The present inventors have adopted an entirely different approach. The inventors have identified specific positions within the sequence of IdeS which, when modified as described herein, lead to novel polypeptides for which the problems associated with immunogenicity are reduced as compared to IdeS. Some modifications may increase the efficacy at cleaving IgG of the polypeptide of the disclosure relative to IdeS, thereby indirectly reducing immunogenicity by permitting the use of a lower dose or concentration to achieve the same effect. Alternatively, or in addition, other modifications may directly reduce immunogenicity by reducing the ability of IdeS-specific antibodies to recognise the polypeptide of the disclosure relative to IdeS.

The full sequence of IdeS is publically available as NCBI Reference Sequence no WP_010922160.1 and is provided herein as SEQ ID NO: 1. This sequence includes an N terminal methionine followed by a 28 amino acid secretion signal sequence. The N terminal methionine and the signal sequence (a total of 29 amino acids at the N terminus) are typically removed to form the mature IdeS protein, the sequence of which is publically available as Genbank accession no. ADF13949.1 and is provided herein as SEQ ID NO: 2.

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: 1, starting from the N terminus. Thus, since SEQ ID NO: 2 lacks the N terminal methionine and 28 amino acid signal sequence of SEQ ID NO: 1, the aspartic acid (D) residue at the N terminus of SEQ ID NO: 2 is referred to as position 30 as this the corresponding position in SEQ ID NO: 1. Applying this numbering scheme, the most critical residue for IgG cysteine protease activity of IdeS is the cysteine (C) at position 94 (65^{th} residue from the N terminus of SEQ ID NO: 2). Other residues likely to be important for IgG cysteine protease activity are the lysine (K) at position 84, the histidine (H) at position 262, and the aspartic acid (D) at each of positions 284 and 286. These are the 55^{th}, 233^{rd}, 255^{th} and 257^{th} residues from the N terminus of SEQ ID NO: 2, respectively.

In accordance with the present invention, in one aspect, there is thus provided a polypeptide having IgG cysteine protease activity and comprising a variant of the sequence of SEQ ID NO:2, which variant:

(a) is at least 80% identical to SEQ ID NO: 2;

(b) has a cysteine (C) at the position in said variant sequence which corresponds to position 94 of SEQ ID NO: 1; and optionally

CLAIMS

1. A polypeptide having IgG cysteine protease activity and comprising a variant of the sequence of SEQ ID NO:2, which variant:

(a) is at least 80% identical to SEQ ID NO: 2;

(b) has a cysteine (C) at the position in said variant sequence which corresponds to position 94 of SEQ ID NO: 1; and optionally

(c) has, at the positions in said variant sequence which correspond to positions 84, 262, 284 and 286 of SEQ ID NO: 1, a lysine (K), a histidine (H), an aspartic acid (D) and an aspartic acid (D), respectively;

wherein said polypeptide is more effective at cleaving IgG than IdeS and/or is less immunogenic than IdeS.

2. A polypeptide according to claim 1, wherein said variant of the sequence of SEQ ID NO: 2:

(1) has a positively charged amino acid at the position in said variant which corresponds to position 130 of SEQ ID NO: 1, 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 131 of SEQ ID NO: 1, optionally wherein said positively charged amino acid is arginine (R) or lysine (K); and/or

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

(4) does not include the contiguous sequence DSFSANQEIR YSEVTPYHVT.

3. A polypeptide according to claim 1 or 2, wherein said variant of the sequence of SEQ ID NO: 2 is at least 90%, 95% or 99% identical to SEQ ID NO: 2.

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: 3 to 16, optionally wherein said sequence includes an additional methionine at the N terminus and/or a histidine tag at the C terminus.