Claims

1. A peptide ligand specific for human Kallikrein comprising a polypeptide comprising at least three reactive groups, separated by at least two loop sequences, and a molecular scaffold which forms covalent bonds with the reactive groups of the polypeptide such that at least two polypeptide loops are formed on the molecular scaffold, wherein the loops of the peptide ligand comprises five amino acids and one loop comprises the motif $G_r{}^{T}/_{L}H^{Q}/_{T}xLG_r$.

2. A peptide ligand according to claim 1, wherein the loops of the peptide ligand comprise five amino acids and one loop comprises the motif $G_rxHxDLG_r$, wherein G_r is a reactive group.

3. A peptide ligand according to claim 1, wherein the loops of the peptide ligand comprise five amino acids and one loop comprises the motif $G_rTHxxLG_r$, wherein G_r is a reactive group.

4. A peptide ligand according to any one of claims 1 to 3, wherein two adjacent loops comprise the motif $G_rx^{W}/_{F}Px^{K}/_{R}G_r{}^{T}/_{L}H^{Q}/_{T}DLG_r$.

5. A peptide ligand according to any one of claims 7 to 11, which comprises one of the polypeptides set forth in Table 4, Table 5, Table 6, Table 25b, Table 26a, Table 26b or Figure 22.

6. A peptide ligand according to any preceding claim, wherein removal of His 7 in loop 2, or replacement of the histidine side chain with any non-charged or charged chemical entities, enhances the stability of the peptide ligand.

7. A peptide ligand according to claim 6, wherein proteolytic stability is enhanced by chemical modification of the peptide bonds N- or C-terminally adjacent to His7.

8. A peptide ligand according to claim 7, wherein the chemical modification is α–N-alkylation, or modification of the peptide bond with its reduced amide form.

9. A peptide ligand according to claim 6, wherein proteolytic stability is enhanced by steric obstruction of nearby amino acids to His 7.

10. A peptide ligand according to claim 9, wherein the steric obstruction results from replacement of position 9 with its D- amino acid enantiomer, or α–N-alkylation.

11. A peptide ligand according to claim 6, wherein proteolytic stability is enhanced by Introduction of sterically obstructive amino acids at position 6.

12. A peptide ligand according to claim 6, wherein proteolytic stability is enhanced by introduction of Cβ-derivatised amino acids such as phenylglycine or cyclohexylglycine at position 6, which enhance the potency of the peptide ligand sequence towards human plasma kallikrein and reduce the proteolytic hydrolysis of the C-terminal peptide bond.

13. A peptide ligand according to ant preceding claim, which comprises one or more non-natural amino acid substituents and is resistant to protease degradation.

15. A peptide ligand according to any preceding claim, wherein the polypeptide comprises a first loop which comprises the motif G_rxWPARG_r or G_rxFPYRG_r and a second loop comprising the motif $G_r^T/_L H^Q/_T$xLG_r.

16. A peptide ligand according to claim 15, wherein in the first loop Pro is replaced with azetidine carboxylic acid; and/or the first loop R is replaced with N-methyl arginine; and/or R is replaced with homoarginine; and/or R is replaced with guanidylphenylalanine.

17. A peptide ligand according to claim 16, wherein the polypeptide comprises a first loop which comprises the motif G_rxFPYRG_r, wherein R is replaced with N-methyl arginine; and/or R is replaced with homoarginine, and/or R is replaced with guanidylphenylalanine, and wherein Pro is replaced with azetidine carboxylic acid.

CLAIMS

1. A peptide ligand specific for human Kallikrein comprising a polypeptide comprising at least three reactive groups, separated by at least two loop sequences, and a molecular scaffold which forms covalent bonds with the reactive groups of the polypeptide such that at least two polypeptide loops are formed on the molecular scaffold, in which the loops of the peptide ligand comprises five amino acids and one loop comprises the motif $G_r{}^{T}/_{L}H^{Q}/_{T}xLG_r$.

2. A peptide ligand according to Claim 1, in which the loops of the peptide ligand comprise five amino acids and one loop comprises the motif $G_rxHxDLG_r$, in which G_r is a reactive group.

3. A peptide ligand according to Claim 1, in which the loops of the peptide ligand comprise five amino acids and one loop comprises the motif $G_rTHxxLG_r$, in which G_r is a reactive group.

4. A peptide ligand according to any of Claims 1, 2 or 3, in which two adjacent loops comprise the motif $G_rx^{W}/_{F}Px^{K}/_{R}G_r{}^{T}/_{L}H^{Q}/_{T}DLG_r$.

5. A peptide ligand according to any preceding claim, which comprises one of the polypeptides set forth in Table 4, Table 5, Table 6, Table 25b, Table 26a, Table 26b or Figure 22.

6. A peptide ligand according to any preceding claim, in which removal of His 7 in loop 2, or replacement of the histidine side chain with any non-charged or charged chemical entities, enhances the stability of the peptide ligand.

7. A peptide ligand according to Claim 6, in which proteolytic stability is enhanced by chemical modification of the peptide bonds N- or C-terminally adjacent to His7.

8. A peptide ligand according to Claim 7, in which the chemical modification is α-N-alkylation, or modification of the peptide bond with its reduced amide form.

9. A peptide ligand according to Claim 6, in which proteolytic stability is enhanced by steric obstruction of nearby amino acids to His 7.

10. A peptide ligand according to Claim 9, in which the steric obstruction results from replacement of position 9 with its D- amino acid enantiomer, or α-N-alkylation.

11. A peptide ligand according to Claim 6, in which proteolytic stability is enhanced by Introduction of sterically obstructive amino acids at position 6.

12. A peptide ligand according to Claim 6, in which proteolytic stability is enhanced by introduction of Cβ-derivatised amino acids such as phenylglycine or cyclohexylglycine at position 6, which enhance the potency of the peptide ligand sequence towards human plasma kallikrein and reduce the proteolytic hydrolysis of the C-terminal peptide bond.

13. A peptide ligand according to any preceding claim, which comprises one or more non-natural amino acid substituents and is resistant to protease degradation.

14. A peptide ligand according to any preceding claim, in which the polypeptide comprises a first loop which comprises the motif G_rxWPARG_r or G_rxFPYRG_r and a second loop comprising the motif $G_r{}^{T}/_{L}H^{Q}/_{T}$xLG_r.

15. A peptide ligand according to Claim 14, in which in the first loop Pro is replaced with azetidine carboxylic acid; and/or in the first loop R is replaced with N-methyl arginine or homoarginine or guanidylphenylalanine.

16. A peptide ligand according to Claim 15, in which the polypeptide comprises a first loop which comprises the motif G_rxFPYRG_r, in which Pro is replaced with azetidine carboxylic acid and/or R is replaced with N-methyl arginine or homoarginine or guanidylphenylalanine.