molecule than the second chain (see schematic representation in Figure 18), particularly when the IgG is an IgG2 isotype. A polypeptide of the invention may be more effective at cleaving IgG1 than IgG2. The polypeptide of the invention is typically less immunogenic than IdeS and may preferably be no more immunogenic than IdeZ or IdeS/Z.

Unless otherwise stated, all references to numbering of amino acid positions in the polypeptides disclosed herein is based on the numbering of the corresponding positions in SEQ ID NO: 3, starting from the N terminus. Thus, since SEQ ID NOs: 4 and 5 lack the N terminal methionine and 33 amino acid signal sequence of SEQ ID NO: 3, the aspartic acid (D) residue at the N terminus of SEQ ID NOs: 4 and 5 is referred to as position 35 as this the corresponding position in SEQ ID NO: 3. Applying this numbering scheme, the most critical residue for IgG cysteine protease activity of IdeS is the cysteine (C) at position 102 (68^{th} residue from the N terminus of SEQ ID NOs: 4 and 5). Other residues likely to be important for IgG cysteine protease activity are the lysine (K) at position 92, the histidine (H) at position 272, and the aspartic acid (D) at each of positions 294 and 296 of SEQ ID NO: 3. These are the 58^{th}, 238^{th}, 260^{th} and 262^{nd} residues from the N terminus of SEQ ID NO: 4 and the 58^{th}, 236^{th}, 258^{th} and 260^{th} from the N terminus of SEQ ID NO: 5, respectively.

In one aspect, the present invention provides a polypeptide having IgG cysteine protease activity and comprising a variant of the sequence of SEQ ID NO:4, which variant:

(a) is at least 90% identical to SEQ ID NO: 4;

(b) has a cysteine (C) at the position in said variant sequence which corresponds to position 102 of SEQ ID NO: 3; and optionally

(c) has, at the positions in said variant sequence which correspond to positions 92, 272, 294 and 296 of SEQ ID NO: 3, a lysine (K), a histidine (H), an aspartic acid (D) and an aspartic acid (D), respectively;

wherein said polypeptide is more effective at cleaving human IgG than IdeZ, and

wherein the polypeptide is less immunogenic than IdeS, wherein preferably the immunogenicity of said polypeptide is no more than 85% of the immunogenicity of IdeS when measured in the same assay

and wherein the variant sequence of SEQ ID NO: 4:

(1) has a positively charged amino acid at the position in said variant which corresponds to position 138 of SEQ ID NO: 3, optionally wherein said positively charged amino acid is arginine (R) or lysine (K); and/or

(2) has a positively charged amino acid at the position in said variant which corresponds to position 139 of SEQ ID NO: 3, optionally wherein said positively charged amino acid is arginine (R) or lysine (K); and/or

(3) does not include the contiguous sequence DDYQRNATEA YAKEVPHQIT; and/or

(4) has at least one of the following modifications:

i. a deletion of the leucine (L) and threonine (T) residues at the positions in said variant which correspond to positions 64 and 65 of SEQ ID NO: 3;

ii. a threonine (T) in place of the arginine (R) at the position in said variant which corresponds to position 70 of SEQ ID NO: 3;

iii. a deletion of the tyrosine (Y) at the position in said variant which corresponds to position 71 of SEQ ID NO: 3;

iv. a glutamine (Q) in place of the asparagine (N) at the position in said variant which corresponds to position 72 of SEQ ID NO: 3;

v. a glycine (G) in place of the asparagine (N) at the position in said variant which corresponds to position 73 of SEQ ID NO: 3;

vi. a alanine (A) in place of the glutamic acid (E) at the position in said variant which corresponds to position 67 of SEQ ID NO: 3;

a asparagine (N) in place of the glutamine (Q) at the position in said variant which corresponds to position 68 of SEQ ID NO: 3.

In accordance with the present disclosure, there is thus provided a polypeptide having IgG cysteine protease activity and comprising a variant of the sequence of SEQ ID NO:4 or 5, which variant:

(a) is at least 80% identical to SEQ ID NO: 4 or 5;

(b) has a cysteine (C) at the position in said variant sequence which corresponds to position 102 of SEQ ID NO: 3; and optionally

(c) has, at the positions in said variant sequence which correspond to positions 92, 272, 294 and 296 of SEQ ID NO: 3, a lysine (K), a histidine (H), an aspartic acid (D) and an aspartic acid (D), respectively;

wherein said polypeptide is more effective at cleaving human IgG than IdeZ and/or is at least as effective at cleaving human IgG as IdeS.

Preferably, said variant of SEQ ID NO: 4 or 5:

(1) has a positively charged amino acid at the position in said variant which corresponds to position 138 of SEQ ID NO: 3, optionally wherein said positively charged amino acid is arginine (R) or lysine (K); and/or

(2) has a positively charged amino acid at the position in said variant which corresponds to position 139 of SEQ ID NO: 3, optionally wherein said positively charged amino acid is arginine (R) or lysine (K); and/or

CLAIMS

1. A polypeptide having IgG cysteine protease activity and comprising a variant of the sequence of SEQ ID NO:4, which variant:

(a) is at least 90% identical to SEQ ID NO: 4;

(b) has a cysteine (C) at the position in said variant sequence which corresponds to position 102 of SEQ ID NO: 3; and optionally

(c) has, at the positions in said variant sequence which correspond to positions 92, 272, 294 and 296 of SEQ ID NO: 3, a lysine (K), a histidine (H), an aspartic acid (D) and an aspartic acid (D), respectively;

wherein said polypeptide is more effective at cleaving human IgG than IdeZ, and

wherein the polypeptide is less immunogenic than IdeS, wherein preferably the immunogenicity of said polypeptide is no more than 85% of the immunogenicity of IdeS when measured in the same assay

and wherein the variant sequence of SEQ ID NO: 4:

(1) has a positively charged amino acid at the position in said variant which corresponds to position 138 of SEQ ID NO: 3, optionally wherein said positively charged amino acid is arginine (R) or lysine (K); and/or

(2) has a positively charged amino acid at the position in said variant which corresponds to position 139 of SEQ ID NO: 3, optionally wherein said positively charged amino acid is arginine (R) or lysine (K); and/or

(3) does not include the contiguous sequence DDYQRNATEA YAKEVPHQIT; and/or

(4) has at least one of the following modifications:

i. a deletion of the leucine (L) and threonine (T) residues at the positions in said variant which correspond to positions 64 and 65 of SEQ ID NO: 3;

ii. a threonine (T) in place of the arginine (R) at the position in said variant which corresponds to position 70 of SEQ ID NO: 3;

iii. a deletion of the tyrosine (Y) at the position in said variant which corresponds to position 71 of SEQ ID NO: 3;

iv. a glutamine (Q) in place of the asparagine (N) at the position in said variant which corresponds to position 72 of SEQ ID NO: 3;

v. a glycine (G) in place of the asparagine (N) at the position in said variant which corresponds to position 73 of SEQ ID NO: 3;

vi. a alanine (A) in place of the glutamic acid (E) at the position in said variant which corresponds to position 67 of SEQ ID NO: 3;

vii. a asparagine (N) in place of the glutamine (Q) at the position in said variant which corresponds to position 68 of SEQ ID NO: 3.

2. A polypeptide according to claim 1, wherein the variant sequence of SEQ ID NO: 4 comprises a positively charged amino acid at the position in said variant which corresponds to position 138 of SEQ ID NO: 3, optionally wherein said positively charged amino acid is arginine (R) or lysine (K); and also the following modifications:

i. a deletion of the leucine (L) and threonine (T) residues at the positions in said variant which correspond to positions 64 and 65 of SEQ ID NO: 3;

ii. a threonine (T) in place of the arginine (R) at the position in said variant which corresponds to position 70 of SEQ ID NO: 3;

iii. a deletion of the tyrosine (Y) at the position in said variant which corresponds to position 71 of SEQ ID NO: 3;

iv. a glutamine (Q) in place of the asparagine (N) at the position in said variant which corresponds to position 72 of SEQ ID NO: 3; and

v. a glycine (G) in place of the asparagine (N) at the position in said variant which corresponds to position 73 of SEQ ID NO: 3.

3. A polypeptide according to claim 1 or 2, wherein said variant of the sequence of SEQ ID NO: 4 is at least 95% or 99% identical to SEQ ID NO: 4, and/or wherein said polypeptide is less immunogenic than IdeS and is preferably no more immunogenic than IdeZ or IdeS/Z, when measured in the same assay.

4. A polypeptide according to any one of the preceding claims, which comprises or consists of the sequence of any one of SEQ ID NOs: 6 to 20, optionally wherein said sequence includes an additional methionine at the N terminus and/or a histidine tag at the C terminus.

5. A polypeptide according to any one of the preceding claims, wherein said polypeptide is at least 2.0 fold more effective than IdeZ at cleaving human IgG, when measured in the same assay.

6. A polynucleotide or expression vector which comprises a nucleic acid sequence encoding a polypeptide of any one of the preceding claims.

7. A host cell comprising the polynucleotide or expression vector of claim 6, which is preferably bacterial cell, most preferable a cell of *E. coli.*

8. A composition comprising a polypeptide according to any one of claims 1 to 5 and at least one pharmaceutically acceptable carrier or diluent.

9. A polypeptide according to any one of claims 1 to 5 for use in the treatment of the human or animal body.

10. A polypeptide according to any one of claims 1 to 5 for use in the prevention or treatment of a disease or condition in a subject.

11. The polypeptide according to claim 10, wherein said disease or condition is a disease or condition mediated in whole or in part by pathogenic IgG antibodies, preferably wherein said disease or condition is listed in Table D.

12. A method for the cleavage of IgG, the method comprising contacting a sample containing IgG with a polypeptide according to any one of claims 1 to 5 under conditions which permit IgG cysteine protease activity to occur.

13. A method according to claim 12 which is carried out *ex vivo* and/or is conducted to generate Fc and Fab fragments and/or wherein the sample is a blood sample taken from a subject suffering from a disease or condition as defined in claim 11.