Claims:

1. An asymmetric antibody comprising two heavy chains or heavy chain fragments each comprising at least a variable region, a hinge region and a C_H1 domain, wherein a first heavy chain or fragment thereof is a class IgG4 and has:

a. the inter-chain cysteine at position 127, numbered according to the Kabat numbering system, in the C_H1 domain is substituted with another amino acid; and

b. one or more of the amino acids positioned in the upper hinge region is substituted with cysteine, and

wherein the second heavy chain or fragment thereof is characterised in that part or all of the chain has a different amino acid sequence to said first heavy chain in at least the region outside the variable region (for example the constant region).

~~2. An asymmetric antibody comprising a first and second heavy chain or heavy chain fragment(s) each comprising at least a variable region, a hinge region and a C_H1 domain wherein the first heavy chain or fragment thereof is a class IgG4 and has an IgG1 type hinge and the second heavy chain or fragment thereof has a different amino acid sequence to said first heavy chain in at least the region outside the variable region.~~

~~3.~~2. The asymmetric antibody according to claim 1 ~~or 2~~, wherein the one or more amino acids positioned in the upper hinge region of the first heavy chain is substituted with cysteine and is selected from 227, 228, 229 and 230, numbered according to the Kabat numbering system.

~~4.~~3. The asymmetric antibody according to claim ~~3~~2, wherein the glycine at position 230, numbered according to the Kabat numbering system, is substituted with cysteine.

~~5.~~4. The asymmetric antibody according to claim ~~3 or 4~~ 2 or 3, wherein the tyrosine at position 229, numbered according to the Kabat numbering system, is substituted with cysteine.

~~6.~~5. The asymmetric antibody according to any one of claims ~~3 to 5~~ 2 to 4, wherein the lysine at position 228, numbered according to the Kabat numbering system, is substituted with cysteine.

~~7.~~6. The asymmetric antibody according to any one of claims ~~3 to 6~~ 2 to 5, wherein the serine at position 227, numbered according to the Kabat numbering system, is substituted with cysteine.

~~8.~~7. The asymmetric antibody according to any of claims ~~1 to 7~~ 1 to 6, wherein the cysteine at position 239 and the cysteine at position 242, numbered according to the Kabat numbering system, in the first heavy chain are substituted with another amino acid.

~~9.~~8. The asymmetric antibody according to any of claim ~~1 to 7~~ 1 to 6, wherein the cysteine at position 239, numbered according to the Kabat numbering system, in the first heavy chain is substituted with another amino acid.

~~10.~~9. The asymmetric antibody according to any of claims ~~1 to 7~~ 1 to 6, wherein the cysteine at position 242, numbered according to the Kabat numbering system, in the first heavy chain is substituted with another amino acid.

~~11. An asymmetric antibody comprising two heavy chains each comprising at least a variable region, a hinge region and a C_H1 domain, wherein in a first heavy chain or fragment thereof is characterised in that it is a class IgG4 and has:~~

~~a) the inter-chain cysteine at position 127, numbered according to the Kabat numbering system, is substituted with another amino acid; and~~

~~b) optionally the cysteine at position 239 or the cysteine at position 242, numbered according to the Kabat numbering system, is substituted with another amino acid; wherein the second heavy chain or fragment thereof is characterised in that it has a different amino acid sequence to said first heavy chain in a region outside the variable region.~~

~~12.~~10. The asymmetric antibody according to any of claims ~~8 to 11~~ 7 to 9, wherein the cysteine at position 239 and/or the cysteine at position 242 of a first heavy chain is substituted by a non-thiol containing amino acid.

~~13.~~11. The asymmetric antibody according to claim ~~12~~10, wherein the non-thiol containing amino acid is serine.

~~14.~~12. The asymmetric antibody according to any preceding claim wherein an amino acid at residue 240 and / or 241 according to Kabat number is replaced by another amino acid.

~~15.~~13. The asymmetric antibody according to any preceding claim, wherein the cysteine at position 127 is substituted by a non-thiol containing amino acid.

~~16.~~14. The asymmetric antibody according to claim ~~15~~13, wherein the non-thiol containing amino acid is serine.

~~17.~~15. The asymmetric antibody according to any preceding claim, wherein the heavy chain is mutated to insert three amino acids between amino acids 226-243, numbered according to the Kabat numbering system.

~~18.~~16. The asymmetric antibody according to claim ~~17~~15, wherein the first heavy chain is mutated to insert three amino acids between positions 238 and 239, numbered according to the Kabat numbering system.

~~19.~~17. The asymmetric antibody according to claim ~~18~~16, wherein three alanines are inserted between positions 238 and 239, of the first heavy chain numbered according to the Kabat numbering system.

~~20.~~18. The asymmetric antibody according to claim ~~18~~16, wherein a threonine, a histidine and a further theronine are inserted between positions 238 and 239, of the first heavy chain numbered according to the Kabat numbering system.

~~21.~~19. The asymmetric antibody according to any preceding claim, wherein the serine at position 241, of the first heavy chain numbered according to the Kabat numbering system, is substituted with proline.

~~22.~~20. The asymmetric antibody according to any preceding claim, wherein in the first heavy chain the glycine at position 230 is substituted with cysteine, the serine at position 227 is

substituted with proline, the tyrosine at position 229 is substituted with serine, the proline at position 237 is substituted with aspartic acid, the proline at position 238 is substituted with lysine, the amino acid sequence threonine-histidine-threonine is inserted between positions 238 and 239 and the serine at position 241 is substituted with proline.

~~23.~~21. The asymmetric antibody according to any preceding claim, wherein one or more of the heavy chains or fragments thereof comprises a C_H2 domain and/or a C_H3 domain.

~~24.~~22. The asymmetric antibody according to any preceding claim, wherein each heavy chain comprises a variable region and the two variable regions are identical.

~~25.~~23. The asymmetric mixed antibody according to any one of claims ~~1 to 23~~ 1 to 21, wherein each heavy chain comprises a variable region and the two variable regions are different.

~~26.~~24. The asymmetric antibody according to claim ~~25~~23, wherein the antibody is bi-specific.

~~27.~~25. The asymmetric antibody according to any preceding claim, wherein hinge region in each heavy chain or heavy chain fragment is different, for example a different amino acid sequence and/or a different sequence length

~~28.~~26. The asymmetric antibody according to any one of claims ~~1 to 27~~ 1 to 25 wherein hinge region in each heavy chain or heavy chain fragment is the same, for example the same amino acid sequence.

~~29.~~27. The asymmetric antibody according to any one of claims ~~1 to 28~~ 1 to 26, wherein the heavy chain or each heavy chain comprises an upper hinge region and core region of 12 to 17 amino acids in length, for example 15 amino acids in length.

~~30.~~28. The asymmetric antibody according to any one of claims, wherein the second heavy chain is class IgG4 or class IgG1, such as a class IgG4.

~~31.~~29. An expression vector comprising a sequence which encodes an antibody as defined in any one of claims ~~1 to 30~~ 1 to 28.

~~32.~~30. A host cell comprising a vector as defined in claim ~~31~~29.

~~33.~~31. An antibody as defined in any one of claims ~~1 to 30~~ 1 to 28 for use in the treatment of a disease disorder.

~~34.~~32. A method of generating an antibody as defined in any one of claims ~~1 to 30~~ 1 to 28 comprising the steps of taking a symmetrical antibody comprising a first heavy chain sequence or a fragment thereof as defined herein and mixing the said antibody *in vitro* with a second symmetrical antibody comprising a second heavy chain sequence or a fragment thereof which is different to said first heavy chain sequence, under conditions conducive to heavy chain exchange between the two antibodies, and optionally isolation of the asymmetric mixed antibody obtained therefrom.