What is claimed is:

1. A mutein of human tear lipocalin having detectable binding affinity to a given non-natural ligand of human tear lipocalin, wherein at least one of the cysteine residues at sequence positions 61 and 153 of the linear polypeptide sequence of the mature human tear lipocalin has been mutated to any other amino acid residue and wherein at least 12, 14, or 16 mutated amino acid residues are present at any of the sequence positions 26-34, 56-58, 80, 83, 104-106, and 108 of the linear polypeptide sequence of mature human tear lipocalin, wherein the non-natural ligand is VEGF or a fragment thereof.

2. The mutein according to claim 1, wherein said mutein acts as a VEGF antagonist by inhibiting binding of VEGF to its receptor, wherein the receptor for VEGF is selected from the group consisting of VEGF-R1, VEGF-R2, and Neuropilin-I.

3. The mutein according to claim 2, wherein the receptor for VEGF is VEGF-R2.

4. The mutein of any one of claims 1 to 3, wherein the mutein binds VEGF with a K_D of 200 nM or less, with a K_D of 100 nM or less, with a K_D of 20 nM or less, or with a K_D of 1 nM or less.

5. The mutein according to any one of claims 1 to 4, wherein the mutein comprises at least 12, 14, 16 amino acid substitutions with respect to the amino acid sequence of mature human tear lipocalin, which are selected from the group consisting of Arg 26 → Ser, Pro, Val, Leu, Ile; Glu 27 → Gly; Phe 28 → Ala; Pro 29 → Leu; Glu 30 → Arg; Met 31 → Cys; Asn 32 → Leu; Leu 33 → Ala; Glu 34 → Gly; Leu 56 → His, Arg, Tyr, Gln; Ile 57 → Val, Thr, Leu; Ser 58 → Lys; Asp 80 → Ile; Lys 83 → Ile; Glu 104 → Cys; His 106 → Asn, Ser; and Lys 108 → Ala, Val.

6. The mutein according to claim 5, further comprising at least one amino acid substitution selected from the group consisting of Val 36 → Ala; Thr 37 → Ala, Ile; Met 39 → Thr; Thr 40 → Ala, Ser; Asn 48 → Asp, Ala 51 → Val; Lys 52 → Arg; Thr 54 → Val; Met 55 → Val; Ser 61 → Pro; Lys 65 → Arg; Ala 66 → Val; Val 67 → Ile; Glu 69 → Gly, Ser, Thr; Lys 76 → Arg, Ile, Ala, Met, Pro; Tyr 87→ Arg, His,

Lys, Gln; Ile 89 → Thr, Val, Gly, His, Met, Lys; Arg 90 → Gly; Ile 98 → Val; and Gly 107 → Glu.

7. The mutein according to claim 5 or 6, wherein the mutein comprises the amino acid substitutions: Glu 27 → Gly; Phe 28 → Ala; Pro 29 → Leu; Glu 30 → Arg; Met 31 → Cys; Asn 32 → Leu; Leu 33 → Ala; Glu 34 → Gly; Asp 80 → Ile; Lys 83 → Ile; Glu 104 → Cys; and Lys 108 → Val.

8. The mutein of any one of claims 5 to 7, wherein the mutein comprises one of the following sets of amino acid substitutions:

(1) Arg 26 → Ser; Glu 27 → Gly; Phe 28 → Ala; Pro 29 → Leu; Glu 30 → Arg; Met 31 → Cys; Asn 32 → Leu; Leu 33 → Ala; Glu 34 → Gly; Leu 56 → His; Ser 58 → Lys; Asp 80 → Ile; Lys 83 → Ile; Glu 104 → Cys; His 106 → Asn; Lys 108 → Val;

(2) Arg 26 → Pro; Glu 27 → Gly; Phe 28 → Ala; Pro 29 → Leu; Glu 30 → Arg; Met 31 → Cys; Asn 32 → Leu; Leu 33 → Ala; Glu 34 → Gly; Leu 56 → His; Ser 58 → Glu; Asp 80 → Ile; Lys 83 → Ile; Glu 104 → Cys; His 106 → Ser; Lys 108 → Val;

(3) Arg 26 → Pro; Glu 27 → Gly; Phe 28 → Ala; Pro 29 → Leu; Glu 30 → Arg; Met 31 → Cys; Asn 32 → Leu; Leu 33 → Ala; Glu 34 → Gly; Leu 56 → His; Ser 58 → Lys; Asp 80 → Ile; Lys 83 → Ile; Glu 104 → Cys; His 106 → Asn; Lys 108 → Val;

(4) Arg 26 → Pro; Glu 27 → Gly; Phe 28 → Ala; Pro 29 → Leu; Glu 30 → Arg; Met 31 → Cys; Asn 32 → Leu; Leu 33 → Ala; Glu 34 → Gly; Leu 56 → Arg; Ser 58 → Lys; Asp 80 → Ile; Lys 83 → Ile; Glu 104 → Cys; His 106 → Ser; Lys 108 → Val;

(5) Arg 26 → Pro; Glu 27 → Gly; Phe 28 → Ala; Pro 29 → Leu; Glu 30 → Arg; Met 31 → Cys; Asn 32 → Leu; Leu 33 → Ala; Glu 34 → Gly; Leu 56 → His; Ser 58 → Lys; Asp 80 → Ile; Lys 83 → Ile;Glu 104 → Cys; His 106 → Ser; Lys 108 → Val;

(6) Arg 26 → Ser; Glu 27 → Gly; Phe 28 → Ala; Pro 29 → Leu; Glu 30 → Arg; Met 31 → Cys; Asn 32 → Leu; Leu 33 → Ala; Glu 34 → Gly; Leu 56 → His; Ser 58 → Lys; Asp 80 → Ile; Lys 83 → Ile; Glu 104 → Cys; His 106 → Ser; Lys 108 → Val;

(7) Arg 26 → Val; Glu 27 → Gly; Phe 28 → Ala; Pro 29 → Leu; Glu 30 → Arg; Met 31 → Cys; Asn 32 → Leu; Leu 33 → Ala; Glu 34 → Gly; Leu 56 → His; Ser 58 → Lys; Asp 80 → Ile; Lys 83 → Ile; Glu 104 → Cys; His 106 → Ser; Lys 108 → Val;

(8) Arg 26 → Leu; Glu 27 → Gly; Phe 28 → Ala; Pro 29 → Leu; Glu 30 → Arg; Met 31 → Cys; Asn 32 → Leu; Leu 33 → Ala; Glu 34 → Gly; Leu 56 → His; Ser 58 → Lys; Asp 80 → Ile; Lys 83 → Ile; Glu 104 → Cys; His 106 → Ser; Lys 108 → Val; and

(9) Arg 26 → Ile; Glu 27 → Gly; Phe 28 → Ala; Pro 29 → Leu; Glu 30 → Arg; Met 31 → Cys; Asn 32 → Leu; Leu 33 → Ala; Glu 34 → Gly; Leu 56 → His; Ser 58 → Lys; Asp 80 → Ile; Lys 83 → Ile; Glu 104 → Cys; His 106 → Ser; Lys 108 → Val.

9. The mutein according to any one of claims 1 to 8, wherein the mutein has an amino acid sequence as set forth in SEQ ID Nos.: 26-33 or 44-47.

10. A nucleic acid molecule comprising a nucleotide sequence encoding a mutein of any of claims 1 to 9.

11. The nucleic acid molecule of claim 10 comprised in a vector.

12. A host cell containing a nucleic acid molecule of any claim 10 or 11.

13. A pharmaceutical composition comprising a mutein of human tear lipocalin as defined in any one of claims 1 to 10 and a pharmaceutically acceptable excipient.

14. A method for producing a mutein of human tear lipocalin as defined in any of claims 1 to 9, wherein the mutein is produced starting from the nucleic acid encoding the mutein by means of genetic engineering methods in a bacterial or eukaryotic host organism and is isolated from this host organism or its culture.

15. A method of treating a disease or disorder, comprising administering a pharmaceutical composition containing a mutein as defined in any of claims 1 to 9.

16. The method according to claim 15, wherein the disease or disorder is selected from the group consisting of diseases or disorders that are caused or promoted by increased vascularisation.

17. The method according to claim 16, wherein the disease or disorder is selected from the group consisting of cancer, neovascular wet age-related macular degeneration (AMD), diabetic retinopathy, macular edema, retinopathy of prematurity and retinal vein occlusion.

18. The method according to claim 17, wherein said cancer is selected from the group consisting of carcinomas of the gastrointestinal tract, rectum, colon, prostate, ovaries, pancreas, breast, bladder, kidney, endometrium, and lung, leukaemia, and melanoma

Claims:

1. A mutein of human tear lipocalin having detectable binding affinity to a given non-natural ligand of human tear lipocalin, wherein at least one of the cysteine residues at sequence positions 61 and 153 of the linear polypeptide sequence of the mature human tear lipocalin has been mutated to any other amino acid residue and wherein at least 12, 14, or 16 mutated amino acid residues are present at any of the sequence positions 26-34, 56-58, 80, 83, 104-106, and 108 of the linear polypeptide sequence of mature human tear lipocalin, wherein the non-natural ligand is VEGF or a fragment thereof.

2. The mutein according to claim 1, wherein said mutein acts as a VEGF antagonist by inhibiting binding of VEGF to its receptor, wherein the receptor for VEGF is selected from the group consisting of VEGF-R1, VEGF-R2, and Neuropilin-I.

3. The mutein according to claim 2, wherein the receptor for VEGF is VEGF-R2.

4. The mutein of any one of claims 1 to 3, wherein the mutein binds VEGF with a K_D of 200 nM or less, with a K_D of 100 nM or less, with a K_D of 20 nM or less, or with a K_D of 1 nM or less.

5. The mutein according to any one of claims 1 to 4, wherein the mutein comprises at least 12, 14, 16 amino acid substitutions with respect to the amino acid sequence of mature human tear lipocalin, which are selected from the group consisting of Arg 26 → Ser, Pro, Val, Leu, Ile; Glu 27 → Gly; Phe 28 → Ala; Pro 29 → Leu; Glu 30 → Arg; Met 31 → Cys; Asn 32 → Leu; Leu 33 → Ala; Glu 34 → Gly; Leu 56 → His, Arg, Tyr, Gln; Ile 57 → Val, Thr, Leu; Ser 58 → Lys; Asp 80 → Ile; Lys 83 → Ile; Glu 104 → Cys; His 106 → Asn, Ser; and Lys 108 → Ala, Val.

6. The mutein according to claim 5, further comprising at least one amino acid substitution selected from the group consisting of Val 36 → Ala; Thr 37 → Ala, Ile; Met 39 → Thr; Thr 40 → Ala, Ser; Asn 48 → Asp, Ala 51 → Val; Lys 52 → Arg; Thr 54 → Val; Met 55 → Val; Ser 61 → Pro; Lys 65 → Arg; Ala 66 → Val; Val 67 → Ile; Glu 69 → Gly, Ser, Thr; Lys 76 → Arg, Ile, Ala, Met, Pro; Tyr 87→ Arg,

His, Lys, Gln; Ile 89 → Thr, Val, Gly, His, Met, Lys; Arg 90 → Gly; Ile 98 → Val; and Gly 107 → Glu.

7. The mutein according to claim 5 or 6, wherein the mutein comprises the amino acid substitutions: Glu 27 → Gly; Phe 28 → Ala; Pro 29 → Leu; Glu 30 → Arg; Met 31 → Cys; Asn 32 → Leu; Leu 33 → Ala; Glu 34 → Gly; Asp 80 → Ile; Lys 83 → Ile; Glu 104 → Cys; and Lys 108 → Val.

8. The mutein of any one of claims 5 to 7, wherein the mutein comprises one of the following sets of amino acid substitutions:
   (1) Arg 26 → Ser; Glu 27 → Gly; Phe 28 → Ala; Pro 29 → Leu; Glu 30 → Arg; Met 31 → Cys; Asn 32 → Leu; Leu 33 → Ala; Glu 34 → Gly; Leu 56 → His; Ser 58 → Lys; Asp 80 → Ile; Lys 83 → Ile; Glu 104 → Cys; His 106 → Asn; Lys 108 → Val;
   (2) Arg 26 → Pro; Glu 27 → Gly; Phe 28 → Ala; Pro 29 → Leu; Glu 30 → Arg; Met 31 → Cys; Asn 32 → Leu; Leu 33 → Ala; Glu 34 → Gly; Leu 56 → His; Ser 58 → Glu; Asp 80 → Ile; Lys 83 → Ile; Glu 104 → Cys; His 106 → Ser; Lys 108 → Val;
   (3) Arg 26 → Pro; Glu 27 → Gly; Phe 28 → Ala; Pro 29 → Leu; Glu 30 → Arg; Met 31 → Cys; Asn 32 → Leu; Leu 33 → Ala; Glu 34 → Gly; Leu 56 → His; Ser 58 → Lys; Asp 80 → Ile; Lys 83 → Ile; Glu 104 → Cys; His 106 → Asn; Lys 108 → Val;
   (4) Arg 26 → Pro; Glu 27 → Gly; Phe 28 → Ala; Pro 29 → Leu; Glu 30 → Arg; Met 31 → Cys; Asn 32 → Leu; Leu 33 → Ala; Glu 34 → Gly; Leu 56 → Arg; Ser 58 → Lys; Asp 80 → Ile; Lys 83 → Ile; Glu 104 → Cys; His 106 → Ser; Lys 108 → Val;
   (5) Arg 26 → Pro; Glu 27 → Gly; Phe 28 → Ala; Pro 29 → Leu; Glu 30 → Arg; Met 31 → Cys; Asn 32 → Leu; Leu 33 → Ala; Glu 34 → Gly; Leu 56 → His; Ser 58 → Lys; Asp 80 → Ile; Lys 83 → Ile;Glu 104 → Cys; His 106 → Ser; Lys 108 → Val;
   (6) Arg 26 → Ser; Glu 27 → Gly; Phe 28 → Ala; Pro 29 → Leu; Glu 30 → Arg; Met 31 → Cys; Asn 32 → Leu; Leu 33 → Ala; Glu 34 → Gly; Leu 56 → His; Ser 58 → Lys; Asp 80 → Ile; Lys 83 → Ile; Glu 104 → Cys; His 106 → Ser; Lys 108 → Val;

(7) Arg 26 → Val; Glu 27 → Gly; Phe 28 → Ala; Pro 29 → Leu; Glu 30 → Arg; Met 31 → Cys; Asn 32 → Leu; Leu 33 → Ala; Glu 34 → Gly; Leu 56 → His; Ser 58 → Lys; Asp 80 → Ile; Lys 83 → Ile; Glu 104 → Cys; His 106 → Ser; Lys 108 → Val;

(8) Arg 26 → Leu; Glu 27 → Gly; Phe 28 → Ala; Pro 29 → Leu; Glu 30 → Arg; Met 31 → Cys; Asn 32 → Leu; Leu 33 → Ala; Glu 34 → Gly; Leu 56 → His; Ser 58 → Lys; Asp 80 → Ile; Lys 83 → Ile; Glu 104 → Cys; His 106 → Ser; Lys 108 → Val; and

(9) Arg 26 → Ile; Glu 27 → Gly; Phe 28 → Ala; Pro 29 → Leu; Glu 30 → Arg; Met 31 → Cys; Asn 32 → Leu; Leu 33 → Ala; Glu 34 → Gly; Leu 56 → His; Ser 58 → Lys; Asp 80 → Ile; Lys 83 → Ile; Glu 104 → Cys; His 106 → Ser; Lys 108 → Val.

9. The mutein according to any one of claims 1 to 8, wherein the mutein has an amino acid sequence as set forth in SEQ ID Nos.: 26-33 or 44-47.

10. A nucleic acid molecule comprising a nucleotide sequence encoding a mutein of any of claims 1 to 9.

11. The nucleic acid molecule of claim 10 comprised in a vector.

12. A host cell containing a nucleic acid molecule of any claim 10 or 11.

13. A pharmaceutical composition comprising a mutein of human tear lipocalin as defined in any one of claims 1 to 10 and a pharmaceutically acceptable excipient.

14. A method for producing a mutein of human tear lipocalin as defined in any of claims 1 to 9, wherein the mutein is produced starting from the nucleic acid encoding the mutein by means of genetic engineering methods in a bacterial or eukaryotic host organism and is isolated from this host organism or its culture.

15. A method of treating a disease or disorder, comprising administering a pharmaceutical composition containing a mutein as defined in any of claims 1 to 9.

16. The method according to claim 15, wherein the disease or disorder is selected from the group consisting of diseases or disorders that are caused or promoted by increased vascularisation.

17. The method according to claim 16, wherein the disease or disorder is selected from the group consisting of cancer, neovascular wet age-related macular degeneration (AMD), diabetic retinopathy, macular edema, retinopathy of prematurity and retinal vein occlusion.

18. The method according to claim 17, wherein said cancer is selected from the group consisting of carcinomas of the gastrointestinal tract, rectum, colon, prostate, ovaries, pancreas, breast, bladder, kidney, endometrium, and lung, leukaemia, and melanoma.