CLAIMS

1. A method for preparing one or more peptide ligands, comprising polypeptides covalently linked to a molecular scaffold at two or more amino acid residues, comprising the steps of:

(a) displaying one or more peptide ligands in a genetic display system, in which the polypeptide comprises two or more reactive groups which form a covalent linkage to the molecular scaffold, and at least one loop which comprises a sequence of amino acids subtended between two of the reactive groups;

(b) exposing the peptide ligands to protease; and

(c) screening the peptide ligands for binding against a target, and selecting the protease resistant ligands which bind to the target.

2. A method for preparing one or more peptide ligands, comprising polypeptides covalently linked to a molecular scaffold at two or more amino acid residues, comprising the steps of:

(a) displaying one or more peptide ligand in a genetic display system, in which the polypeptide comprises two or more reactive groups which form a covalent linkage to the molecular scaffold, and at least one loop which comprises a sequence of amino acids subtended between two of the reactive groups;

(b) screening the peptide ligands for binding against a target, and selecting the ligands which bind to the target;

(c) exposing the peptide ligands which bind to the target to protease; and

(d) further screening for protease resistant peptide ligands which bind a target.

3. A method according to Claim 1 or Claim 2, in which the genetic display system is phage display.

4. A repertoire of peptide ligands, each comprising a polypeptide comprising two or more reactive groups, covalently linked to a molecular scaffold, and at least one loop which comprises a sequence of amino acids subtended between two of the reactive groups, which repertoire is protease resistant.

5. A repertoire according to Claim 4, in which each polypeptide comprises three or more reactive groups covalently linked to a molecular scaffold.

6. A method according to any of Claims 1 to 3, in which the peptide ligands which bind to the target are further modified by

(a) amino acid side chain modification or substitution; or

(b) polypeptide backbone modification.

7. A method according to Claim 6, in which the backbone modification is selected from the group consisting of introducing, near the site of protease cleavage, a D-amino acid, a reduced peptide bond, and N-methylation.

CLAIMS

1. A method for preparing one or more peptide ligands, comprising polypeptides covalently linked to a molecular scaffold at two or more amino acid residues, comprising the steps of:

(a) displaying one or more peptide ligands in a genetic display system, in which the polypeptide comprises two or more reactive groups which form a covalent linkage to the molecular scaffold, and at least one loop which comprises a sequence of amino acids subtended between two of the reactive groups;

(b) subjecting the peptide ligands to selection for protease resistance; and

(c) after proteolytic treatment in step (b), screening the peptide ligands for binding against a target, and selecting the protease resistant ligands which bind to the target.

2. A method for preparing one or more peptide ligands, comprising polypeptides covalently linked to a molecular scaffold at two or more amino acid residues, comprising the steps of:

(a) displaying one or more peptide ligands in a genetic display system, in which the polypeptide comprises two or more reactive groups which form a covalent linkage to the molecular scaffold, and at least one loop which comprises a sequence of amino acids subtended between two of the reactive groups;

(b) screening the peptide ligands for binding against a target, and selecting the protease resistant-ligands which bind to the target, before subjecting the ligands to proteolytic treatment; and

(c) subjecting the peptide ligands to selection for protease resistance.

3. A method for preparing one or more peptide ligands, comprising polypeptides covalently linked to a molecular scaffold at two or more amino acid residues, comprising the steps of:

(a) displaying one or more peptide ligands in a genetic display system, in which the polypeptide comprises two or more reactive groups which form a covalent linkage to the molecular scaffold, and at least one loop which comprises a sequence of amino acids subtended between two of the reactive groups;

(b) screening the peptide ligands for binding against a target, and selecting the ligands which bind to the target, before subjecting the ligands to proteolytic treatment;

(c) subjecting the peptide ligands which bind to the target to selection for protease resistance; and

(d) further screening for protease resistant peptide ligands which bind a target.

4. A method according to any preceding claim, in which the genetic display system is phage display.

5. A repertoire of peptide ligands, each comprising a polypeptide comprising two or more reactive groups, covalently linked to a molecular scaffold, and at least one loop which comprises a sequence of amino acids subtended between two of the reactive groups, which repertoire is protease resistant, in which the peptide ligands are modified by

(a) amino acid side chain modification or substitution; or

(b) polypeptide backbone modification.

6. A repertoire according to Claim 5, in which each polypeptide comprises three or more reactive groups covalently linked to a molecular scaffold.

7. A repertoire according to Claim 5, in which the backbone modification is selected from the group consisting of introducing, near the site of protease cleavage, a D-amino acid, a reduced peptide bond, and N-methylation.