

characteristics and domains that bind heparin proteoglycans. In examples, the present disclosure provides an anti-VEGF agent, wherein the anti-VEGF agent is an Fc-IgG construct having the ability to bind heparin and contains one or more domains with VEGF binding characteristics. In examples, the present disclosure provides an anti-VEGF agent, wherein the anti-VEGF agent is a fusion protein with improved efficacy for binding to VEGF and heparin. In examples, the present disclosure provides an anti-VEGF agent, wherein the anti-VEGF agent is a fusion protein with very low endotoxin levels.

[0011] In examples, the present disclosure provides an anti-VEGF agent, wherein the anti-VEGF agent is an IgG chimeric protein comprising elements of VEGF receptors. In examples, the present disclosure provides an IgG chimeric protein, wherein the IgG chimeric protein comprises one or more fragments of the seven immunoglobulin (Ig)-like domains in the extracellular portion of VEGF tyrosine kinase receptors. In examples, the present disclosure provides an IgG chimeric protein, wherein the IgG chimeric protein comprises one or more extracellular domain fragments of VEGFR-1 fused with Fc-IgG. In examples, the present disclosure provides an IgG chimeric protein comprising at least one VEGF binding domain VEGFR-1 domain 2 and at least one additional VEGFR-1 domain 1 or 3, and not including domain 4. In examples, the present disclosure provides an IgG chimeric protein, wherein the IgG chimeric protein comprises one or more extracellular domain fragments of VEGFR-2 fused with Fc-IgG. In examples, the present disclosure provides an IgG chimeric protein, wherein the IgG chimeric protein comprises one or more extracellular domain fragments of VEGFR-1 and VEGFR-2 fused with Fc-IgG.

[0012] In one aspect, the present disclosure refers to an purified anti-VEGF agent comprising a VEGF binding portion consisting essentially of domains 2 and 3 of VEGFR 1 (V₂₋₃) operatively linked to a Fc-IgG, wherein ~~the VEGF binding portion comprises at least one VEGF binding domain that is an IgG-like domain 2 of VEGFR 1, and wherein the anti-VEGF agent has a VEGF stimulated mitogenesis inhibiting ability greater than aflibercept. In~~ examples, the present disclosure provides an anti-

~~VEGF agent comprising a VEGF binding portion operatively linked to a Fe-IgG, wherein the VEGF binding portion comprises at least one VEGF binding domain that is an IgG-like domain 2 of VEGFR-1, and wherein the anti-VEGF agent has a VEGF-stimulated mitogenesis inhibiting ability greater than aflibercept~~ the anti-VEGF agent has an amino acid sequence according to amino acids 27 to 459 of SEQ ID NO: 3. In examples, the present disclosure provides that the anti-VEGF agent has a vitreous binding ability greater than aflibercept. In examples, the present disclosure provides that the anti-VEGF agent has a vitreous bound VEGF-stimulated endothelial cell proliferation-inhibiting ability greater than aflibercept. In examples, the

[0018] In yet another aspect, the present disclosure refers to use a therapeutically effective amount of ~~an anti-VEGF agent as disclosed herein~~ a purified, non-glycosylated anti-VEGF agent consisting essentially of domains 2 and 3 of VEGFR 1 (V₂₋₃) in the manufacture of a medicament for treating a VEGF-related disorder. In yet another aspect, the present disclosure refers to use of a therapeutically effective amount of the pharmaceutical composition as disclosed herein in the manufacture of a medicament for treating a VEGF-related disorder. In examples, the present disclosure provides a method for treating ocular disease, wherein an anti-VEGF agent is administered locally to the eye at a dosage corresponding to a molar ratio of 2:1 compared to VEGF. In examples, the present disclosure provides a method for treating ocular disease, wherein an anti-VEGF agent is administered by intravitreal injection. In examples, the present disclosure provides a method for treating ocular disease, wherein an anti-VEGF agent is administered every 4-6 weeks, and in other examples, the treatment is continued for a period of at least one year. In another aspect, the present disclosure refers to a nucleic acid comprising a sequence according to SEQ ID NO: 4. In yet another aspect, the present disclosure refers to an expression plasmid comprising the nucleic acid sequence of SEQ ID NO: 4.

What is claimed is:

1. A purified anti-VEGF agent comprising a VEGF binding portion consisting essentially of domains 2 and 3 of VEGFR 1 (V₂₋₃) operatively linked to a Fc-IgG, wherein the anti-VEGF agent has an amino acid sequence according to amino acids 27 to 459 of SEQ ID NO: 3 ~~wherein the VEGF binding portion comprises at least one VEGF binding domain that is an IgG-like domain 2 of VEGFR 1, and wherein the anti-VEGF agent has a VEGF-stimulated mitogenesis-inhibiting ability greater than aflibercept.~~
2. The anti-VEGF agent of claim 1, wherein the anti-VEGF agent has a vitreous binding ability greater than aflibercept.
3. The anti-VEGF agent of claim 2, wherein the anti-VEGF agent has a vitreous bound VEGF-stimulated endothelial cell proliferation-inhibiting ability greater than aflibercept.
4. The anti-VEGF agent of claim 3, wherein the agent has an increased half-life in vivo compared to aflibercept.
- ~~5. The anti-VEGF agent of claim 4, wherein the VEGF binding portion consists essentially of IgG-like domains 1, 2, and 3 of VEGFR 1 (V₁₋₂₋₃).~~
- ~~6. The anti-VEGF agent of claim 5, wherein the anti-VEGF agent comprises amino acid sequence as defined in SEQ ID No: 1.~~
- ~~7. The anti-VEGF agent of claim 4, wherein the VEGF binding portion consists essentially of IgG-like domains 2 and 3 of VEGFR 1 (V₂₋₃).~~
- ~~8. The anti-VEGF agent of claim 5, wherein the anti-VEGF agent comprises amino acid sequence as defined in SEQ ID No: 3.~~
- ~~9. The anti-VEGF agent of claim 4, wherein the VEGF binding portion consists essentially of IgG-like domains 1, 2, 3 and 3 of VEGFR 1 (V₁₋₂₋₃₋₃).~~
- ~~10. The anti-VEGF agent of claim 5, wherein the anti-VEGF agent comprises amino acid sequence as defined in SEQ ID No: 5.~~
- ~~11. The anti-VEGF agent of claim 4, wherein the VEGF binding portion consists essentially of IgG-like domains 2, 3 and 3 of VEGFR 1 (V₂₋₃₋₃).~~

~~12.~~ The anti-VEGF agent of claim ~~5~~, wherein the anti-VEGF agent comprises amino acid sequence as defined in SEQ ID No: 7.

~~13.~~5. A pharmaceutical composition comprising a therapeutically effective amount of an anti-VEGF agent of ~~any of the preceding claims~~claim 1 and a pharmaceutically acceptable excipient.

~~14.~~6. Use of a therapeutically effective amount of ~~an~~ a purified, non-glycosylated anti-VEGF agent ~~of any of claims 1-12~~ consisting essentially of domains 2 and 3 of VEGFR 1 (V₂₋₃) in the manufacture of a medicament for treating a VEGF-related disorder.

~~15.~~7. The use of claim ~~14~~6, wherein the anti-VEGF agent is to be directly injected into the affected tissue or organ.

~~16.~~8. The use of claim ~~15~~7, wherein the said affected tissue or organ is an eye.

~~17.~~9. The use of claim ~~14~~6, wherein the VEGF-related disorder is selected from the group comprising neovascular age related macular degeneration, choroidal neovascularization secondary to myopia, proliferative diabetic retinopathy, diabetic macular edema, retinal vascular obstruction such as retinal vein occlusion, ocular tumors, von Hippel Lindau syndrome, retinopathy of prematurity, polypoid choroidal vasculopathy, colorectal cancer, lung cancer, cervical cancer, endometrial cancer, ovarian cancer, kidney cancer, schwannomas, gliomas, ependimomas, and neoplastic or non-neoplastic disorders that benefits from anti-VEGF therapy.

~~18.~~10. Use of a therapeutically effective amount of the pharmaceutical composition of claim ~~13-5~~ in the manufacture of a medicament for treating a VEGF-related disorder.

~~19.~~11. The use of claim ~~18~~10, wherein the anti-VEGF agent is to be directly injected into the affected tissue or organ.

~~20.~~12. The use of claim ~~20~~11, wherein the said affected tissue or organ is an eye.

~~21.~~13. The use of claim ~~19~~18, wherein the VEGF related disorder is selected from the group comprising neovascular age related macular degeneration, choroidal neovascularization secondary to myopia, proliferative diabetic retinopathy, diabetic macular edema retinal vascular obstruction such as retinal vein occlusion, ocular tumors, polypoid choroidal vasculopathy, von Hippel Lindau syndrome, retinopathy of

prematurity, colorectal cancer, lung cancer, cervical cancer, ovarian cancer, endometrial cancer, kidney cancer, schwannomas, gliomas, ependimomas, and neoplastic or non-neoplastic disorders that benefit from anti-VEGF therapy.

14. A nucleic acid comprising a sequence according to SEQ ID NO: 4.

15. An expression plasmid comprising the nucleic acid sequence of SEQ ID NO: 4.