Claims

1. An isolated heterodimeric protein comprising a first human IgG CH3-containing polypeptide and a second human IgG CH3-containing polypeptide,

wherein said first human IgG CH3-containing polypeptide comprises the amino acid variant L351D and L368E and said second human IgG CH3-containing polypeptide comprises the amino acid variant T366K and L351K, and

wherein the first human IgG CH3-containing polypeptide comprises a further amino acid variant at position S364, K409 and/or K360 wherein:

a) the S364 amino acid is valine, isoleucine, threonine, glutamine or leucine; and/or

b) the K409 amino acid is isoleucine, leucine, or glutamate; and/or

c) the K360 amino acid is aspartate;

wherein the position of the amino acid is defined according to EU numbering system.

2. The isolated heterodimeric protein of claim 1, wherein the heterodimeric protein comprises a human IgG1, an IgG2, an IgG3 or an IgG4 CH3-region.

3. The isolated heterodimeric protein of claim 1 or 2, wherein the heterodimeric protein comprises a human immunoglobulin Fc region.

4. The isolated heterodimeric protein of claim 3, wherein the human immunoglobulin Fc region comprises an IgG1, an IgG2, an IgG3, or an IgG4 Fc region.

5. The isolated heterodimeric protein of claim 4, wherein the heterodimeric protein comprises a human IgG1 Fc region.

6. The isolated heterodimeric protein of any one of claims 1 to 5, wherein:

a) the first CH3-containing polypeptide is an antibody heavy chain; and/or

b) the second CH3-containing polypeptide is an antibody heavy chain; and/or

c) the heterodimeric protein further comprises one or more antibody light chains.

7. The isolated heterodimeric protein of claim 6, wherein the antibody light chain is a common antibody light chain.

8. A pharmaceutical composition comprising the isolated heterodimeric protein of any one of claims 1-7.

9. An isolated nucleic acid encoding the first and second human IgG CH3-containing polypeptides of any one of claims 1-7.

10. A recombinant host cell comprising the isolated nucleic acid of claim 9.

11. A method of producing the isolated heterodimeric protein of claims 1 to 7, comprising culturing the recombinant host cell of claim 10 under conditions that allow expression of the first and second human IgG CH3-containing polypeptides.

12. A method for improving stability of a heterodimeric protein that contains a first human IgG CH3-containing polypeptide which comprises the amino acid variant L351D and L368E, and a second human IgG CH3-containing polypeptide which comprises the amino acid variant T366K and L351K, the method comprising introducing an amino acid variant into the first human IgG CH3-containing polypeptide at position S364, K409 and/or K360; wherein:
a) the S364 amino acid is valine, isoleucine, threonine, glutamine or leucine; and/or
b) the K409 amino acid is isoleucine, leucine or glutamate; and/or
c) the K360 amino acid is aspartate;
wherein the position of the amino acid is defined according to EU numbering system.

13. A method for decreasing the stability of a homodimeric protein that contains a first human IgG CH3-containing polypeptide which comprises the amino acid variant L351D and L368E, the method comprising introducing an amino acid variant into the first human IgG CH3-containing polypeptide at position S364, K409 and/or K360; wherein:
a) the S364 amino acid is valine, isoleucine, threonine, glutamine or leucine; and/or
b) the K409 amino acid is isoleucine, leucine or glutamate; and/or
c) the K360 amino acid is aspartate;
wherein the position of the amino acid is defined according to EU numbering system.

14. A method for improving the yield of a heterodimeric protein comprising a first human IgG CH3-containing polypeptide and a second human IgG CH3-containing polypeptide, wherein said first human IgG CH3-containing polypeptide comprises the amino acid variant L351D and L368E and said second human IgG CH3-containing polypeptide comprises the amino acid variant T366K and L351K, comprising introducing an amino acid variant into the first human IgG CH3-containing polypeptide at position S364, K409 and/or K360; wherein:
a) the S364 amino acid is valine, isoleucine, threonine, glutamine or leucine; and/or
b) the K409 amino acid is isoleucine, leucine or glutamate; and/or
c) the K360 amino acid is aspartate;

wherein the position of the amino acid is defined according to EU numbering system.

15. A method of increasing the purity of a heterodimeric protein comprising a first human IgG CH3-containing polypeptide and a second human IgG CH3-containing polypeptide, wherein said first human IgG CH3-containing polypeptide comprises the amino acid variant L351D and L368E and said second human IgG CH3-containing polypeptide comprises the amino acid variant T366K and L351K, the method comprising (a) introducing an amino acid variant into the first human IgG CH3-containing polypeptide at position S364, K409 and/or K360; and (b) subjecting the heterodimeric protein to ion exchange chromatography;
wherein:
a) the S364 amino acid is valine, isoleucine, threonine, glutamine or leucine; and/or
b) the K409 amino acid is isoleucine, leucine or glutamate; and/or
c) the K360 amino acid is aspartate;
wherein the position of the amino acid is defined according to EU numbering system.