to human VEGF-A121 with a K_D of less than 50 pM as measured by KinExA, and (ii) to human ANG2 with a K_D of less than 50 pM as measured by KinExA.
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35 ~~In one aspect the invention~~The disclosure provides an antibody that binds to human VEGF-A and to human ANG2 comprising (a) CDR-H1 comprising the amino acid

sequence of SEQ ID NO:3, (b) CDR-H2 comprising the amino acid sequence of SEQ ID NO:21, and (c) CDR-H3 comprising the amino acid sequence of SEQ ID NO:14, and a VL domain comprising (d) CDR-L1 comprising the amino acid sequence of SEQ ID NO:22, (e) CDR-L2 comprising the amino acid sequence of SEQ ID NO:23, and (f) CDR-L3 comprising the amino acid sequence of SEQ ID NO:8, wherein an antibody Fab fragment of the antibody exhibits an aggregation onset temperature of 70 °C or more.

~~In one aspect the invention~~The disclosure provides an antibody that binds to human VEGF-A and to human ANG2 comprising a VH domain comprising (a) CDR-H1 comprising the amino acid sequence of SEQ ID NO:3, (b) CDR-H2 comprising the amino acid sequence of SEQ ID NO:21, and (c) CDR-H3 comprising the amino acid sequence of SEQ ID NO:14, (d) a human heavy chain framework with (i) FR1 comprising amino acid residues H3, D26, F27, E29, and Y30, (ii) FR3 comprising amino acid residues R66 and R94; and a VL domain comprising (e) CDR-L1 comprising the amino acid sequence of SEQ ID NO:22, (f) CDR-L2 comprising the amino acid sequence of SEQ ID NO:23, (g) CDR-L3 comprising the amino acid sequence of SEQ ID NO:8, and (h) a human light chain framework with (i) FR1 comprising amino acid residues I2 and Y3, (ii) FR2 comprising amino acid residues L46 and F49, (iii) FR3 comprising amino acid residue E57, wherein the numbering of the VH and VL domains is according to the Kabat numbering system, wherein the antibody comprises (a) a VH domain comprising an amino acid sequence having at least 90% sequence identity to the amino acid sequence of SEQ ID NO:19; and (b) a VL domain comprising an amino acid sequence having at least 90% sequence identity to the amino acid sequence of SEQ ID NO:20; and wherein an antibody Fab fragment of the antibody exhibits an aggregation onset temperature of 70 °C or more.

~~In one aspect the invention~~The disclosure provides an antibody that binds to human VEGF-A and to human ANG2 comprising (a) CDR-H1 comprising the amino acid sequence of SEQ ID NO:3, (b) CDR-H2 comprising the amino acid sequence of SEQ ID NO:21, and (c) CDR-H3 comprising the amino acid sequence of SEQ ID NO:14, and a VL domain comprising (d) CDR-L1 comprising the amino acid sequence of SEQ ID NO:22, (e) CDR-L2 comprising the amino acid sequence of SEQ ID NO:23, and (f) CDR-L3 comprising the amino acid sequence of SEQ ID NO:8, wherein an antibody Fab fragment of the antibody exhibits a melting temperature of more than 80 °C as measured by dynamic light scattering.

~~In one aspect the invention~~The disclosure provides an antibody that binds to human VEGF-A and to human ANG2 comprising a VH domain comprising (a) CDR-H1 comprising the amino acid sequence of SEQ ID NO:3, (b) CDR-H2 comprising the amino acid sequence of SEQ ID NO:21, and (c) CDR-H3 comprising the amino acid sequence of SEQ ID NO:14, (d) a human heavy chain framework with (i) FR1 comprising amino acid residues H3, D26, F27, E29, and Y30, (ii) FR3 comprising amino acid residues R66 and R94; and a VL domain comprising (e) CDR-L1 comprising the amino acid sequence of SEQ ID NO:22, (f) CDR-L2 comprising the amino acid sequence of SEQ ID NO:23, (g) CDR-L3 comprising the amino acid sequence of SEQ ID NO:8, and (h) a human light chain framework with (i) FR1 comprising amino acid residues I2 and Y3, (ii) FR2 comprising amino acid residues L46 and F49, (iii) FR3 comprising amino acid residue E57, wherein the numbering of the VH and VL domains is according to the Kabat numbering system, wherein the antibody comprises (a) a VH domain comprising an amino acid sequence having at least 90% sequence identity to the amino acid sequence of SEQ ID NO:19; and (b) a VL domain comprising an amino acid sequence having at least 90% sequence identity to the amino acid sequence of SEQ ID NO:20; and an antibody Fab fragment of the antibody exhibits a melting temperature of more than 80 °C as measured by dynamic light scattering.

~~In one aspect the invention~~The disclosure provides an antibody that binds to human VEGF-A and to human ANG2 comprising (a) CDR-H1 comprising the amino acid sequence of SEQ ID NO:3, (b) CDR-H2 comprising the amino acid sequence of SEQ ID NO:21, and (c) CDR-H3 comprising the amino acid sequence of SEQ ID NO:14, and a VL domain comprising (d) CDR-L1 comprising the amino acid sequence of SEQ ID NO:22, (e) CDR-L2 comprising the amino acid sequence of SEQ ID NO:23, and (f) CDR-L3 comprising the amino acid sequence of SEQ ID NO:8, wherein a 20mM His/HisHCl, pH 6.0 solution comprising 180 mg/ml of the antibody Fab fragment has a viscosity of less than 20 cP at 20 °C as detected by dynamic light scattering with a latex-bead DLS method as described in Example 8.

~~In one aspect the invention~~The disclosure provides an antibody that binds to human VEGF-A and to human ANG2 comprising a VH domain comprising (a) CDR-H1 comprising the amino acid sequence of SEQ ID NO:3, (b) CDR-H2 comprising the amino acid sequence of SEQ ID NO:21, and (c) CDR-H3 comprising the amino acid sequence of SEQ ID NO:14, (d) a human heavy chain framework with (i) FR1 comprising amino acid residues H3, D26, F27, E29, and Y30, (ii) FR3 comprising amino acid residues R66 and R94; and a VL domain comprising (e) CDR-L1

comprising the amino acid sequence of SEQ ID NO:22, (f) CDR-L2 comprising the amino acid sequence of SEQ ID NO:23, (g) CDR-L3 comprising the amino acid sequence of SEQ ID NO:8, and (h) a human light chain framework with (i) FR1 comprising amino acid residues I2 and Y3, (ii) FR2 comprising amino acid residues L46 and F49, (iii) FR3 comprising amino acid residue E57, wherein the numbering of the VH and VL domains is according to the Kabat numbering system, wherein the antibody comprises (a) a VH domain comprising an amino acid sequence having at least 90% sequence identity to the amino acid sequence of SEQ ID NO:19; and (b) a VL domain comprising an amino acid sequence having at least 90% sequence identity to the amino acid sequence of SEQ ID NO:20; and wherein a 20mM His/HisHCl, pH 6.0 solution comprising 180 mg/ml of the antibody Fab fragment has a viscosity of less than 20 cP at 20 °C as detected by dynamic light scattering with a latex-bead DLS method as described in Example 8.

~~One embodiment of the invention~~The disclosure relates to an antibody fragment that binds to human VEGF-A and to human ANG2. One ~~embodiment~~example of the ~~invention~~disclosure relates to a bispecific antibody fragment that binds to human VEGF-A and to human ANG2. In one ~~embodiment~~example the antibody fragment is selected from Fv, Fab, Fab', Fab'-SH, F(ab')₂ or single chain antibodies derived therefrom. One ~~embodiment~~example of the ~~invention~~disclosure relates to a Fab fragment that binds to human VEGF-A and to human ANG2. One ~~embodiment~~example of the ~~invention~~disclosure relates to an Fv fragment that binds to human VEGF-A and to human ANG2.

~~One embodiment of the invention~~The disclosure relates to a full length IgG antibody that binds to human VEGF-A and to human ANG2.

In ~~one another~~ aspect the ~~invention~~disclosure provides an isolated nucleic acid encoding the antibody of the ~~invention~~disclosure.

In ~~one another~~ aspect the ~~invention~~disclosure provides a host cell comprising the nucleic acid of the ~~invention~~disclosure. In one ~~embodiment~~example the host cell is a CHO cell. In one ~~embodiment~~example the host cell is an E. coli cell.

~~In one aspect the invention~~The disclosure provides an expression vector comprising the nucleic acid of the ~~invention~~disclosure.

In ~~one another~~ aspect the ~~invention~~disclosure provides a method of producing an antibody that binds to human VEGF-A and to human ANG2 comprising culturing the host cell of the ~~invention~~disclosure so that the antibody is produced.

~~In one aspect the invention~~The disclosure provides the antibody produced by the method of the ~~invention~~disclosure.

In ~~one another~~ aspect the ~~invention~~disclosure provides a pharmaceutical formulation comprising the antibody of the ~~invention~~disclosure and a pharmaceutically acceptable carrier.

~~In one aspect the invention~~The disclosure provides a pre-filled syringe comprising the antibody of the ~~invention~~disclosure and a pharmaceutically acceptable carrier.

~~In one aspect the invention~~The disclosure provides an ocular implant comprising the antibody of the ~~invention~~disclosure and a pharmaceutically acceptable carrier. ~~In one embodiment, the invention comprises~~In another aspect, the present disclosure provides a port delivery device comprising the antibody of the ~~invention~~disclosure.

In ~~one aspect of~~ the ~~invention~~disclosure the antibody or the pharmaceutical formulation is administered by a port delivery device.

~~In one aspect the invention~~The disclosure provides the antibody of the ~~invention~~disclosure for use as a medicament, in one ~~embodiment~~example for use in the treatment of a vascular disease. In another aspect, the present disclosure provides the antibody of the disclosure for use as a medicament.

~~In one aspect the invention~~The disclosure provides the use of the antibody of the ~~invention~~disclosure or the pharmaceutical composition of the ~~invention~~disclosure in the manufacture of a medicament, in one ~~embodiment~~example a medicament for the treatment of a vascular disease.

~~In one aspect the invention~~The disclosure provides a method of treating an individual having a vascular disease comprising administering to the individual an effective amount of the antibody of the ~~invention~~disclosure or the pharmaceutical composition of the ~~invention~~disclosure.

~~In one aspect the invention~~The disclosure provides a method of inhibiting angiogenesis in an individual comprising administering to the individual an effective amount of the antibody of the ~~invention~~disclosure or the pharmaceutical composition of the ~~invention~~disclosure to inhibit angiogenesis

According to the ~~invention~~disclosure a therapeutic anti-VEGF-A/anti-ANG2 antibody is provided that is capable of binding to its target antigens independently, even when it is provided in the form of an antibody Fab fragment. The antibody of the ~~invention~~disclosure is suitable for the treatment of ocular vascular diseases. The antibody of the ~~invention~~disclosure provides several valuable properties that allow its therapeutic application, like high affinities to both targets supporting a low efficacious dose, and a high stability

advantageous for long duration. Compared to non-antibody approaches the antibody of the ~~invention~~disclosure tends to be more acceptable due to its high humanness and lack of artificial domains and linkers. Also, the antibody of the ~~invention~~disclosure is advantageous to be provided in high concentrations liquid formulations with a viscosity suitable for ocular application. Due to being providable in high concentrations, treatment with an antibody of the ~~invention~~disclosure is more acceptable for a patient as a higher dose of the therapeutic can be applied at one treatment allowing for a longer treatment cycle. Furthermore, When used as a bispecific Fab fragment for therapy the antibody of the ~~invention~~disclosure allows more binding sites per dose when compared to a bispecific full length IgG antibody.

DESCRIPTION OF THE FIGURES

Figure 1: Schematic illustration of the Fab fragment of an anti-VEGF-A/anti-ANG2 antibody of the invention. Shown is a top down view of a cognate VH/VL pair including the arrangement of CDR amino acid (upper image). VH domain is indicated in grey, VL domain is indicated in white. Furthermore, the spatial arrangement of the CDR regions is indicated. Paratope regions of an antibody of the invention is highlighted (lower image), with the VEGF-A paratope being arranged in the regions of H-CDR2, L-CDR1 and L-CDR2 and the ANG2 paratope being arranged in the regions of H-CDR1, H-CDR3 and L-CDR2.

Figure 2: Amino acid sequences of VH domains of exemplary anti-VEGF-A/anti-ANG2 antibodies of the invention. Kabat numbering of the amino acid position is indicated, as well as the CDR and FR regions. Amino acid positions contributing to the VEGF-A paratope, as well as the ANG2 paratope as identified in Example 13 are highlighted.

Figure 3: Amino acid sequences of VL domains of exemplary anti-VEGF-A/anti-ANG2 antibodies of the invention. Kabat numbering of the amino acid position is indicated, as well as the CDR and FR regions. Amino acid positions contributing to the VEGF-A paratope, as well as the ANG2 paratope as identified in Example 13 are highlighted.

Figure 4: Independent antigen binding of bispecific antibody P1AD9820 to VEGF-A and ANG2 as assessed via SPR according to Example 5.