N.W., et al., Dev. Cell 3 (2002) 411-23. They also found that deletion of ANG-2 results in profound defects in the patterning and function of the lymphatic vasculature. Gale, N.W., et al., Dev. Cell 3 (2002) 411-23. Genetic rescue with Ang-1 corrects the lymphatic, but not the angiogenesis defects. Gale, N.W., et al., Dev. Cell 3 (2002) 411-23.

Peters and his colleagues reported that soluble Tie2, when delivered either as recombinant protein or in a viral expression vector, inhibited in vivo growth of murine mammary carcinoma and melanoma in mouse models. Lin, P., et al., Proc. Natl. Acad. Sci. USA 95 (1998) 8829-34; Lin , P., et al., J. Clin. Invest. 100 (1997) 2072-78. Vascular densities in the tumor tissues so treated were greatly reduced. In addition, soluble Tie2 blocked angiogenesis in the rat corneal stimulated by tumor cell conditioned media. Lin, P., et al., J. Clin. Invest. 100 (1997) 2072-78. Furthermore, Isner and his team demonstrated that addition of ANG-2 to VEGF promoted significantly longer and more circumferential neovascularity than VEGF alone. Asahara, T., et al., Circ. Res., 83 (1998) 233-40. Excess soluble Tie2 receptor precluded modulation of VEGF-induced neovascularization by ANG-2. Asahara, T., et al., Circ. Res., 83, (1998) 233-40. Siemeister, G., et al., Cancer Res. 59 (1999) 3185-91 showed with nude mouse xenografts that overexpression of the extracellular ligand-binding domains of either Flt-1 or Tie2 in the xenografts results in significant inhibition of pathway could not be compensated by the other one, suggesting that the VEGF receptor pathway and the Tie2 pathway should be considered as two independent mediators essential for the process of in vivo angiogenesis. Siemeister, G., et al., Cancer Res. 59 (1999) 3185-91. This is proven by a more recent publication by White, R.R., et al., Proc. Natl. Acad. Sci. USA 100 (2003) 5028-33. In their study, it was demonstrated that a nuclease-resistant RNA aptamer that specifically binds and inhibits ANG-2 significantly inhibited neovascularization induced by bFGF in the rat corneal micropocket angiogenesis model.

Summary ~~of the Invention~~

The disclosure~~invention~~ comprises an antibody specifically binding to human angiopoietin-2 (ANG-2), characterized in comprising as heavy chain variable domain CDR3 region a CDR3 region of SEQ ID NO: 1, SEQ ID NO: 9, SEQ ID NO: 17, SEQ ID NO: 25, SEQ ID NO: 33, SEQ ID NO: 41, or SEQ ID NO: 49.

Preferably the antibody is characterized in that

a) the heavy chain variable domain comprises a CDR3 region of SEQ ID NO: 1, SEQ ID NO: 9, SEQ ID NO: 17, SEQ ID NO: 25, SEQ ID NO: 33, SEQ ID NO: 41, or SEQ ID NO: 49, a CDR2 region of SEQ ID NO: 2, SEQ ID NO: 10, SEQ ID NO: 18, SEQ ID NO: 26, SEQ ID NO: 34, SEQ ID NO: 42, or SEQ ID NO: 50, and a CDR1 region of SEQ ID NO: 3, SEQ ID NO: 11, SEQ ID NO: 19, SEQ ID NO: 27, SEQ ID NO: 35, SEQ ID NO: 43, or SEQ ID NO: 51, and

b) the light chain variable domain comprises a CDR3 region of SEQ ID NO: 4, SEQ ID NO: 12, SEQ ID NO: 20, SEQ ID NO: 28, SEQ ID NO: 36, SEQ ID NO: 44, or SEQ ID NO: 52, a CDR2 region of SEQ ID NO: 5, SEQ ID NO: 13, SEQ ID NO: 21, SEQ ID NO: 29, SEQ ID NO: 37, SEQ ID NO: 45, or SEQ ID NO: 53, and a CDR1 region of SEQ ID NO: 6, SEQ ID NO: 14, SEQ ID NO: 22, SEQ ID NO: 30, SEQ ID NO: 38, SEQ ID NO: 46, or SEQ ID NO: 54.

In one aspect, there is provided an antibody or antibody fragment specifically binding to human angiopoietin-2 (ANG-2), wherein a) the heavy chain variable domain comprises a CDR3 region of SEQ ID NO: 33, a CDR2 region of SEQ ID NO: 34, and a CDR1 region of SEQ ID NO: 35, and b) the light chain variable domain comprises a CDR3 region of SEQ ID NO: 36, a CDR2 region of SEQ ID NO: 37, and a CDR1 region of SEQ ID NO: 38.

Preferably the antibody is characterized in comprising

a) the heavy chain variable domain of SEQ ID NO: 7, SEQ ID NO: 15, SEQ ID NO: 23, SEQ ID NO: 31, SEQ ID NO: 39, SEQ ID NO: 47, or SEQ ID NO: 55; and

b) the light chain variable domain of SEQ ID NO: 8, SEQ ID NO: 16, SEQ ID NO: 24, SEQ ID NO: 32, SEQ ID NO: 40, SEQ ID NO: 48, or SEQ ID NO: 56.

Preferably the antibody is characterized in that the antibody is not specifically binding to Angiopoietin 1 (ANG-1).

A further embodiment of the disclosure~~invention~~ is a pharmaceutical composition comprising an antibody as described herein~~according to the invention~~. In another aspect, there is provided a pharmaceutical composition characterized in comprising an antibody or fragment as defined above.

A further embodiment of the disclosure~~invention~~ is the use of an antibody as described herein~~according to the invention~~ for the manufacture of a pharmaceutical composition.

A further embodiment of the disclosure~~invention~~ is the use of an antibody as described herein~~according to the invention~~ for the prevention of metastasis. In another aspect, there is provided the use of the antibody or antibody fragment as defined above for the manufacture of a medicament for the prevention of metastasis.

A further embodiment of the disclosure~~invention~~ is the use of an antibody as described herein~~according to the invention~~ for the treatment of cancer. In another aspect, there is provided the use of the antibody or antibody fragment as defined above for the manufacture of a medicament for the treatment of cancer.

A further embodiment of the disclosure~~invention~~ is the use of an antibody as described herein~~according to the invention~~ for the treatment of vascular diseases. In another aspect, there is provided the use of the antibody or antibody fragment as defined above for the manufacture of a medicament for the treatment of vascular diseases.

A further embodiment of the disclosure~~invention~~ is the use of an antibody as described herein~~according to the invention~~ for the treatment of retinopathy.

A further embodiment of the disclosure~~invention~~ is a nucleic acid encoding a heavy chain variable domain and/or a light chain variable domain of an antibody as described herein~~according to the invention~~. In another aspect, there is provided a nucleic acid encoding a heavy chain of an antibody specifically binding to human angiopoietin-2 (ANG-2), characterized in that said antibody comprises a heavy chain variable domain and a light chain variable domain as defined above.

The disclosure~~invention~~ further provides expression vectors containing nucleic acid as described herein~~according to the invention~~ capable of expressing said nucleic acid in a prokaryotic or eukaryotic host cell, and host cells containing such vectors for the recombinant production of such an antibody. In another aspect, there is provided an expression vector characterized in comprising a nucleic acid as defined above for the expression of an antibody specifically binding to human angiopoietin-2 (ANG-2) in a prokaryotic or eukaryotic host cell.

The disclosure~~invention~~ further comprises a prokaryotic or eukaryotic host cell comprising a vector as described herein~~according to the invention~~. In another aspect, there is provided prokaryotic or eukaryotic host cell comprising a vector as defined above.

The disclosure~~invention~~ further comprises a method for the production of a recombinant human or humanized antibody as described herein~~according to the invention~~, characterized by expressing a nucleic acid as described herein~~according to the invention~~ in a prokaryotic or eukaryotic host cell and recovering said antibody from said cell or the cell culture supernatant. The disclosure~~invention~~ further comprises the antibody obtainable by such a recombinant method.

The antibodies according to the disclosure~~invention~~ are especially useful for the prevention of secondary tumors/metastasis or in the treatment of vascular diseases such as retinopathies.

Detailed Description of the Invention

The invention comprises an antibody specifically binding to human angiopoietin-2 (ANG-2), characterized in comprising as heavy chain variable domain CDR3 region a CDR3 region of SEQ ID NO: 1, SEQ ID NO: 9, SEQ ID NO: 17, SEQ ID NO: 25, SEQ ID NO: 33, SEQ ID NO: 41, or SEQ ID NO: 49.

In one embodiment of the invention the antibody is characterized in that

a) the heavy chain variable domain comprises a CDR3 region of SEQ ID NO: 1, SEQ ID NO: 9, SEQ ID NO: 17, SEQ ID NO: 25, SEQ ID NO: 33, SEQ