

We claim:

1. An isolated VEGF mini-trap comprising the following domain structure:

$((R1D2)-(R2D3))_a-(MC)_c$;

wherein one or more histidines of said VEGF mini-trap are oxidized to 2-oxo-histidine,

and/or one or more tryptophans are dioxidated,

and/or one or more asparagines thereof are glycosylated,

or,

$((R1D2)-(R2D3)-(R2D4))_a-(MC)_b$,

$((R1D2)-(R2D3))_c$ -linker- $((R1D2)-(R2D3))_d$; or

$((R1D2)-(R2D3)-(R2D4))_e$ -linker- $((R1D2)-(R2D3)-(R2D4))_f$;

wherein,

R1D2 is the VEGFR1 Ig domain 2;

R2D3 is the VEGFR2 Ig domain 3;

R2D4 is the VEGFR2 Ig domain 4;

MC is a multimerizing component which is a fragment of an immunoglobulin hinge region or a polypeptide consisting of the amino acid sequence:

DKTHTCPPC (SEQ ID NO: 22),

DKTHTCPPCPCPC (SEQ ID NO: 23),

DKTHTCPPCPCPCPC (SEQ ID NO: 24),

DKTHTC (PPC)_h (SEQ ID NO: 25), wherein h is 1, 2, 3, 4, or 5,

DKTHTCPPCPAPELLG (SEQ ID NO: 6),

DKTHTCPLCPAPELLG (SEQ ID NO: 7),

DKTHTC (SEQ ID NO: 8) or

DKTHTCPLCPAP (SEQ ID NO: 9)

and

linker is a peptide comprising about 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15 or 16 amino acids;

and, independently, a= 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14 or 15; b=1, 2, 3, 4, 5, 6, 7,

8, 9, 10, 11, 12, 13, 14 or 15; c=1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14 or 15; d=1, 2, 3, 4,

5, 6, 7, 8, 9, 10, 11, 12, 13, 14 or 15; e=1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14 or 15; and

f=1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14 or 15;

or a composition thereof.

2. The VEGF mini-trap or composition thereof of claim 1 selected from

(i) (R1D2)₁-(R2D3)₁-(MC)₁;

and

(ii) (R1D2)₁-(R2D3)₁-(R2D4)₁-(MC)₁.

3. A VEGF mini-trap or composition thereof comprising an amino acid sequence set forth in a member selected from the group consisting of:

SDTGRPFVEMYSEIPEIIHMTGRELVIPCRVTSPNITVTLKKFPLDTLIPDGKRIIWDSRKGFIISNATYKEIGLL
TCEATVNGHLYKTNLYLTHRQTNTIIDVVLSPSHGIELSVGEKLVNCTARTELVGIDFNWEYPSSKHQHKLVNRD
LKTQSGSEMKKFLSTLTIDGVTRSDQGLYTCAASSGLMTKKNSTFVRVHEKDKTHTCPPCPAPELLG

(SEQ ID NO: 12);

GRPFVEMYSEIPEIIHMTGRELVIPCRVTSPNITVTLKKFPLDTLIPDGKRIIWDSRKGFIISNATYKEIGLLTCE
ATVNGHLYKTNLYLTHRQTNTIIDVVLSPSHGIELSVGEKLVNCTARTELVGIDFNWEYPSSKHQHKLVNRDLKT
QSGSEMKKFLSTLTIDGVTRSDQGLYTCAASSGLMTKKNSTFVRVHENLSVAFSGMESLVEATVGERVRIPAKYLG
YPPPEIKWYKNGIPLESNHTIKAGHVLTIMEVSRDTGNYTVILTNPISKEKQSHVVSLLVYVPPGPGDKTHTCPLC
PAPELLG

(SEQ ID NO: 13);

SDTGRPFVEMYSEIPEIIHMTGRELVIPCRVTSPNITVTLKKFPLDTLIPDGKRIIWDSRKGFIISNATYKEIGLL
TCEATVNGHLYKTNLYLTHRQTNTIIDVVLSPSHGIELSVGEKLVNCTARTELVGIDFNWEYPSSKHQHKLVNRD
LKTQSGSEMKKFLSTLTIDGVTRSDQGLYTCAASSGLMTKKNSTFVRVHEKDKTHTCPPC

(SEQ ID NO: 26);

SDTGRPFVEMYSEIPEIIHMTGRELVIPCRVTSPNITVTLKKFPLDTLIPDGKRIIWDSRKGFIISNATYKEIGLL
TCEATVNGHLYKTNLYLTHRQTNTIIDVVLSPSHGIELSVGEKLVNCTARTELVGIDFNWEYPSSKHQHKLVNRD
LKTQSGSEMKKFLSTLTIDGVTRSDQGLYTCAASSGLMTKKNSTFVRVHEKDKTHTCPPCPPC

(SEQ ID NO: 27);

SDTGRPFVEMYSEIPEIIHMTGRELVIPCRVTSPNITVTLKKFPLDTLIPDGKRIIWDSRKGFIISNATYKEIGLL
TCEATVNGHLYKTNLYLTHRQTNTIIDVVLSPSHGIELSVGEKLVNCTARTELVGIDFNWEYPSSKHQHKLVNRD
LKTQSGSEMKKFLSTLTIDGVTRSDQGLYTCAASSGLMTKKNSTFVRVHEKDKTHTCPPCPPCPPC

(SEQ ID NO: 28);

SDTGRPFVEMYSEIPEIIHMTGRELVIPCRVTSPNITVTLKKFPLDTLIPDGKRIIWDSRKGFIISNATYKEIGLL
TCEATVNGHLYKTNLYLTHRQTNTIIDVVLSPSHGIELSVGEKLVNCTARTELVGIDFNWEYPSSKHQHKLVNRD
LKTQSGSEMKKFLSTLTIDGVTRSDQGLYTCAASSGLMTKKNSTFVRVHEKDKTHTC- (PPC) x

(SEQ ID NO: 29; wherein x is 1, 2, 3, 4 or 5);

SDTGRPFVEMYSEIPEIIHMTGRELVIPCRVTSPNITVTLKKFPLDTLIPDGKRIIWDSRKGFIISNATYKEIGLL
TCEATVNGHLYKTNLYLTHRQTNTIIDVVLSPSHGIELSVGEKLVNCTARTELVGIDFNWEYPSSKHQHKLVNRD

- (i) (R1D2)_a-(R2D3)_b-linker-(R1D2)_c-(R2D3)_d; or
 - (ii) (R1D2)_a-(R2D3)_b-(R2D4)_c-linker-(R1D2)_d-(R2D3)_e-(R2D4)_f; and
- having a secondary structure wherein:
- (i) said R1D2 domains coordinate;
 - (ii) said R2D3 domains coordinate; and/or
 - (iii) said R2D4 domains coordinate,
- to form a VEGF binding domain.

5. The VEGF mini-trap or composition thereof of any one of claims 1, 3 or 4, wherein linker is (Gly₄Ser)_n wherein n is 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14 or 15; or wherein the MC is a fragment of an immunoglobulin hinge region that forms 2, 3 or 4 cysteine bridges with another MC.

6. The VEGF mini-trap or composition thereof of any one of claims 1-5 wherein said polypeptides are homodimerized.

7. The VEGF mini-trap or composition thereof of any one of claims 1-6, wherein one or more histidines of said VEGF mini-trap are oxidized to 2-oxo-histidine, and/or one or more tryptophans of said VEGF mini-trap are dioxidated, and/or one or more asparagines of said VEGF mini-trap thereof are glycosylated.

8. The VEGF mini-trap or composition thereof of any one of claims 1-7 which is a composition comprising said VEGF mini-trap wherein between 0.1% and 2% of histidines in the VEGF mini-trap are 2-oxo-histidine.

9. The VEGF mini-trap or composition thereof of any one of claims 1-8 which is a composition comprising said VEGF mini-trap polypeptide wherein oligopeptide products of digestion of said VEGF mini-trap, which comprises one or more carboxymethylated cysteines and 2-oxo-histidines, with Lys-C and trypsin proteases are:

EIGLLTC*EATVNGH*LYK (amino acids 73-89 of SEQ ID NO: 12) which comprises about 0.006-0.013% 2-oxo-histidines,

QTNTIIDVVLSPSH*GIELSVGEK (amino acids 97-119 of SEQ ID NO: 12) which comprises about 0.019-0.028% 2-oxo-histidines,

TELNVGIDFNWEYPSSKH*QHK (amino acids 128-148 of SEQ ID NO: 12) which comprises about 0.049-0.085% 2-oxo-histidines,

DKTH*TC*PPC*PAPELLG (amino acids 206-221 of SEQ ID NO: 12) which comprises about 0.057-0.092% 2-oxo-histidines, and/or

TNYLTH*R (amino acids 90-96 of SEQ ID NO: 12) which comprises about 0.010-0.022% 2-oxo-histidines, and

optionally, IIW*DSR (amino acids 56-61 of SEQ ID NO: 12) which comprises about 0.198-0.298% 2-oxo-histidines,

wherein H* is a histidine that may be oxidized to 2-oxo-histidine, W* is tryptophan that may be dioxidated and wherein C* is a cysteine that may be carboxymethylated.

10. The VEGF mini-trap or composition thereof of any one of claims 1-9 which is a composition comprising said VEGF mini-trap wherein oligopeptide products of digestion of said VEGF mini-trap, which comprises one or more carboxymethylated cysteines and 2-oxo-histidines, with Lys-C and trypsin proteases are:

EIGLLTC*EATVNGH*LYK (amino acids 73-89 of SEQ ID NO: 12) which comprises about 0.0095% 2-oxo-histidines,

QTNTIIDVVLSPSH*GIELSVGEK (amino acids 97-119 of SEQ ID NO: 12) which comprises about 0.0235% 2-oxo-histidines,

TELNVGIDFNWEYPSSKH*QHK (amino acids 128-148 of SEQ ID NO: 12) which comprises about 0.067% 2-oxo-histidines,

DKTH*TC*PPC*PAPELLG (amino acids 206-221 of SEQ ID NO: 12) which comprises about 0.0745% 2-oxo-histidines, and/or

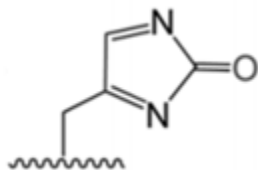
TNYLTH*R (amino acids 90-96 of SEQ ID NO: 12) which comprises about 0.016% 2-oxo-histidines, and

optionally, IIW*DSR (amino acids 56-61 of SEQ ID NO: 12) which comprises about 0.248% 2-oxo-histidines,

wherein H* is a histidine that may be oxidized to 2-oxo-histidine, W* is tryptophan that may be dioxidated and wherein C* is a cysteine that may be carboxymethylated.

11. The VEGF mini-trap or composition thereof of any one of claims 1-10 which is a composition wherein one or more tryptophans are dioxidized.

12. The VEGF mini-trap or composition thereof of any one of claims 1-11 which is a composition wherein the 2-oxo-histidine is characterized by the chemical formula:



13. The VEGF mini-trap or composition thereof of any one of claims 1-12 which is a composition characterized by a color:

- (i) which is no more brown-yellow than European Color Standard BY2;
 - (ii) which is no more brown-yellow than European Color Standard BY3;
 - (iii) which is no more brown-yellow than European Color Standard BY4;
 - (iv) which is no more brown-yellow than European Color Standard BY5;
 - (v) which is no more brown-yellow than European Color Standard BY6;
 - (vi) which is no more brown-yellow than European Color Standard BY7;
 - (vi) which is between European Color Standard BY2 and BY3;
 - (vii) which is between European Color Standard BY2 and BY4;
 - (vii) wherein, in the CIEL*a*b* color space, L* is about 70-99, a* is about -2-0 and b* is about 20 or less; and/or
 - (viii) wherein, in the CIEL*a*b* color space, L* is about 98-99, a* is about -1-0 and b* is about 5-10 and the mini-trap concentration is between 75 and 100 mg/ml;
- optionally, wherein the concentration of VEGF mini-trap is about 70-200 mg/ml or
- optionally, wherein the concentration of VEGF mini-trap is about 70-200 mg/ml, but is characterized by said color when diluted to about 10, 11, 10-11, 80 or 90 mg/ml.

14. The VEGF mini-trap or composition thereof of any one of claims 1-12 which is a composition wherein the color of the composition is characterized by the following formula:
 $0.046 + (0.066 \times \text{concentration of mini-trap (mg/ml)}) = b^*$ or $b^* = (0.11 \times \text{concentration of mini-trap (mg/ml)} - 0.56)$, wherein L* = about 97-99 and a = about -0.085-0.06.

15. The VEGF mini-trap or composition thereof of any one of claims 1-14 which is a composition that is the product of a process comprising:

- (i) expressing aflibercept or said VEGF mini-trap in a host cell in a chemically-defined liquid medium wherein said aflibercept or VEGF mini-trap is secreted from the host cell into the medium; and
- (ii) if aflibercept is expressed, further comprising proteolytic cleavage of the aflibercept to produce peptides comprising the Fc domain, or a fragment thereof, and said VEGF mini-trap, and removal of the Fc domain or fragment thereof from the VEGF mini-trap;
- (iii) applying the VEGF mini-trap to an anion-exchange chromatography resin; and
- (iv) retaining said VEGF mini-trap polypeptide in the chromatographic flow-through thereof.

16. The VEGF mini-trap or composition thereof of claim 15, which is a composition, wherein if said aflibercept is expressed, the process further comprises, prior to said proteolytic cleavage, protein-A purification of the aflibercept.

17. The VEGF mini-trap or composition of any one of claims 15-16, which is a composition, wherein the anion exchange resin comprises:

- a strong anion exchange resin;
- a quaternary amine functional group;
- a $-O-CH_2CHOHCH_2OCH_2CHOHCH_2N^+(CH_3)_3$ functional group; or
- a quaternized polyethyleneimine functional group.

18. The VEGF mini-trap or composition of any one of claims 15-17, which is a composition, wherein the proteolytic cleavage is performed by incubating the aflibercept with *Streptococcus pyogenes* IdeS protease or a variant thereof comprising one or more point mutations.

19. The VEGF mini-trap or composition of any one of claims 15-18, which is a composition, wherein said VEGF mini-trap, is applied to the anion-exchange (AEX) chromatography resin under a condition selected from the group consisting of:

- (1) the AEX resin comprises a quaternized polyethyleneimine functional group and is equilibrated with a buffer at pH 8.30 – 8.50 having a conductivity of 1.90 – 2.10 mS/cm;

(2) the AEX resin comprises a $-O-CH_2CHOHCH_2OCH_2CHOHCH_2N^+(CH_3)_3$ or $-N^+(CH_3)_3$ or a quaternary amine functional group and is equilibrated with a buffer at pH 7.90 – 8.10 having a conductivity of 2.40 – 2.60 mS/cm;

(3) the AEX resin comprises a quaternized polyethyleneimine functional group and is equilibrated with a buffer at pH 7.90 – 8.10 having a conductivity of 2.40 – 2.60 mS/cm;

(4) the AEX resin comprises a $-O-CH_2CHOHCH_2OCH_2CHOHCH_2N^+(CH_3)_3$ or $-N^+(CH_3)_3$ or a quaternary amine functional group and is equilibrated with a buffer at pH 7.70 – 7.90 having a conductivity of 3.90 – 4.10 mS/cm;

(5) the AEX resin comprises a quaternized polyethyleneimine functional group and is equilibrated with a buffer at pH 7.70 – 7.90 having a conductivity of 3.90 – 4.10 mS/cm;

(6) the AEX resin comprises a $-O-CH_2CHOHCH_2OCH_2CHOHCH_2N^+(CH_3)_3$ or $-N^+(CH_3)_3$ or a quaternary amine functional group and is equilibrated with a buffer at pH 7.70 ± 0.1 having a conductivity of 9.0 ± 0.1 mS/cm; and

(7) the AEX resin comprises a quaternized polyethyleneimine functional group and is equilibrated with a buffer at pH 8.4 ± 0.1 having a conductivity of 2.0 ± 0.1 mS/cm; optionally wherein:

the buffer under condition (1) comprises: 50 mM Tris, pH 8.4 and 2.0 mS/cm;

the buffer under conditions (2)-(3) comprises: 50 mM Tris, 10 mM acetate, pH 8.0 and 2.5 mS/cm;

the buffer under conditions (4)-(5) comprises: 50 mM Tris, 10 mM Acetate, 10 mM NaCl, pH 7.8 and 4.0 mS/cm;

the buffer under condition (6) comprises: 50 mM Tris, 60 mM NaCl, pH 7.7 ± 0.1 ; and/or

the buffer under condition (7) comprises: 50 mM Tris, pH 8.4 ± 0.1 ;

the VEGF mini-trap is in a loading buffer before application to the resin which is the equilibration buffer;

and/or

following application of the VEGF mini-trap to the resin, said resin is washed with said aqueous buffer.

20. The VEGF mini-trap or composition of any one of claims 15-19, which is a composition, wherein the Fc domain or fragment thereof is chromatographically removed from the VEGF mini-trap, following proteolytic cleavage, by applying the composition comprising Fc domain

or fragment and VEGF mini-trap to a protein-A chromatography resin and retaining the VEGF mini-trap in the flow-through fraction.

21. The VEGF mini-trap or composition of any one of claims 15-20, which is a composition, wherein the process further comprises adjustment of the pH to about 5.5, 5.6, 5.7, 5.8, 5.9, 6.0, 6.1 or 6.2, filtration, diafiltration, viral inactivation, protein-A chromatographic purification and/or hydrophobic interaction chromatographic purification.

22. The VEGF mini-trap or composition of any one of claims 15-20, which is a composition, wherein the process further comprises hydrophobic interaction chromatographic purification on a resin the comprises a phenyl functional group.

23. The VEGF mini-trap or composition of any one of claims 15-22, which is a composition, wherein the hydrophobic interaction chromatographic purification is done in bind-and-elute mode or flow-through mode.

24. The VEGF mini-trap or composition of any one of claims 15-20, which is a composition, wherein:

said mini-trap was expressed in a host cell which is in a chemically defined medium (CDM) or wherein said mini-trap is the product of a process comprising proteolytic cleavage of aflibercept, with IdeS enzyme, wherein said aflibercept was expressed in a host cell which is in a liquid chemically defined medium wherein said host cell was cultured in a process comprising the steps:

- (i) introducing the host cell to a CDM comprising:
 - about 68 micromoles Fe per liter of culture,
 - about 6 micromoles Zn per liter of culture,
 - about 0.1 micromoles Cu per liter of culture,
 - about 76 micromoles EDTA per liter of culture,
 - about 45 micromoles citrate per liter of culture, and
 - about 0.5 micromoles Ni per liter of culture and, optionally
 - about 1.2 millimoles cysteine per liter of culture;
- adding, to the culture, every two days:
 - about 1.2 millimoles cysteine per liter of culture,

- about 1 micromole Fe per liter of culture,
- about 6 micromoles Zn per liter of culture,
- about 0.1 micromoles Cu per liter of culture,
- about 8 micromoles EDTA per liter of culture, and
- about 1 micromoles citrate per liter of culture;

optionally, wherein the CDM includes thioctic acid, vitamin C and/or a mixture of hypotaurine, taurine and glycine

optionally wherein the CDM includes uridine, manganese, galactose and/or dexamethasone.

25. The VEGF mini-trap or composition of any one of claims 1-24, wherein:

- one or more asparagines of the VEGF mini-trap are N-glycosylated;
- one more more serines or threonines of the VEGF mini-trap are O-glycosylated;
- one or more asparagines of the VEGF mini-trap are deamidated;
- one or more Aspartate-Glycine motifs of the VEGF mini-trap are converted to iso-aspartate-glycine and/or Asn-Gly;
- one or more methionines of the VEGF mini-trap are oxidized;
- one or more tryptophans of the VEGF mini-trap are converted to N-formylkynurenin;
- one or more arginines of the VEGF mini-trap are converted to Arg 3-deoxyglucosone;
- the C-terminal Glycine of the VEGF mini-trap is not present;
- there are one or more non-glycosylated glycosites in the VEGF mini-trap;
- the VEGF mini-trap comprises about 40 % to about 50% total fucosylated glycans;
- the VEGF mini-trap comprises about 30% to about 55% total sialylated glycans;
- the VEGF mini-trap comprises about 6% to about 15% mannose-5;
- the VEGF mini-trap comprises about 60% to about 79% galactosylated glycans;
- the VEGF mini-trap is xylosylated;
- the VEGF mini-trap is glycated at a lysine;
- the VEGF mini-trap comprises a cystine with a free-thiol group;
- the VEGF mini-trap comprises a trisulfide bridge;
- the VEGF mini-trap comprises an intrachain disulfide bridge;
- the VEGF mini-trap comprises disulfide bridges in parallel orientation; and/or

- the VEGF mini-trap comprises a lysine or arginine which is carboxymethylated.

26. The VEGF mini-trap or composition of any one of claims 1-25, wherein one or more asparagines of the VEGF mini-trap comprise:

- G0-GlcNAc glycosylation;
- G1-GlcNAc glycosylation;
- G1S-GlcNAc glycosylation;
- G0 glycosylation;
- G1 glycosylation;
- G1S glycosylation;
- G2 glycosylation;
- G2S glycosylation;
- G2S2 glycosylation;
- G0F glycosylation;
- G2F2S glycosylation;
- G2F2S2 glycosylation;
- G1F glycosylation;
- G1FS glycosylation;
- G2F glycosylation;
- G2FS glycosylation;
- G2FS2 glycosylation;
- G3FS glycosylation;
- G3FS3 glycosylation;
- G0-2GlcNAc glycosylation;
- Man4 glycosylation;
- Man4_A1G1 glycosylation;
- Man4_A1G1S1 glycosylation;
- Man5 glycosylation;
- Man5_A1G1 glycosylation;
- Man5_A1G1S1 glycosylation;
- Man6 glycosylation;

- Man6_G0+Phosphate glycosylation;
- Man6+Phosphate glycosylation; and/or
- Man7 glycosylation.

27. The VEGF mini-trap or composition of any one of claims 1-26, wherein the VEGF mini-trap comprises:

- Man5 glycosylation at about 30-35% of asparagine 123 residues;
- Man5 glycosylation at about 25-30% of asparagine 196 residues;
- Man6-phosphate glycosylation at about 6-8% of asparagine 36 residues;
- Man7 glycosylation at about 3-4% of asparagine 123 residues;
- High mannose glycosylation at about 38% of asparagine 123 residues; and/or
- High mannose glycosylation at about 29% of asparagine 196 residues.

28. The VEGF mini-trap or composition of any one of claims 1-27, which is a composition that comprises the VEGF mini-trap at a concentration of about 80, 85, 90, 80-90, 100, 105, 110, 115, 120, 125, 130 or 90-120 mg/ml.

29. The VEGF mini-trap or composition of any one of claims 1-28, wherein

- the composition is aqueous;
- the mini-trap was expressed in a Chinese hamster ovary cell;
- the pH of the composition is about 5.5, 5.6, 5.7, 5.8, 5.9, 6.0, 6.1 or 6.2;

and/or

- the mini-trap has not been exposed to any greater than about 0.24, 0.6, 0.96, 1.2 or 2.4 million lux*hr white light; and/or any greater than about 40, 100, 160, 200 or 400 W*h/m² ultra-violet A (UVA) light.

30. The VEGF mini-trap or composition of any one of claims 1-29, wherein the VEGF mini-trap is a monomer, homodimer or multimer.

31. A pharmaceutical formulation comprising the VEGF mini-trap or composition of any one of claims 1-30 and a pharmaceutically acceptable carrier.

32. An injection device comprising the VEGF mini-trap polypeptide, composition or formulation of any one of claims 1-31.
33. The injection device of claim 32 which is a sterile pre-filled syringe.
34. The VEGF mini-trap polypeptide, composition or formulation of any one of claims 1-31 in association with a further therapeutic agent.
35. An isolated polynucleotide encoding a VEGF mini-trap of any one of claims 1-7.
36. A vector comprising the polynucleotide of claim 35.
37. A host cell comprising the VEGF mini-trap, polynucleotide and/or vector of any one of claims 1-7, 35 or 36.
38. The host cell of claim 37 which is a Chinese hamster ovary cell.
39. A method for making a VEGF mini-trap of any one of claims 1-7 comprising introducing a polynucleotide encoding said polypeptide into a host cell, culturing the host cell in a medium under conditions wherein the polypeptide is expressed and, optionally, isolating the polypeptide from the host cell and/or medium.
40. The method of claim 39 wherein the host cell is a Chinese hamster ovary cell.
41. A VEGF mini-trap which is the product of any one of claims 39-40.
42. A method for making a VEGF mini-trap of any one of claims 1-7 consisting essentially of proteolyzing a VEGF Trap with an enzyme that cleaves an immunoglobulin Fc polypeptide after the following sequence: DKTHTCPPCPAPELLG (SEQ ID NO: 20).
43. The method of claim 42 wherein the VEGF Trap is aflibercept or conbercept.

44. The method of any one of claims 42-43 wherein the enzyme is *S.pyogenes* IdeS or *Streptococcus equi* subspecies *zooepidemicus* IdeZ.

~~45. A method for administering said VEGF mini-trap or composition or a pharmaceutical formulation of any one of claims 1-31 and 34 to a subject comprising introducing the VEGF mini-trap, composition or formulation, and optionally a further therapeutic agent, into the body of the subject.~~

~~46. The method of claim 45 wherein said VEGF mini-trap is administered to the body of the subject by intraocular injection.~~

~~47. The method of any one of claims 45-46 wherein said VEGF mini-trap is administered intraocularly to the body of the subject by intravitreal injection.~~

~~48. A method for treating an angiogenic eye disorder in a subject in need thereof, the method comprising intraocularly injecting a therapeutically effective amount of the VEGF mini-trap or composition or pharmaceutical formulation thereof of any one of claims 1-31 or 34 or 41, and optionally a further therapeutic agent, into an eye of the subject.~~

45. Use of a therapeutically effective amount of the VEGF mini-trap or composition or pharmaceutical formulation thereof of any one of claims 1-31 or 34 or 41, and optionally a further therapeutic agent in the manufacture of a medicament for treating an angiogenic eye disorder in a subject in need thereof.

49. 46. The use of the therapeutically effective amount of the VEGF mini-trap or composition or the pharmaceutical formulation of claim 45 method of claim 45-48, wherein about 0.5 mg, 2 mg, 4 mg, 6 mg, 8 mg or 10 mg of the VEGF mini-trap is intravitreally injected into the eye of the subject.

50. 47. The use of the therapeutically effective amount of the VEGF mini-trap or composition or the pharmaceutical formulation of method of any one of claims 48-49 45-46, wherein the angiogenic eye disorder is

- age-related macular degeneration (wet),

- age-related macular degeneration (dry),
- macular edema,
- macular edema following retinal vein occlusion,
- retinal vein occlusion (RVO),
- central retinal vein occlusion (CRVO),
- branch retinal vein occlusion (BRVO),
- diabetic macular edema (DME),
- choroidal neovascularization (CNV),
- iris neovascularization,
- neovascular glaucoma,
- post-surgical fibrosis in glaucoma,
- proliferative vitreoretinopathy (PVR),
- optic disc neovascularization,
- corneal neovascularization,
- retinal neovascularization,
- vitreal neovascularization,
- pannus,
- pterygium,
- vascular retinopathy,
- diabetic retinopathy, wherein the subject also has diabetic macular edema; and
- diabetic retinopathy.

~~51- 48.~~ The use of the therapeutically effective amount of the VEGF mini-trap or composition or the pharmaceutical formulation of ~~method of any one of claims 45-50~~ 47 wherein the VEGF mini-trap is to be administered in about 100 microliters or less.