

Claims:

~~1. An antigen-binding molecule, optionally isolated, which binds to VEGFA, wherein the antigen-binding molecule comprises a single domain antibody sequence incorporating the following CDRs:~~

~~CDR1 having the amino acid sequence of SEQ ID NO:45~~

~~CDR2 having the amino acid sequence of SEQ ID NO:46~~

~~CDR3 having the amino acid sequence of SEQ ID NO:48.~~

~~2. The antigen-binding molecule according to claim 1, wherein the antigen-binding molecule comprises, or consists of, an amino acid sequence having at least 70% sequence identity to the amino acid sequence of SEQ ID NO:49.~~

~~3. The antigen-binding molecule according to claim 1 or claim 2, wherein the antigen-binding molecule comprises a single domain antibody sequence incorporating the following FRs:~~

~~FR1 having the amino acid sequence of SEQ ID NO:40~~

~~FR2 having the amino acid sequence of SEQ ID NO:41~~

~~FR3 having the amino acid sequence of SEQ ID NO:47~~

~~FR4 having the amino acid sequence of SEQ ID NO:44.~~

~~41. The An antigen-binding molecule, optionally isolated, according to any one of claims 1 to 3, wherein the antigen-binding molecule comprises a single domain antibody sequence incorporating the following CDRs:~~

~~(a)~~

~~CDR1 having the amino acid sequence of SEQ ID NO:50~~

~~CDR2 having the amino acid sequence of SEQ ID NO:51~~

~~CDR3 having the amino acid sequence of SEQ ID NO:52; or~~

~~(b) _____~~

~~CDR1 having the amino acid sequence of SEQ ID NO:54~~

~~CDR2 having the amino acid sequence of SEQ ID NO:55~~

~~CDR3 having the amino acid sequence of SEQ ID NO:56; or~~

~~(c) _____~~

~~CDR1 having the amino acid sequence of SEQ ID NO:37~~

~~CDR2 having the amino acid sequence of SEQ ID NO:38~~

~~CDR3 having the amino acid sequence of SEQ ID NO:39; or~~

~~(d) _____~~

~~CDR1 having the amino acid sequence of SEQ ID NO:2~~

~~CDR2 having the amino acid sequence of SEQ ID NO:3~~

~~CDR3 having the amino acid sequence of SEQ ID NO:4; or~~

~~(e) _____~~

~~CDR1 having the amino acid sequence of SEQ ID NO:2~~

CDR2 having the amino acid sequence of SEQ ID NO:10

CDR3 having the amino acid sequence of SEQ ID NO:11.

~~5. The antigen-binding molecule according to any one of claims 1 to 4, wherein the antigen-binding molecule comprises, or consists of, an amino acid sequence having at least 70% sequence identity to the amino acid sequence of SEQ ID NO:53.~~

~~62.~~ The antigen-binding molecule according to ~~any one of claims 1 to 5,~~ wherein the antigen-binding molecule comprises:

(~~ia~~) a single domain antibody sequence incorporating the following CDRs:

CDR1 having the amino acid sequence of SEQ ID NO:17

CDR2 having the amino acid sequence of SEQ ID NO:18

CDR3 having the amino acid sequence of SEQ ID NO:19; or

(~~ib~~) a single domain antibody sequence incorporating the following CDRs:

CDR1 having the amino acid sequence of SEQ ID NO:6

CDR2 having the amino acid sequence of SEQ ID NO:7

CDR3 having the amino acid sequence of SEQ ID NO:8; or

(~~iiic~~) a single domain antibody sequence incorporating the following CDRs:

CDR1 having the amino acid sequence of SEQ ID NO:13

CDR2 having the amino acid sequence of SEQ ID NO:14

CDR3 having the amino acid sequence of SEQ ID NO:15.

3. The antigen-binding molecule according to claim 1, wherein the antigen-binding molecule comprises:

(a) a single domain antibody sequence incorporating the following CDRs:

CDR1 having the amino acid sequence of SEQ ID NO:21

CDR2 having the amino acid sequence of SEQ ID NO:22

CDR3 having the amino acid sequence of SEQ ID NO:23; or

(b) a single domain antibody sequence incorporating the following CDRs:

CDR1 having the amino acid sequence of SEQ ID NO:25

CDR2 having the amino acid sequence of SEQ ID NO:26

CDR3 having the amino acid sequence of SEQ ID NO:27; or

(c) a single domain antibody sequence incorporating the following CDRs:

CDR1 having the amino acid sequence of SEQ ID NO:29

CDR2 having the amino acid sequence of SEQ ID NO:30

CDR3 having the amino acid sequence of SEQ ID NO:31; or

(d) a single domain antibody sequence incorporating the following CDRs:

CDR1 having the amino acid sequence of SEQ ID NO:33

CDR2 having the amino acid sequence of SEQ ID NO:34

CDR3 having the amino acid sequence of SEQ ID NO:35.

~~74.~~ The antigen-binding molecule according to any one of claims 1 to ~~63~~, wherein the antigen-binding molecule comprises, or consists of, an amino acid sequence having at least 70% sequence identity to the amino acid sequence of SEQ ID NO: ~~53~~, 16, 5, ~~or~~ 12, ~~57, 20, 24, 28, 32, 36, 1 or 9.~~

~~8. The antigen-binding molecule according to any one of claims 1 to 3, wherein the antigen-binding molecule comprises a single domain antibody sequence incorporating the following CDRs:~~

~~CDR1 having the amino acid sequence of SEQ ID NO:54~~

~~CDR2 having the amino acid sequence of SEQ ID NO:55~~

~~CDR3 having the amino acid sequence of SEQ ID NO:56.~~

~~9. The antigen-binding molecule according to any one of claims 1 to 3 or claim 8, wherein the antigen-binding molecule comprises, or consists of, an amino acid sequence having at least 70% sequence identity to the amino acid sequence of SEQ ID NO:57.~~

~~10. The antigen-binding molecule according to any one of claims 1 to 3, claim 8 or claim 9, wherein the antigen-binding molecule comprises:~~

~~(i) a single domain antibody sequence incorporating the following CDRs:~~

~~CDR1 having the amino acid sequence of SEQ ID NO:21~~

~~CDR2 having the amino acid sequence of SEQ ID NO:22~~

~~CDR3 having the amino acid sequence of SEQ ID NO:23; or~~

~~(ii) a single domain antibody sequence incorporating the following CDRs:~~

~~CDR1 having the amino acid sequence of SEQ ID NO:25~~

~~CDR2 having the amino acid sequence of SEQ ID NO:26~~

~~CDR3 having the amino acid sequence of SEQ ID NO:27; or~~

~~(iii) a single domain antibody sequence incorporating the following CDRs:~~

~~CDR1 having the amino acid sequence of SEQ ID NO:29~~

~~CDR2 having the amino acid sequence of SEQ ID NO:30~~

~~CDR3 having the amino acid sequence of SEQ ID NO:31; or~~

~~(iv) a single domain antibody sequence incorporating the following CDRs:~~

~~CDR1 having the amino acid sequence of SEQ ID NO:33~~

~~CDR2 having the amino acid sequence of SEQ ID NO:34~~

~~CDR3 having the amino acid sequence of SEQ ID NO:35; or~~

~~(v) a single domain antibody sequence incorporating the following CDRs:~~

~~CDR1 having the amino acid sequence of SEQ ID NO:37~~

~~CDR2 having the amino acid sequence of SEQ ID NO:38~~

~~CDR3 having the amino acid sequence of SEQ ID NO:39.~~

~~11. The antigen-binding molecule according to any one of claims 1 to 3 or claims 8 to 10, wherein the antigen-binding molecule comprises, or consists of, an amino acid sequence having at least 70% sequence identity to the amino acid sequence of SEQ ID NO:20, 24, 28, 32 or 36.~~

~~12. The antigen-binding molecule according to any one of claims 1 to 3, wherein the antigen-binding molecule comprises a single domain antibody sequence incorporating the following CDRs:~~

~~CDR1 having the amino acid sequence of SEQ ID NO:2~~

~~CDR2 having the amino acid sequence of SEQ ID NO:3~~

~~CDR3 having the amino acid sequence of SEQ ID NO:4.~~

~~13. The antigen-binding molecule according to any one of claims 1 to 3 or claim 12, wherein the antigen-binding molecule comprises, or consists of, an amino acid sequence having at least 70% sequence identity to the amino acid sequence of SEQ ID NO:1.~~

~~14. The antigen-binding molecule according to any one of claims 1 to 3, wherein the antigen-binding molecule comprises a single domain antibody sequence incorporating the following CDRs:~~

~~CDR1 having the amino acid sequence of SEQ ID NO:2~~

~~CDR2 having the amino acid sequence of SEQ ID NO:10~~

~~CDR3 having the amino acid sequence of SEQ ID NO:11.~~

~~15. The antigen-binding molecule according to any one of claims 1 to 3 or claim 14, wherein the antigen-binding molecule comprises, or consists of, an amino acid sequence having at least 70% sequence identity to the amino acid sequence of SEQ ID NO:9.~~

~~165.~~ The antigen-binding molecule according to any one of claims 1 to ~~134~~, wherein the antigen-binding molecule comprises a single domain antibody sequence incorporating the following FRs:

FR1 having the amino acid sequence of SEQ ID NO:40

FR2 having the amino acid sequence of SEQ ID NO:41

FR3 having the amino acid sequence of SEQ ID NO:42

FR4 having the amino acid sequence of SEQ ID NO:44.

~~176.~~ The antigen-binding molecule according to any one of claims ~~1 to 3, claim 15 or claim 16~~, wherein the antigen-binding molecule comprises a single domain antibody sequence incorporating the following FRs:

FR1 having the amino acid sequence of SEQ ID NO:40

FR2 having the amino acid sequence of SEQ ID NO:41

FR3 having the amino acid sequence of SEQ ID NO:43

FR4 having the amino acid sequence of SEQ ID NO:44.

~~187.~~ The antigen-binding molecule according to any one of claims 1 to ~~176~~, wherein the antigen-binding molecule inhibits interaction between VEGFA and VEGFR.

~~198.~~ The antigen-binding molecule according to any one of claims 1 to ~~187~~, wherein the antigen-binding molecule is a multispecific antigen-binding molecule, further comprising an antigen-binding domain specific for a target antigen other than VEGFA.

~~209.~~ A chimeric antigen receptor (CAR) comprising an antigen-binding molecule according to any one of claims 1 to ~~498~~.

~~2410.~~ A nucleic acid, optionally isolated, encoding an antigen-binding molecule according to any one of claims 1 to ~~498~~, or a CAR according to claim ~~209~~.

~~2211.~~ An expression vector comprising a nucleic acid according to claim ~~2410~~.

~~2312.~~ A cell comprising an antigen-binding molecule according to any one of claims 1 to ~~498~~, a CAR according to claim ~~209~~, a nucleic acid according to claim ~~2410~~, or an expression vector according to claim ~~2211~~.

~~2413.~~ A method for producing an antigen-binding molecule which binds to VEGFA, comprising culturing a cell according to claim ~~2312~~ under conditions suitable for expression of an antigen-binding molecule or CAR by the cell.

~~2514.~~ A composition comprising an antigen-binding molecule according to any one of claims 1 to ~~498~~, a CAR according to claim ~~209~~, a nucleic acid according to claim ~~2410~~, an expression vector according to claim ~~2211~~, or a cell according to claim ~~2312~~, and a pharmaceutically acceptable carrier, diluent, excipient or adjuvant.

~~2615.~~ An antigen-binding molecule according to any one of claims 1 to ~~498~~, a CAR according to claim ~~209~~, a nucleic acid according to claim ~~2410~~, an expression vector according to claim ~~2211~~, a cell according to claim ~~2312~~, or a composition according to claim ~~2514~~, for use in a method of medical treatment or prophylaxis.

~~27. An antigen-binding molecule according to any one of claims 1 to 19, a CAR according to claim 20, a nucleic acid according to claim 21, an expression vector according to claim 22, a cell according to claim 23, or a composition according to claim 25, for use in a method of treatment or prevention of a disease in which VEGFA/VEGFR-mediated signalling is pathologically implicated.~~

~~2816.~~ Use of an antigen-binding molecule according to any one of claims 1 to ~~498~~, a CAR according to claim ~~209~~, a nucleic acid according to claim ~~2410~~, an expression vector according to claim ~~2211~~, a cell according to claim ~~2312~~, or a composition according to claim ~~2514~~, in the manufacture of a medicament for treating or preventing a disease in which VEGFA/VEGFR-mediated signalling is pathologically implicated.

~~29. A method of treating or preventing a disease in which VEGFA/VEGFR-mediated signalling is pathologically implicated, comprising administering to a subject a therapeutically or prophylactically effective amount of an antigen-binding molecule according to any one of claims 1 to 19, a CAR according to claim 20, a nucleic acid according to claim 21, an expression vector according to claim 22, a cell according to claim 23, or a composition according to claim 25.~~

~~3017.~~ The antigen-binding molecule, CAR, nucleic acid, expression vector, cell or composition for use according to claim ~~27~~, the use according to claim ~~1628~~, or the method according to claim ~~29~~, wherein the disease is selected from: a disease characterised by pathological angiogenesis, a cancer, a VEGFA-

expressing cancer, a VEGFR-expressing cancer, an ocular disease, retinopathy, diabetic retinopathy, macular degeneration, age-related macular degeneration, wet age-related macular degeneration, retinal vein occlusion, myopic choroidal neovascularisation, retinopathy of prematurity, neovascular glaucoma, central serous retinopathy, ocular tumor, corneal neovascularisation, an inflammatory disease, an autoimmune disease, arthritis, rheumatoid arthritis, osteoarthritis, psoriasis, multiple sclerosis, sepsis, motor neuron disease and amyotrophic lateral sclerosis.

3418. An *in vitro* complex, optionally isolated, comprising an antigen-binding molecule according to any one of claims 1 to **498** bound to VEGFA.

3219. A method for detecting VEGFA in a sample, comprising contacting a sample containing, or suspected to contain, VEGFA with an antigen-binding molecule according to any one of claims 1 to **498**, and detecting the formation of a complex of the antigen-binding molecule with VEGFA.

3320. Use of an antigen-binding molecule according to any one of claims 1 to **498** in a method for detecting, localizing or imaging VEGFA, or cells comprising or expressing VEGFA.

3421. A method of selecting or stratifying a subject for treatment with a VEGFA-targeted agent, the method comprising contacting, *in vitro*, a sample from the subject with an antigen-binding molecule according to any one of claims 1 to **498**, and detecting the formation of a complex of the antigen-binding molecule with VEGFA.

3522. Use of an antigen-binding molecule according to any one of claims 1 to **498** as an *in vitro* or *in vivo* diagnostic or prognostic agent.

3623. Use of an antigen-binding molecule according to any one of claims 1 to **498** in a method for detecting, localizing or imaging a disease/condition characterised by expression of VEGFA.