types of polypeptide dimers is reported in US 2005/0163782. Bispecific tetravalent receptors are reported in US 5,959,083. Engineered antibodies with three or more functional antigen binding sites are reported in WO 2001/077342.

Multispecific and multivalent antigen-binding polypeptides are reported in WO 1997/001580. WO 1992/004053 reports homoconjugates, typically prepared from monoclonal antibodies of the IgG class which bind to the same antigenic determinant are covalently linked by synthetic cross-linking. Oligomeric monoclonal antibodies with high avidity for antigen are reported in WO 1991/06305 whereby the oligomers, typically of the IgG class, are secreted having two or more immunoglobulin monomers associated together to form tetravalent or hexavalent IgG molecules. Sheep-derived antibodies and engineered antibody constructs are reported in US 6,350,860, which can be used to treat diseases wherein interferon gamma activity is pathogenic. In US 2005/0100543 are reported targetable constructs that are multivalent carriers of bi-specific antibodies, i.e., each molecule of a targetable construct can serve as a carrier of two or more bi-specific antibodies. Genetically engineered bispecific tetravalent antibodies are reported in WO 1995/009917. In WO 2007/109254 stabilized binding molecules that consist of or comprise a stabilized scFv are reported.

Combination of VEGF and ANG-2 Inhibitors

WO 2007/068895 refers to a combination of an ANG-2 antagonist and a VEGF, KDR and/or FLTL antagonists. WO 2007/089445 refers to ANG-2 and VEGF inhibitor combinations.

WO 2003/106501 refers to fusion proteins binding to Angiopoietin and containing a multimerization domain. WO 2008/132568 relates to fusion proteins binding to Angiopoietin and VEGF. WO 2003/020906 relates to multivalent protein conjugates with multiple ligand-binding domains of receptors.

WO 2009/136352 relates to anti-angiogenic compounds.

Summary ~~of the Invention~~

The ~~invention~~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, characterized in that

i) said first antigen-binding site comprises as heavy chain variable domain (VH) the SEQ ID NO: 1, and as light chain variable domain (VL) the SEQ ID NO: 2; and

ii) said second antigen-binding site comprises as heavy chain variable domain (VH) the SEQ ID NO: 3, and as light chain variable domain (VL) the SEQ ID NO: 4.

~~In one aspect of the invention~~ the bispecific antibody according to the disclosure may be~~invention is~~ characterized in comprising

a) the heavy chain and the light chain of a first full length antibody that specifically binds to VEGF; and

b) the modified heavy chain and modified light chain of a full length antibody that specifically binds to ANG-2, wherein the constant domains CL and CH1 are replaced by each other.

In one aspect of the disclosure, there is provided 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 that

i) said first antigen-binding site comprises as heavy chain variable domain (VH) the SEQ ID NO: 1, and as light chain variable domain (VL) the SEQ ID NO: 2; and

ii) said second antigen-binding site comprises as heavy chain variable domain (VH) the SEQ ID NO: 3, and as light chain variable domain (VL) the SEQ ID NO: 4;and further

characterized in comprising

a) the heavy chain and the light chain of a first full length antibody that specifically binds to VEGF;

b) the modified heavy chain and modified light chain of a full length antibody that specifically binds to ANG-2, wherein the constant domains CL and CH1 are replaced by each other.

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

a) as heavy chain of the first full length antibody the amino acid sequence of SEQ ID NO: 7, and as light chain of the first full length antibody the amino acid sequence of SEQ ID NO: 5, and
b) as modified heavy chain of the second full length antibody the amino acid sequence of SEQ ID NO: 8, and as modified light chain of the second full length antibody the amino acid sequence of SEQ ID NO: 6.

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

a) as heavy chain of the first full length antibody the amino acid sequence of SEQ ID NO: 11, and as light chain of the first full length antibody the amino acid sequence of SEQ ID NO: 9, and
b) as modified heavy chain of the second full length antibody the amino acid sequence of SEQ ID NO: 12, and as modified light chain of the second full length antibody the amino acid sequence of SEQ ID NO: 10.

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

a) as heavy chain of the first full length antibody the amino acid sequence of SEQ ID NO: 15, and as light chain of the first full length antibody the amino acid sequence of SEQ ID NO: 13, and

b) as modified heavy chain of the second full length antibody the amino acid sequence of SEQ ID NO: 16, and as modified light chain of the second full length antibody the amino acid sequence of SEQ ID NO: 14.

The disclosure also relates to~~Still further aspects of the invention are~~ a pharmaceutical composition comprising said bispecific antibody, said composition for the treatment of cancer, the use of said bispecific antibody for the manufacture of a medicament for the treatment of cancer, a method of treatment of patient suffering from cancer by administering said bispecific antibody. to a patient in the need of such treatment.

In a second aspect, there is provided a pharmaceutical composition comprising an antibody as defined above.

In a third aspect, there is provided the bispecific antibody as defined above for the treatment of cancer.

In a fourth aspect, there is provided the use of the bispecific antibody as defined above for the manufacture of a medicament for the treatment of cancer.

The disclosure also relates to~~Still further aspects of the invention are~~ a pharmaceutical composition comprising said bispecific antibody, said composition for the treatment of vascular diseases, the use of said bispecific antibody for the manufacture of a medicament for the treatment of vascular diseases, a method of treatment of patient suffering from vascular diseases by administering said bispecific antibody. to a patient in the need of such treatment.

In a fifth aspect, there is provided the bispecific antibody as defined above for use in the treatment of a condition selected from intraocular neovascular syndromes, rheumatoid arthritis or psoriasis.

In a sixth aspect, there is provided the use of the bispecific antibody as defined above for the manufacture of a medicament for the treatment of a condition selected from intraocular neovascular syndromes, rheumatoid arthritis or psoriasis.

The disclosure further provides~~A further aspect of the invention is~~ a nucleic acid molecule encoding a chain of a bispecific antibody according to the ~~invention~~disclosure.

In a seventh aspect, there is provided a nucleic acid encoding a bispecific antibody as defined above.

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

In an eighth aspect, there is provided an expression vector containing said nucleic acid as defined above capable of expressing said nucleic acid in a prokaryotic or eukaryotic host cell.

In a ninth aspect, there is provided~~The invention further comprises~~ a prokaryotic or eukaryotic host cell comprising a vector according to the ~~invention~~disclosure.

The ~~invention~~disclosure further comprises a method for the production of a bispecific antibody according to the ~~invention~~disclosure, characterized by expressing a nucleic acid according to the ~~invention~~disclosure in a prokaryotic or eukaryotic host cell and recovering said bispecific antibody from said cell or the cell culture supernatant. The ~~invention~~disclosure further comprises the antibody obtained by such method for the production of a bispecific antibody.

Accordingly one embodiment of the ~~invention~~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: 5, of SEQ ID NO: 6, of SEQ ID NO: 7, and of SEQ ID NO: 8.

Accordingly one embodiment of the ~~invention~~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: 9, of SEQ ID NO: 10, of SEQ ID NO: 11, and of SEQ ID NO: 12.

Accordingly one embodiment of the ~~invention~~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: 13, of SEQ ID NO: 14, of SEQ ID NO: 15, and of SEQ ID NO: 16.

The bispecific, bivalent antibodies according to the ~~invention~~disclosure show benefits for human patients in need of a VEGF and ANG-2 targeting therapy. The antibodies according to the ~~invention~~disclosure have highly valuable properties causing a benefit for a patient suffering from such a disease, especially suffering from cancer. The bispecific antibodies according to the ~~invention~~disclosure are highly effective in tumor growth and/or inhibition of tumor angiogenesis or vascular diseases. The bispecific, bivalent antibodies according to the ~~invention~~disclosure The bispecific, bivalent <VEGF-ANG-2> antibodies according to the ~~invention~~disclosure show valuable pharmacokinetic/-dynamic properties like e.g. stability, good (i.e. slow) clearance (e.g. at low doses).

The bispecific antibodies according to the ~~invention~~disclosure are highly effective in

a) tumor growth inhibition (e.g. with the bispecific antibodies according to the invention tumor stasis could be achieved already at lower concentrations compared to the combination of the two monospecific antibodies (e.g. in the Colo205 and the KPL-4 tumor models of Example 9 and 10, tumor stasis was already achieved with 10 mg/kg XMAb1 compared to the combination of 10 mg/kg of ANG2i-LC06 + 10 mg/kg of Avastin), and/or