Claims

1. A method of making a construct suitable for oral administration comprising a first immunoglobulin chain variable domain and a second immunoglobulin chain variable domain connected by a labile peptide linker, wherein:
(i) the labile peptide linker is labile to one or more proteases present in the intestinal tract,
(ii) the labile peptide linker is stable to yeast proteases, and
(iii) the first and second immunoglobulin chain variable domains are substantially resistant to said one or more proteases;
comprising the step of producing the construct in yeast, and
wherein the labile peptide linker comprises at least 1 K residue and/or at least 1 R residue.

2. The method according to claim 1 wherein the yeast is *S. cerevisiae.*

3. The method according to either claim 1 or 2 wherein the labile peptide linker is labile to one or more proteases present in the intestinal tract such that greater than 50% by mass of the construct is cleaved into first and second immunoglobulin chain variable domains after 160 minutes after mixing in the Trypsin Protease Assay.

4. The method according to any one of claims 1 to 3 wherein the labile peptide linker is stable to yeast proteases such that no more than 10% by mass of the construct is cleaved into first and second immunoglobulin chain variable domains after producing the construct using the Yeast Expression Protocol.

5. The method according to any one of claims 1 to 4 wherein the first immunoglobulin chain variable domain and the second immunoglobulin chain variable domain are substantially resistant to one or more proteases present in the intestinal tract such that at least 70% by mass of the first immunoglobulin chain variable domain and at least 70% by mass of the second immunoglobulin chain variable domain remain uncleaved after 10 minutes after mixing in the Trypsin Protease Assay.

6. The method according to any one of claims 1 to 5, wherein the one or more proteases are present in the small or large intestine.

7. The method according to any one of claims 1 to 6, wherein the labile peptide linker comprises a cleavage site for trypsin or a trypsin-like protease.

8. The method according to any one of claims 1 to 7, wherein the labile peptide linker has a length of at least 3 residues.

9. The method according to any one of claims 1 to 8, wherein the labile peptide linker has a length of no greater than 40 residues.

10. The method according to any one of claims 1 to 9, wherein the labile peptide linker comprises or consists of a polypeptide sequence of the format:

$[-(G_aS)_x-B-(G_bS)_y-]_z$

wherein

a is 1 to 10;
b is 1 to 10;
x is 1 to 10;
y is 1 to 10;
z is 1 to 10 and
B is K or R.

11. The method according to any one of claims 1 to 9, wherein the labile peptide linker comprises or consists of a polypeptide sequence of the format:

$-B-(G_aS)_x-B'-$

wherein

a is 1 to 10;
x is 1 to 10;
B is K or R and
B' is K or R.

12 The method according to any one of claims 1 to 11, wherein the first immunoglobulin chain variable domain binds to a first target accessible via the intestinal tract.

13. The method according to any one of claims 1 to 12, wherein the first target is a first deleterious agent originating from an intestinal tract resident pathogenic microbe.

14. The method according to any one of claims 1 to 12, wherein the first target is selected from the group consisting of: an interleukin, an interleukin receptor, a transcription factor, a cytokine, a transmembrane protein, a surface glycoprotein, a soluble protein, an integrin, an adhesion molecule, a chemokine, a chemokine receptor, an inhibitory protein, a kinase, a G protein-coupled receptor or a toxin.

15. The method according to any one of claims 1 to 14, wherein the first immunoglobulin chain variable domain is selected from the group consisting of: a VL, a V-NAR, an scFv, a Fab fragment, a F(ab')2 fragment, a VHH and a VH.

16. The method according to claim 15, wherein the second immunoglobulin chain variable domain is selected from the group consisting of: a VL, a V-NAR, an scFv, a Fab fragment, a F(ab')2 fragment, a VHH and a VH.

17. The method according to claim 1 wherein the labile peptide linker comprises a sequence selected from the group consisting of SEQ ID NOs: 2 to 5.

18. The method according to claim 17 wherein the labile peptide linker consists of a sequence selected from the group consisting of SEQ ID NOs: 2 to 5.