

## WHAT IS CLAIMED IS:

1. A fusion protein comprising:
  - an integrin binding peptide selected from a group consisting of disintegrin, anti-integrin  $\alpha v \beta x$  antibody, anti-integrin  $\alpha 5 \beta 1$  antibody, fibronectin targeting integrin  $\alpha v \beta x$  or  $\alpha 5 \beta 1$  and their integrin binding fragments;
  - other protein binding peptide targeting an angiogenic factor; and
  - a Fc domain;wherein x is 1, 3, 5, 6 or 8.
2. A fusion protein comprising:
  - an integrin binding peptide having an amino acid sequence selected from a group consisting of SEQ ID NO: 1, SEQ ID NO: 2, SEQ ID NO: 3, SEQ ID NO: 4, SEQ ID NO: 5, SEQ ID NO: 6, and SEQ ID NO: 7, or amino acid sequence having at least 85% sequence identity to SEQ ID NO: 1, SEQ ID NO: 2, SEQ ID NO: 3, SEQ ID NO: 4, SEQ ID NO: 5, SEQ ID NO: 6, and SEQ ID NO: 7;
  - other protein binding peptide comprising extracellular domains of VEGF receptors;
  - and
  - a Fc domain;wherein the integrin binding peptide has at least one mutation on or adjacent to a RGD motif.
3. A fusion protein comprising:
  - an integrin binding peptide comprising disintegrin and its integrin binding fragments;
  - other protein binding peptide comprising extracellular domains of VEGF receptors;
  - and
  - a Fc domain;wherein the integrin binding peptide comprising at least one mutation on or adjacent to a RGD motif.
4. A fusion protein comprising:
  - an integrin binding portion selected from a group consisting of an amino acid sequence of SEQ ID NO:1 with at least one mutation on or adjacent to a RGD motif, an amino acid sequence having at least 85% sequence identity to SEQ ID NO: 1, and an amino acid sequence of SEQ ID NO: 2;

a human or humanized constant sub-region comprising an immunoglobulin CH2 domain and a CH3 domain;

other protein binding peptide having an Ig-like domain D2 of a VEGFR1 and an Ig-like domain D3 of a VEGFR2.

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5. The fusion protein according to claims 1, 2 or 3 comprising the integrin binding peptide, the Fc domain and the other protein binding peptide from C-terminus to N-terminus.

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6. The fusion protein according to claims 1, 2 or 3 comprising the integrin binding peptide, the Fc domain and the other protein binding peptide from N-terminus to C-terminus.

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7. The fusion protein according to any of claims 1-4, wherein the integrin binding peptide has at least 85% sequence identity to SEQ ID NO: 1, SEQ ID NO: 2, SEQ ID NO: 3, SEQ ID NO: 4, SEQ ID NO: 5, SEQ ID NO: 6 or SEQ ID NO: 7.

8. The fusion protein according to claim 7, wherein the integrin binding peptide has at least 85% sequence identity to SEQ ID NO: 2.

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9. A nucleic acid encoding the fusion protein of any of claims 1-4.

10. A dimer of the fusion protein of any of claims 1-4.

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11. A vector comprising a nucleotide sequence encoding the fusion protein of any of claims 1-4.

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12. A method of producing a fusion protein, comprising culturing a host cell comprising a nucleic acid encoding the fusion protein of any of claims 1-4 under a condition that produces the fusion protein, and recovering the fusion protein produced by the host cell.

13. A method of treating/preventing an angiogenic disease comprising administering an effective amount of the fusion protein of any of claims 1-4 to a subject in need thereof.

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14. The fusion protein of any of claims 1-4 further comprising a linker sequence between the integrin binding peptide and the other protein binding peptide.

15. The fusion protein of any of claims 1-4 further comprising a signal peptide sequence upstream of the other protein binding peptide.
16. The fusion protein of claim 1, wherein the angiogenic factor comprises
- 5 Angiopoietin (ANG), Ephrin (Eph), Fibroblast Growth Factor (FGF), Neuropilin (NRP), Plasminogen Activators, urokinase-type plasminogen activator receptor (uPAR), Platelet-Derived Growth Factor (PDGF), Tumor Growth Factor beta (TGF- $\beta$ ), Vascular Endothelial Growth Factor (VEGF), Vascular Endothelial cadherin (VE-cadherin), Insulin-like Growth Factor (IGF), Connective-Tissue Growth Factor (CTGF), Tumor Necrosis Factor alpha
- 10 (TNF- $\alpha$ ), Interlukine 1 (IL-1), Interlukine 6 (IL-6), Granulocyte Macrophage Colony-Stimulating Factor (GM-CSF), and receptors thereof.
17. A composition comprising the fusion protein according to any of claims 1-4 and a pharmaceutically acceptable adjuvant, carrier or excipient.
- 15 18. The method of claim 13, wherein the angiogenic disease comprises rheumatoid arthritis, inflammatory arthritis, osteoarthritis, ocular and systemic cancer, tumor related metastasis and invasion, systemic fibrosis diseases including idiopathic lung fibrosis (IPF), nonalcoholic steatohepatitis (NASH) or liver fibrosis, diabetic nephropathy and/or
- 20 kidney fibrosis, dermal fibrosis or keloid, wound healing, cardio-fibrosis, ischemia induced stroke, ocular disease characterized by neovascularization or ischemia (such as choroidal neovascularization), uveitis, retinitis pigmentosa, age-related macular degeneration (AMD), diabetic retinopathy and diabetic macular edema (DME).
- 25 19. The fusion protein according to claim 2 or 3, wherein the extracellular domains of VEGF receptors comprise an Ig-like domains D1-D7 of the VEGF receptors.
20. The fusion protein according to claim 2 or 3, wherein extracellular domains of VEGF receptors comprising i) an Ig-like domain D2 of a VEGFR1 and an Ig-like domain
- 30 D3 of a VEGFR2; ii) the amino acid sequence of SED ID NO: 10 or iii) an amino acid sequence having at least 90% identity to SEQ ID NO: 10.
21. The fusion protein of any of claims 1-3 further comprising a GS or G<sub>9</sub> linker between the Fc domain and the integrin binding peptide or the other protein binding
- 35 peptide.