

CLAIMS

1. A lipocalin mutein that is capable of binding LAG-3, wherein the amino acid sequence of the mutein comprises at least eight of the following amino acid mutations in comparison with the linear polypeptide sequence of mature human tear lipocalin (SEQ ID NO: 1): Arg 26 → Ser; Glu 27 → Asp; Phe 28 → Cys; Pro 29 → Phe; Glu 30 → Trp; Met 31 → Ile; Asn 32 → Asp; Leu 33 → Asp; Glu 34 → Val; Leu 56 → Asp; Ser 58 → Phe; Arg 60 → Phe; Cys 61 → Trp; Cys 101 → Ser; Leu 105 → Cys; His 106 → Ala; Lys 108 → Tyr; Arg 111 → Pro; Lys 114 → Trp; Cys 153 → Ser; and one or more of the following amino acid mutations in comparison with the linear polypeptide sequence of mature human tear lipocalin: Ala 5 → Thr; Asp 7 → Gly; Glu 8 → Gln; Ile 10 → Phe; Thr 16 → Met; Leu 44 → His; Gly 46 → Asp; Val 53 → Ala; Glu 63 → Asp; Lys 65 → Glu; Glu 69 → Gly; Lys 70 → Arg; Glu 73 → Ala; Ala 79 → Thr; Asp 80 → Gly; Val 85 → Ala or Asp; Ile 89 → Ser or Asn; Arg 90 → Ser; Val 93 → Glu; His 96 → Asn; Tyr 97 → His; Ile 98 → Val; Leu 124 → Gln; Arg 148 → Trp; Gln 149 → Leu; Ser 150 → Gly; Thr 152 → Pro; and Ser 154 → Ala.
2. A lipocalin mutein that is capable of binding LAG-3, wherein the amino acid sequence of the mutein comprises at least eight the following amino acid mutations in comparison with the linear polypeptide sequence of mature human tear lipocalin (SEQ ID NO: 1): Ser 14 → Pro; Asp 25 → Ser; Phe 28 → Asp; Lys 52 → Arg; Met 55 → Val; Ser 58 → Asp; Ala 66 → Asn; Ala 79 → Glu; Ala 86 → Asp; Cys 101 → Phe; Leu 105 → Gly; Lys 108 → Thr; Lys 114 → Ala; Lys 121 → Thr; and one or more of the following amino acid mutations in comparison with the linear polypeptide sequence of mature human tear lipocalin: Arg 26 → Ser, Asp, Glu, or Ala; Met 31 → Leu; Asn 32 → Thr; Leu 56 → Asp; His 84 → Tyr or Leu; His 106 → Glu, Lys, or Pro; Val 110 → Asn; Gly 112 → Val or Leu; Val 113 → Ala or Leu.
3. The lipocalin mutein of claim 1 or 2, wherein
 - (i) the mutein is capable of binding LAG-3 with an affinity measured by K_d of about 250 nM or lower, about 50 nM or lower, about 3 nM or lower, about 0.1 nM or lower, or about 0.05 nM or lower;
 - (ii) the mutein binds LAG-3 with an EC_{50} value of about 320 nM or lower, about 10 nM or lower., or about 0.2 nM or lower;
 - (iii) the mutein is cross-reactive with both human LAG-3 and cynomolgus LAG-3; or

- (iv) the mutein is capable of interfering with the binding of human LAG-3 to major histocompatibility complex (MHC) class II.

4. The lipocalin mutein of any one of claims 1-3, wherein

- (i) the amino acid sequence of the mutein comprises 21 or more of the following mutated amino acid residues in comparison with the linear polypeptide sequence of mature human tear lipocalin (SEQ ID NO: 1): Ala 5 → Thr; Asp 7 → Gly; Glu 8 → Gln; Ile 10 → Phe; Ser 14 → Pro; Thr 16 → Met; Asp 25 → Ser; Arg 26 → Ser, Asp, Glu, Ala, or Gly; Glu 27 → Asp; Phe 28 → Cys or Asp; Pro 29 → Phe; Glu 30 → Trp; Met 31 → Ile or Leu; Asn 32 → Asp, Met or Thr; Leu 33 → Asp; Glu 34 → Val; Leu 44 → His; Gly 46 → Asp; Lys 52 → Arg; Val 53 → Ala; Met 55 → Val; Leu 56 → Asp; Ser 58 → Phe or Asp; Arg 60 → Phe; Cys 61 → Trp; Glu 63 → Asp; Lys 65 → Glu; Ala 66 → Asn; Glu 69 → Gly; Lys 70 → Arg; Glu 73 → Ala; Ala 79 → Thr or Glu; Asp 80 → Gly; His 84 → Tyr or Leu; Val 85 → Ala or Asp; Ala 86 → Asp; Ile 89 → Ser or Asn; Arg 90 → Ser; Val 93 → Glu; His 96 → Asn; Tyr 97 → His; Ile 98 → Val; Cys 101 → Ser or Phe; Leu 105 → Cys or Gly; His 106 → Ala, Gln, Glu, Lys, or Pro; Lys 108 → Tyr or Thr; Val 110 → Gly or Asn; Arg 111 → Pro; Gly 112 → Met, Val, or Leu; Val 113 → Ala or Leu; Lys 114 → Trp or Ala; Lys 121 → Thr; Leu 124 → Gln; Arg 148 → Trp; Gln 149 → Leu; Ser 150 → Gly; Thr 152 → Pro; Cys 153 → Ser; and Ser 154 → Ala;
- (ii) the amino acid sequence of the mutein comprises at least 20 of the following mutated amino acid residues in comparison with the linear polypeptide sequence of mature human tear lipocalin (SEQ ID NO: 1): Ser 14 → Pro; Asp 25 → Ser; Arg 26 → Ser, Asp, Glu, Ala, or Gly; Phe 28 → Asp; Met 31 → Leu; Asn 32 → Met or Thr; Lys 52 → Arg; Met 55 → Val; Ser 58 → Asp; Ala 66 → Asn; Ala 79 → Glu; His 84 → Tyr or Leu; Ala 86 → Asp; Cys 101 → Phe; Leu 105 → Gly; His 106 → Gln, Glu, Lys, or Pro; Lys 108 → Thr; Val 110 → Gly or Asn; Gly 112 → Met, Val, or Leu; Val 113 → Ala or Leu; Lys 114 → Ala; and Lys 121 → Thr; or
- (iii) the amino acid sequence of the mutein comprises at least 21 of the following mutated amino acid residues in comparison with the linear polypeptide sequence of mature human tear lipocalin (SEQ ID NO: 1): Ala 5 → Thr; Asp 7 → Gly; Glu 8 → Gln; Ile 10 → Phe; Thr 16 → Met; Arg 26 → Ser; Glu 27 → Asp; Phe 28 → Cys; Pro 29 → Phe; Glu 30 → Trp; Met 31 → Ile; Asn 32 → Asp; Leu 33 → Asp; Glu 34 → Val; Leu 44 → His; Gly 46 → Asp; Val 53 → Ala; Leu 56 → Asp; Ser 58 → Phe; Arg 60 → Phe; Cys 61 → Trp; Glu 63 → Asp; Lys 65 → Glu; Glu 69 → Gly; Lys 70 → Arg; Glu 73 → Ala; Ala 79 → Thr; Asp 80 → Gly; Val 85 → Ala or Asp; Ile 89 → Ser or Asn; Arg 90 → Ser; Val 93 → Glu; His 96 → Asn; Tyr 97 →

His; Ile 98 → Val; Cys 101 → Ser; Leu 105 → Cys; His 106 → Ala; Lys 108 → Tyr; Arg 111 → Pro; Lys 114 → Trp; Leu 124 → Gln; Arg 148 → Trp; Gln 149 → Leu; Ser 150 → Gly; Thr 152 → Pro; Cys 153 → Ser; and Ser 154 → Ala.

5. The lipocalin mutein of any one of claims 1–4, wherein the amino acid sequence of the mutein comprises one of the following sets of mutated amino acid residues in comparison with the linear polypeptide sequence of mature human tear lipocalin (SEQ ID NO: 1):

- (a) Ala 5 → Thr; Glu 8 → Gln; Arg 26 → Ser; Glu 27 → Asp; Phe 28 → Cys; Pro 29 → Phe; Glu 30 → Trp; Met 31 → Ile; Asn 32 → Asp; Leu 33 → Asp; Glu 34 → Val; Leu 56 → Asp; Ser 58 → Phe; Arg 60 → Phe; Cys 61 → Trp; Lys 65 → Glu; Glu 69 → Gly; Val 85 → Ala; Cys 101 → Ser; Leu 105 → Cys; His 106 → Ala; Lys 108 → Tyr; Arg 111 → Pro; Lys 114 → Trp; Cys 153 → Ser; and Ser 154 → Ala;
- (b) Ala 5 → Thr; Arg 26 → Ser; Glu 27 → Asp; Phe 28 → Cys; Pro 29 → Phe; Glu 30 → Trp; Met 31 → Ile; Asn 32 → Asp; Leu 33 → Asp; Glu 34 → Val; Gly 46 → Asp; Leu 56 → Asp; Ser 58 → Phe; Arg 60 → Phe; Cys 61 → Trp; Lys 65 → Glu; Val 85 → Ala; Cys 101 → Ser; Leu 105 → Cys; His 106 → Ala; Lys 108 → Tyr; Arg 111 → Pro; Lys 114 → Trp; Ser 150 → Gly; and Cys 153 → Ser;
- (c) Asp 7 → Gly; Arg 26 → Ser; Glu 27 → Asp; Phe 28 → Cys; Pro 29 → Phe; Glu 30 → Trp; Met 31 → Ile; Asn 32 → Asp; Leu 33 → Asp; Glu 34 → Val; Leu 56 → Asp; Ser 58 → Phe; Arg 60 → Phe; Cys 61 → Trp; Val 85 → Asp; Cys 101 → Ser; Leu 105 → Cys; His 106 → Ala; Lys 108 → Tyr; Arg 111 → Pro; Lys 114 → Trp; Arg 148 → Trp; Thr 152 → Pro; and Cys 153 → Ser;
- (d) Ala 5 → Thr; Arg 26 → Ser; Glu 27 → Asp; Phe 28 → Cys; Pro 29 → Phe; Glu 30 → Trp; Met 31 → Ile; Asn 32 → Asp; Leu 33 → Asp; Glu 34 → Val; Val 53 → Ala; Leu 56 → Asp; Ser 58 → Phe; Arg 60 → Phe; Cys 61 → Trp; Lys 65 → Glu; Ala 79 → Thr; Tyr 97 → His; Cys 101 → Ser; Leu 105 → Cys; His 106 → Ala; Lys 108 → Tyr; Arg 111 → Pro; Lys 114 → Trp; and Cys 153 → Ser;
- (e) Arg 26 → Ser; Glu 27 → Asp; Phe 28 → Cys; Pro 29 → Phe; Glu 30 → Trp; Met 31 → Ile; Asn 32 → Asp; Leu 33 → Asp; Glu 34 → Val; Leu 56 → Asp; Ser 58 → Phe; Arg 60 → Phe; Cys 61 → Trp; Glu 63 → Asp; Val 85 → Asp; Arg 90 → Ser; His 96 → Asn; Cys 101 → Ser; Leu 105 → Cys; His 106 → Ala; Lys 108 → Tyr; Arg 111 → Pro; Lys 114 → Trp; Leu 124 → Gln; and Cys 153 → Ser;
- (f) Thr 16 → Met; Arg 26 → Ser; Glu 27 → Asp; Phe 28 → Cys; Pro 29 → Phe; Glu 30 → Trp; Met 31 → Ile; Asn 32 → Asp; Leu 33 → Asp; Glu 34 → Val; Leu 44 → His; Leu 56 → Asp; Ser 58 → Phe; Arg 60 → Phe; Cys 61 → Trp; Lys 65 → Glu;

- Ile 89 → Ser; Cys 101 → Ser; Leu 105 → Cys; His 106 → Ala; Lys 108 → Tyr; Arg 111 → Pro; Lys 114 → Trp; and Cys 153 → Ser;
- (g) Arg 26 → Ser; Glu 27 → Asp; Phe 28 → Cys; Pro 29 → Phe; Glu 30 → Trp; Met 31 → Ile; Asn 32 → Asp; Leu 33 → Asp; Glu 34 → Val; Leu 56 → Asp; Ser 58 → Phe; Arg 60 → Phe; Cys 61 → Trp; Glu 63 → Asp; Lys 65 → Glu; Cys 101 → Ser; Leu 105 → Cys; His 106 → Ala; Lys 108 → Tyr; Arg 111 → Pro; Lys 114 → Trp; Gln 149 → Leu; and Cys 153 → Ser;
- (h) Arg 26 → Ser; Glu 27 → Asp; Phe 28 → Cys; Pro 29 → Phe; Glu 30 → Trp; Met 31 → Ile; Asn 32 → Asp; Leu 33 → Asp; Glu 34 → Val; Leu 56 → Asp; Ser 58 → Phe; Arg 60 → Phe; Cys 61 → Trp; Lys 65 → Glu; Lys 70 → Arg; Cys 101 → Ser; Leu 105 → Cys; His 106 → Ala; Lys 108 → Tyr; Arg 111 → Pro; Lys 114 → Trp; and Cys 153 → Ser;
- (i) Ala 5 → Thr; Arg 26 → Ser; Glu 27 → Asp; Phe 28 → Cys; Pro 29 → Phe; Glu 30 → Trp; Met 31 → Ile; Asn 32 → Asp; Leu 33 → Asp; Glu 34 → Val; Leu 56 → Asp; Ser 58 → Phe; Arg 60 → Phe; Cys 61 → Trp; Lys 65 → Glu; Asp 80 → Gly; Ile 89 → Asn; Ile 98 → Val; Cys 101 → Ser; Leu 105 → Cys; His 106 → Ala; Lys 108 → Tyr; Arg 111 → Pro; Lys 114 → Trp; and Cys 153 → Ser;
- (j) Ile 10 → Phe; Arg 26 → Ser; Glu 27 → Asp; Phe 28 → Cys; Pro 29 → Phe; Glu 30 → Trp; Met 31 → Ile; Asn 32 → Asp; Leu 33 → Asp; Glu 34 → Val; Leu 56 → Asp; Ser 58 → Phe; Arg 60 → Phe; Cys 61 → Trp; Lys 65 → Glu; Glu 73 → Ala; Ile 89 → Asn; Val 93 → Glu; Cys 101 → Ser; Leu 105 → Cys; His 106 → Ala; Lys 108 → Tyr; Arg 111 → Pro; Lys 114 → Trp; and Cys 153 → Ser;
- (k) Ala 5 → Thr; Glu 8 → Gln; Arg 26 → Ser; Glu 27 → Asp; Phe 28 → Cys; Pro 29 → Phe; Glu 30 → Trp; Met 31 → Ile; Asn 32 → Asp; Leu 33 → Asp; Glu 34 → Val; Leu 56 → Asp; Ser 58 → Phe; Arg 60 → Phe; Cys 61 → Trp; Lys 65 → Glu; Glu 69 → Gly; Val 85 → Ala; Cys 101 → Ser; Leu 105 → Cys; His 106 → Ala; Lys 108 → Tyr; Arg 111 → Pro; Lys 114 → Trp; Cys 153 → Ser; and Ser 154 → Ala;
- (l) Arg 26 → Ser; Glu 27 → Asp; Phe 28 → Cys; Pro 29 → Phe; Glu 30 → Trp; Met 31 → Ile; Asn 32 → Asp; Leu 33 → Asp; Glu 34 → Val; Leu 56 → Asp; Ser 58 → Phe; Arg 60 → Phe; Cys 61 → Trp; Cys 101 → Ser; Leu 105 → Cys; His 106 → Ala; Lys 108 → Tyr; Arg 111 → Pro; Lys 114 → Trp; and Cys 153 → Ser;
- (m) Ser 14 → Pro; Asp 25 → Ser; Arg 26 → Asp; Phe 28 → Asp; Asn 32 → Thr; Lys 52 → Arg; Met 55 → Val; Ser 58 → Asp; Ala 66 → Asn; Ala 79 → Glu; His 84 → Tyr; Ala 86 → Asp; Cys 101 → Phe; Leu 105 → Gly; Lys 108 → Thr; Val 110 → Gly; Gly 112 → Met; Lys 114 → Ala; and Lys 121 → Thr;
- (n) Ser 14 → Pro; Asp 25 → Ser; Arg 26 → Glu; Phe 28 → Asp; Met 31 → Leu; Asn

- 32 → Thr; Lys 52 → Arg; Met 55 → Val; Ser 58 → Asp; Ala 66 → Asn; Ala 79 → Glu; His 84 → Tyr; Ala 86 → Asp; Cys 101 → Phe; Leu 105 → Gly; His 106 → Gln; Lys 108 → Thr; Val 110 → Gly; Gly 112 → Met; Lys 114 → Ala; and Lys 121 → Thr;
- (o) Ser 14 → Pro; Asp 25 → Ser; Arg 26 → Glu; Phe 28 → Asp; Asn 32 → Thr; Lys 52 → Arg; Met 55 → Val; Ser 58 → Asp; Ala 66 → Asn; Ala 79 → Glu; His 84 → Tyr; Ala 86 → Asp; Cys 101 → Phe; Leu 105 → Gly; His 106 → Glu; Lys 108 → Thr; Val 110 → Gly; Gly 112 → Val; Lys 114 → Ala; and Lys 121 → Thr;
- (p) Ser 14 → Pro; Asp 25 → Ser; Arg 26 → Asp; Phe 28 → Asp; Asn 32 → Thr; Lys 52 → Arg; Met 55 → Val; Ser 58 → Asp; Ala 66 → Asn; Ala 79 → Glu; His 84 → Tyr; Ala 86 → Asp; Cys 101 → Phe; Leu 105 → Gly; His 106 → Gln; Lys 108 → Thr; Val 110 → Gly; Gly 112 → Leu; Lys 114 → Ala; and Lys 121 → Thr;
- (q) Ser 14 → Pro; Asp 25 → Ser; Arg 26 → Ser; Phe 28 → Asp; Asn 32 → Thr; Lys 52 → Arg; Met 55 → Val; Ser 58 → Asp; Ala 66 → Asn; Ala 79 → Glu; His 84 → Tyr; Ala 86 → Asp; Cys 101 → Phe; Leu 105 → Gly; His 106 → Gln; Lys 108 → Thr; Val 110 → Gly; Gly 112 → Met; Lys 114 → Ala; and Lys 121 → Thr;
- (r) Ser 14 → Pro; Asp 25 → Ser; Arg 26 → Ala; Phe 28 → Asp; Asn 32 → Thr; Lys 52 → Arg; Met 55 → Val; Ser 58 → Asp; Ala 66 → Asn; Ala 79 → Glu; His 84 → Tyr; Ala 86 → Asp; Cys 101 → Phe; Leu 105 → Gly; His 106 → Lys; Lys 108 → Thr; Val 110 → Gly; Gly 112 → Met; Lys 114 → Ala; and Lys 121 → Thr;
- (s) Ser 14 → Pro; Asp 25 → Ser; Phe 28 → Asp; Asn 32 → Thr; Lys 52 → Arg; Met 55 → Val; Ser 58 → Asp; Ala 66 → Asn; Ala 79 → Glu; Ala 86 → Asp; Cys 101 → Phe; Leu 105 → Gly; His 106 → Gln; Lys 108 → Thr; Val 110 → Asn; Gly 112 → Met; Val 113 → Ala; Lys 114 → Ala; and Lys 121 → Thr;
- (t) Ser 14 → Pro; Asp 25 → Ser; Arg 26 → Gly; Phe 28 → Asp; Met 31 → Leu; Asn 32 → Thr; Lys 52 → Arg; Met 55 → Val; Ser 58 → Asp; Ala 66 → Asn; Ala 79 → Glu; His 84 → Tyr; Ala 86 → Asp; Cys 101 → Phe; Leu 105 → Gly; His 106 → Pro; Lys 108 → Thr; Val 110 → Gly; Gly 112 → Met; Lys 114 → Ala; and Lys 121 → Thr;
- (u) Ser 14 → Pro; Asp 25 → Ser; Arg 26 → Asp; Phe 28 → Asp; Asn 32 → Thr; Lys 52 → Arg; Met 55 → Val; Ser 58 → Asp; Ala 66 → Asn; Ala 79 → Glu; His 84 → Leu; Ala 86 → Asp; Cys 101 → Phe; Leu 105 → Gly; His 106 → Gln; Lys 108 → Thr; Val 110 → Gly; Gly 112 → Met; Val 113 → Leu; Lys 114 → Ala; and Lys 121 → Thr;
- (v) Ser 14 → Pro; Asp 25 → Ser; Arg 26 → Gly; Phe 28 → Asp; Asn 32 → Met; Lys 52 → Arg; Met 55 → Val; Ser 58 → Asp; Ala 66 → Asn; Ala 79 → Glu; Ala 86 → Asp; Cys 101 → Phe; Leu 105 → Gly; His 106 → Gln; Lys 108 → Thr; Val 110 →

Gly; Gly 112 → Met; Lys 114 → Ala; and Lys 121 → Thr; or

- (w) Arg 26 → Ser; Glu 27 → Asp; Phe 28 → Cys; Pro 29 → Phe; Glu 30 → Trp; Met 31 → Ile; Asn 32 → Asp; Leu 33 → Asp; Glu 34 → Val; Leu 56 → Asp; Ser 58 → Phe; Arg 60 → Phe; Glu 63 → Asp; Lys 65 → Glu; Cys 101 → Ser; Leu 105 → Cys; His 106 → Ala; Lys 108 → Tyr; Arg 111 → Pro; Lys 114 → Trp; and Gln 149 → Leu.

6. The lipocalin mutein of any one of claims 1–5, wherein the amino acid sequence of the mutein comprises one of the following sets of mutated amino acid residues in comparison with the linear polypeptide sequence of mature human tear lipocalin (SEQ ID NO: 1):

- (a) Ala 5 → Thr; Glu 8 → Gln; Lys 65 → Glu; Glu 69 → Gly; Val 85 → Ala; and Ser 154 → Ala;
- (b) Ala 5 → Thr; Gly 46 → Asp; Lys 65 → Glu; Val 85 → Ala; and Ser 150 → Gly;
- (c) Asp 7 → Gly; Val 85 → Asp; Arg 148 → Trp; and Thr 152 → Pro;
- (d) Ala 5 → Thr; Val 53 → Ala; Lys 65 → Glu; Ala 79 → Thr; and Tyr 97 → His;
- (e) Glu 63 → Asp; Val 85 → Asp; Arg 90 → Ser; His 96 → Asn; and Leu 124 → Gln;
- (f) Thr 16 → Met; Leu 44 → His; Lys 65 → Glu; and Ile 89 → Ser;
- (g) Glu 63 → Asp; Lys 65 → Glu; and Gln 149 → Leu;
- (h) Lys 65 → Glu and Lys 70 → Arg;
- (i) Ala 5 → Thr; Lys 65 → Glu; Asp 80 → Gly; Ile 89 → Asn; and Ile 98 → Val;
- (j) Ile 10 → Phe; Lys 65 → Glu; Glu 73 → Ala; Ile 89 → Asn; and Val 93 → Glu;
- (k) Arg 26 → Asp; Asn 32 → Thr; His 84 → Tyr; Val 110 → Gly; and Gly 112 → Met;
- (l) Arg 26 → Glu; Met 31 → Leu; Asn 32 → Thr; His 84 → Tyr; His 106 → Gln; Val 110 → Gly; and Gly 112 → Met;
- (m) Arg 26 → Glu; Asn 32 → Thr; His 84 → Tyr; His 106 → Glu; and Gly 112 → Val;
- (n) Arg 26 → Asp; Asn 32 → Thr; His 84 → Tyr; His 106 → Gln; Val 110 → Gly; and Gly 112 → Leu;
- (o) Arg 26 → Ser; Asn 32 → Thr; His 84 → Tyr; His 106 → Gln; Val 110 → Gly; and Gly 112 → Met;
- (p) Arg 26 → Ala; Asn 32 → Thr; His 84 → Tyr; His 106 → Lys; Val 110 → Gly; and Gly 112 → Met;
- (q) Asn 32 → Thr; His 106 → Gln; Val 110 → Asn; Gly 112 → Met; and Val 113 → Ala;
- (r) Arg 26 → Gly; Met 31 → Leu; Asn 32 → Thr; His 84 → Tyr; His 106 → Pro; Val 110 → Gly; and Gly 112 → Met; or
- (s) Arg 26 → Asp; Asn 32 → Thr; His 84 → Leu; His 106 → Gln; Val 110 → Gly; Gly

112 → Met; and Val 113 → Leu.

7. The lipocalin mutein of any one of claims 1–6, wherein
 - (i) the amino acid sequence of the mutein comprises cysteine residues at the sequence positions 61 and 153 of the linear polypeptide sequence of mature human tear lipocalin (SEQ ID NO: 1);
 - (ii) the amino acid sequence of the mutein comprises one or two of the following mutated amino acid residues in comparison with the linear polypeptide sequence of mature human tear lipocalin (SEQ ID NO: 1): Ala 5 → Thr and Asp 12 → Asn; or
 - (iii) the amino acid sequence of the mutein comprises at least one of the following mutated amino acid residues in comparison with the linear polypeptide sequence of mature human tear lipocalin (SEQ ID NO: 1): Asp 7 → Asn, Arg, or Lys; Glu 9 → Gln, Arg, or Lys; Asp 12 → Asn or Arg; Glu 45 → Arg; Asp 72 → Asn, Arg, or Lys; Glu 73 → Arg; Asp 80 → Gly; and Asp 95 → Asn, Arg, or Lys.
8. The lipocalin mutein of any one of claims 1–7, wherein the mutein has at least 85%, at least 90%, at least 95%, at least 97.5% or at least 99% sequence identity to an amino acid sequence selected from the group consisting of SEQ ID NOs: SEQ ID NOs: 8–18, 20–28, 57–70, and 85–95.
9. The lipocalin mutein of any one of claims 1–8, wherein the mutein comprises an amino acid sequence selected from the group consisting of SEQ ID NOs: 8–18, 20–28, 57–70, and 85–95.
10. The lipocalin mutein of any one of claims 1–9, wherein
 - (i) the 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;
 - (ii) the mutein is conjugated to a compound that extends the serum half-life of the mutein, wherein the compound that extends the serum half-life is preferably selected from the group consisting of a polyalkylene glycol molecule, polyethylene glycol (PEG) or an activated derivative thereof, hydroxyethyl starch, an Fc part of an immunoglobulin, a C_H3 domain of an immunoglobulin, a C_H4

- domain of an immunoglobulin, an albumin binding peptide, and an albumin binding protein; or
- (iii) the mutein is fused at its N-terminus and/or its C-terminus to a fusion partner that is a protein, a protein domain, or a peptide, wherein the fusion partner is preferably an antibody or antibody fragment.
11. A nucleic acid molecule comprising a nucleotide sequence encoding a lipocalin mutein of any one of claims 1–10.
 12. An expression vector comprising the nucleic acid molecule of claim 11.
 13. A host cell containing a nucleic acid molecule of claim 11.
 14. A method of producing a lipocalin mutein of any one of claims 1–10, wherein the mutein is produced starting from the nucleic acid coding for the mutein.
 15. A pharmaceutical composition comprising a lipocalin mutein of any one of claims 1–10 and a pharmaceutically acceptable excipient.
 16. An immunoconjugate or fusion protein comprising a lipocalin mutein of any one of claims 1–10 linked to a therapeutic agent.
 17. A method of detecting the presence of LAG-3 in a biological sample, the method comprising contacting the sample with a lipocalin mutein of any one of claims 1–10 under conditions that allow the formation of a complex of the mutein and LAG-3.