CLAIMS

1. A human neutrophil gelatinase associated lipocalin (hNGAL) mutein that is capable of binding Ang-2 with detectable affinity, wherein the amino acid sequence of the hNGAL mutein comprises at least sixteen of the following mutated amino acid residues in comparison with the linear polypeptide sequence of mature hNGAL (SEQ ID NO: 16): Gln 28 → His; Leu 36 → Gln, Glu, His, Val, Met or Phe; Ala 40 → Val, Tyr, His or Trp; Ile 41 → His, Tyr, Trp, Val, Arg, Glu, or Asp; Gln 49 → Gly, Ile, Glu or Val; Tyr 52 → Trp, His, Thr or Ser; Asn 65 → Asp; Ser 68 → Gly, Asp, Gln, Glu or Ile; Leu 70 → Ser, Thr, Gly, Arg, Tyr or Ala; Arg 72 → Gly, Ala, Trp, Thr or Glu; Lys 73 → Pro, Phe, Leu, Arg, Ala or Gln; Lys 74 → Glu; Asp 77 → Asn, Lys, Ser or Val; Trp 79 → Thr, Arg, Ser or Asn; Arg 81 → Trp, His or Tyr; Cys 87 → Ser; Asn 96 → Gly, Ala, Pro, Gln or Asp; Tyr 100 → Pro, Trp, Gly, Ser, Leu or Asp; Leu 103 → Gly, Glu, Asp, Met or Gln; Tyr 106 → Thr, Leu, Phe, or Pro; Asn 116 → Asp; Lys 125 → His, Thr or Gly; Val 126 → Met; Ser 127 → Leu, Met, or Tyr; Asn 129 → Asp; Tyr 132 → Phe, Trp or Val; and Lys 134 → Ala, Glu or Trp.

2. A human neutrophil gelatinase associated lipocalin (hNGAL) mutein that is capable of binding Ang-2 with detectable affinity, wherein the hNGAL mutein comprises one of the following sets of mutated amino acid residues in comparison with the linear polypeptide sequence of mature hNGAL (SEQ ID NO: 16):
   (a) Gln 28 → His; Leu 36 → Gln; Ala 40 →Tyr; Gln 49 → Gly; Tyr 52 → Trp; Ser 68 → Gly; Leu 70 → Ser; Arg 72 → Gly; Lys 73 → Pro; Asp 77→ Asn; Trp 79 → Thr; Arg 81 → Trp; Cys 87 → Ser; Asn 96 → Gly; Tyr 100 → Pro; Leu 103 → Gly; Tyr 106 → Thr; Lys 125 → His; Ser 127 → Leu; Tyr 132 → Phe; and Lys 134 → Glu;
   (b) Gln 28 → His; Leu 36 → Phe; Ala 40 →His; Ile 41 → Arg; Gln 49 → Gly; Tyr 52 → His; Ser 68 → Asp; Leu 70 → Thr; Arg 72 → Ala; Lys 73 → Phe; Asp 77→ Asn; Trp 79 → Arg; Arg 81 → His; Cys 87 → Ser; Tyr 100 → Trp; Leu 103 → Glu; Tyr 106 → Thr; Lys 125 → Thr; Ser 127 → Met; Tyr 132 → Trp; and Lys 134 → Trp;
   (c) Gln 28 → His; Leu 36 → Val; Ala 40 → Trp; Ile 41 → Tyr; Gln 49 → Ile; Tyr 52 → Thr; Ser 68 → Gln; Leu 70 → Gly; Arg 72 → Glu; Lys 73 → Gln; Asp 77 → Lys; Trp 79 → Ser; Arg 81 → His; Cys 87 → Ser; Asn 96 → Asp; Tyr 100 → Trp; Leu 103 → Asp; Tyr 106 → Leu; Lys 125 → Gly; Ser 127 → Met; Tyr 132 → Val; and Lys 134 → Ala;
   (d) Gln 28 → His; Leu 36 → Glu, Ala 40 →Val; Ile 41 → Glu; Gln 49 → Val; Tyr 52 → Thr Ser 68 → Glu; Leu 70 → Arg; Arg 72 → Trp; Lys 73 → Leu; Asp 77 → Lys;

Trp 79 → Asn; Arg 81 → His; Cys 87 → Ser; Asn 96 → Ala; Tyr 100 → Gly; Leu 103 → Met; Tyr 106 → Thr; Lys 125 → Thr; Ser 127 → Met; Tyr 132 → Trp; and Lys 134 → Trp;

(e) Gln 28 → His; Leu 36 → Gln; Ala 40 → Tyr; Ile 41 → Trp; Gln 49 → Ile; Tyr 52 → Ser; Ser 68 → Ile; Leu 70 → Tyr; Arg 72 → Thr; Lys 73 → Arg; Asp 77 → Ser; Trp 79 → Arg; Arg 81 → Tyr; Cys 87 → Ser; Asn 96 → Pro; Leu 103 → Asp; Tyr 106 → Thr; Lys 125 → His; Ser 127 → Tyr; Tyr 132 → Trp; and Lys 134 → Glu;

(f) Gln 28 → His; Leu 36 → Gln; Ala 40 → Tyr; Gln 49 → Glu; Tyr 52 → Trp; Asn 65 → Asp; Ser 68 → Gly; Leu 70 → Ser; Arg 72 → Gly; Lys 73 → Pro; Asp 77 → Asn; Trp 79 → Arg; Arg 81 → Trp; Cys 87 → Ser; Asn 96 → Gly; Tyr 100 → Ser; Leu 103 → Gln; Tyr 106 → Thr; Lys 125 → His; Ser 127 → Leu; Tyr 132 → Phe; and Lys 134 → Glu;

(g) Gln 28 → His; Leu 36 → His; Ala 40 →Tyr; Gln 49 → Glu; Tyr 52 → Trp; Asn 65 → Asp; Ser 68 → Glu; Leu 70 → Ser; Arg 72 → Gly; Lys 73 → Pro; Asp 77 → Asn; Trp 79 → Arg; Arg 81 → Trp; Cys 87 → Ser; Asn 96 → Gly; Tyr 100 → Pro; Leu 103 → Asp; Tyr 106 → Thr; Lys 125 → His; Ser 127 → Leu; Tyr 132 → Phe; and Lys 134 → Glu;

(h) Gln 28 → His; Leu 36 → Gln; Ala 40 →Tyr; Gln 49 → Gly; Tyr 52 → Trp; Asn 65 → Asp; Ser 68 → Glu; Leu 70 → Ser; Arg 72 → Gly; Lys 73 → Ala; Asp 77 → Asn; Trp 79 → Arg; Arg 81 → Trp; Cys 87 → Ser; Asn 96 → Gly; Tyr 100 → Asp; Leu 103 → Gly; Tyr 106 → Thr; Lys 125 → His; Ser 127 → Leu; Tyr 132 → Phe; and Lys 134 → Glu;

(i) Gln 28 → His; Leu 36 → His; Ala 40 →Tyr; Gln 49 → Gly; Tyr 52 → Trp; Asn 65 → Asp; Ser 68 → Glu; Leu 70 → Ser; Arg 72 → Gly; Lys 73 → Pro; Asp 77 → Asn; Trp 79 → Arg; Arg 81 → Trp; Cys 87 → Ser; Asn 96 → Gly; Tyr 100 → Pro; Leu 103 → Gly; Tyr 106 → Thr; Lys 125 → His; Ser 127 → Leu; Tyr 132 → Phe; and Lys 134 → Glu;

(j) Gln 28 → His; Leu 36 → Gln; Ala 40 →Tyr; Tyr 52 → Trp; Asn 65 → Asp; Ser 68 → Gly; Leu 70 → Ser; Arg 72 → Gly; Lys 73 → Ala; Asp 77 → Val; Trp 79 → Arg; Arg 81 → Trp; Cys 87 → Ser; Asn 96 → Gly; Tyr 100 → Pro; Leu 103 → Gly; Tyr 106 → Thr; Lys 125 → His; Ser 127 → Leu; Tyr 132 → Phe; and Lys 134 → Glu;

(k) Gln 28 → His; Leu 36 → Gln; Ala 40 →Tyr; Gln 49 → Val; Tyr 52 → Trp; Asn 65 → Asp; Ser 68 → Glu; Leu 70 → Ser; Arg 72 → Gly; Lys 73 → Pro; Asp 77 → Asn; Trp 79 → Arg; Arg 81 → Trp; Cys 87 → Ser; Asn 96 → Gly; Tyr 100 → Leu; Leu 103 → Gly; Tyr 106 → Thr; Lys 125 → His; Ser 127 → Leu; Tyr 132 → Phe; and Lys 134 → Glu;

(l) Gln 28 → His; Leu 36 → Val; Ala 40 → Trp; Ile 41 → Tyr; Gln 49 → Ile; Tyr 52 →

Thr; Asn 65 → Asp; Ser 68 → Gln; Leu 70 → Gly; Arg 72 → Glu; Lys 73 → Gln; Lys 74 → Glu; Asp 77 → Lys; Trp 79 → Ser; Arg 81 → His; Cys 87 → Ser; Tyr 100 → Trp; Leu 103 → Asp; Tyr 106 → Pro; Asn 116 → Asp; Lys 125 → Gly; Ser 127 → Met; Asn 129 → Asp; Tyr 132 → Val; and Lys 134 → Ala;

(m) Gln 28 → His; Leu 36 → Val; Ala 40 → Trp; Ile 41 → Tyr; Gln 49 → Ile; Tyr 52 → Thr; Asn 65 → Asp; Ser 68 → Gln; Leu 70 → Gly; Arg 72 → Glu; Lys 73 → Gln; Lys 74 → Glu; Asp 77 → Lys; Trp 79 → Ser; Arg 81 → His; Cys 87 → Ser; Asn 96 → Asp; Tyr 100 → Trp; Leu 103 → Asp; Tyr 106 → Pro; Lys 125 → Gly; Val 126 → Met; Ser 127 → Met; Asn 129 → Asp; Tyr 132 → Val; and Lys 134 → Ala; or

(n) Gln 28 → His; Leu 36 → Met; Ala 40 → Trp; Ile 41 → Asp; Gln 49 → Ile; Tyr 52 → Thr; Asn 65 → Asp; Ser 68 → Gln; Leu 70 → Ala; Arg 72 → Glu; Lys 73 → Gln; Asp 77 → Lys; Trp 79 → Ser; Arg 81 → His; Cys 87 → Ser; Asn 96 → Gln; Tyr 100 → Trp; Leu 103 → Asp; Tyr 106 → Pro; Lys 125 → Gly; Ser 127 → Met; Tyr 132 → Val; and Lys 134 → Ala.

3. The hNGAL mutein of claim 1 or 2, wherein the hNGAL mutein is capable of binding Ang-2 with a K_D of about 5 nM or lower.

4. The hNGAL mutein of any one of claims 1-3, wherein the hNGAL mutein is capable of inhibiting or reducing endothelial cell proliferation mediated by Ang-2 with an IC50 value of about 5 nM or lower.

5. The hNGAL mutein of any one of claims 1-4, wherein the hNGAL mutein is capable of binding mouse Ang-2 with detectable affinity.

6. The hNGAL mutein of any one of claims 1-5, wherein the hNGAL mutein is capable of blocking binding of human Ang-2 to hTie-2 with an IC50 value of about 25 nM or lower, or wherein the hNGAL mutein is capable of blocking binding of mouse Ang-2 to hTie-2 with an IC50 value of about 25 nM or lower.

7. The hNGAL mutein of any one of claims 1-6, wherein the hNGAL mutein has a sequence identity of at least 80% to a sequence selected from the group consisting of SEQ ID NOs: 1-14.

8. The hNGAL mutein of any one of claims 1-7, wherein the hNGAL mutein comprises an amino acid sequence selected from the group consisting of SEQ ID NOs: 1-14.

9. A human neutrophil gelatinase associated lipocalin (hNGAL) mutein that is capable of binding Ang-2 with detectable affinity, wherein the hNGAL mutein has a sequence identity of at least 95% to a sequence selected from the group consisting of SEQ ID NOs: 1-14.

10. The hNGAL mutein of any one of claims 1-9, wherein the hNGAL mutein has the amino acid sequence set forth in SEQ ID NO: 8.

11. The hNGAL mutein of any one of claims 1-9, wherein the hNGAL mutein has the amino acid sequence set forth in SEQ ID NO: 9.

12. The hNGAL mutein of any one of claims 1-9, wherein the hNGAL mutein has the amino acid sequence set forth in SEQ ID NO: 10.

13. The hNGAL mutein of any one of claims 1-12, wherein the hNGAL mutein is conjugated to a compound selected from the group consisting of an organic molecule, an enzyme label, a radioactive label, a colored label, a fluorescent label, a chromogenic label, a luminescent label, a hapten, digoxigenin, biotin, a cytostatic agent, a toxin, a metal complex, a metal, and colloidal gold or wherein the hNGAL mutein is conjugated to a compound that extends the serum half-life of the mutein.

14. The hNGAL mutein of any one of claims 1-13, wherein the hNGAL mutein is fused at its N-terminus and/or its C-terminus to a fusion partner which is a protein, a protein domain, or a peptide.

15. A nucleic acid molecule comprising a nucleotide sequence encoding the hNGAL mutein of any one of claims 1-14.

16. A method of producing the hNGAL mutein of any one of claims 1-14, wherein the mutein is produced starting from the nucleic acid coding for the mutein by means of genetic engineering methods.

17. A pharmaceutical composition comprising the hNGAL mutein of any one of claims 1-14.

18. A pharmaceutical composition comprising (a) the hNGAL mutein of any one of claims 1-14 and (b) an anti-angiogenic agent.

19. The composition of claim 18, wherein the anti-angiogenic agent is selected from the group consisting of: (i) antagonists of Ang-1, Ang-2, Ang-3, Ang-4 and/or Tie-2; (ii) antagonists of Fltl, KDR, Flt4, VEGF-A, VEGF-B, VEGF-C, VEGF-D, VEGF-E, PIGF and/or EG-VEGF; (iii) delta like ligand 4 (DLL4, a vascular-specific Notch ligand) antagonists, (iv) epidermal growth factor receptor (EGFR) antagonists, and (v) cytokine inhibitors.

20. A use of the hNGAL mutein of any one of claims 1-14 for the manufacture of a pharmaceutical composition suited for the treatment, prevention, or amelioration of a disease or disorder associated with deregulated angiogenesis.

21. A use of the hNGAL mutein of any one of claims 1-14 for the manufacture of a pharmaceutical composition suited for inhibiting angiogenesis in a subject.

22. The use of claim 20, wherein the disease or disorder is selected from the group consisting of: tumor growth, eye disorders, vascular diseases, inflammatory or infectious diseases, cancer, ocular neovascular diseases, arthritis, and psoriasis.