Claims

1. A humanised anti-interleukin-18 antibody comprising a heavy chain and light chain having the following complementarity determining regions (CDRs):

CDRH1:SEQ.I.D.NO:1

CDRH2:SEQ.I.D.NO:2

CDRH3:SEQ.I.D.NO:3

CDRL1:SEQ.I.D.NO:4

CDRL2:SEQ.I.D.NO:5

CDRL3:SEQ.I.D.NO:6.

2. A humanised anti-interleukin-18 antibody comprising a heavy chain and light chain having the following CDRs:

CDRH1:SEQ.I.D.NO:1

CDRH2:SEQ.I.D.NO:2

CDRH3:SEQ.I.D.NO:3

CDRL1:SEQ.I.D.NO:4

CDRL2:SEQ.I.D.NO:5

CDRL3:SEQ.I.D.NO:6

wherein the residue at position 71 of the light chain is substituted by the corresponding residue found in the donor antibody from which the CDRs are derived.

3. A humanised anti-interleukin-18 antibody comprising CDRs derived from a donor antibody grafted onto a human acceptor framework which anti-interleukin 18 antibody comprises CDRs having sequence set forth in SEQ.I.D.NO: 1, 2, 3, 4, 5 and 6 wherein the residue at position 71 of the light chain of said anti-interleukin-18 antibody is identical to the residue found in the corresponding position in the donor antibody framework.

4. A humanised anti-interleukin-18 antibody comprising CDRs set forth in SEQ.I.D.NO: 1, 2, 3, 4, 5 and 6 which antibody comprises a tyrosine at position 71 of the light chain.

5. A humanised anti-interleukin-18 antibody comprising a heavy chain having CDRs set forth in SEQ.I.D.NO: 1, 2 and 3 and a light chain having CDRs set forth in SEQ.I.D.NO: 4, 5 and 6 wherein said light chain CDRs are derived from a donor antibody having a tyrosine at position 71 of the donor antibody light chain.

6. A humanised anti-interleukin-18 antibody comprising CDRs from a donor antibody and a tyrosine at position 71 of the light chain of said humanised antibody wherein the donor antibody is 2C10 or a framework variant thereof (i.e. comprises the same CDRs but a different framework as 2C10, see US patent 6,706,487).

7. A humanised anti-interleukin-18 antibody comprising;

(a) a heavy chain having CDRs with the sequences set forth in SEQ.I.D.NO:1, 2 and 3 grafted onto a human heavy chain acceptor framework and

(b) a light chain having CDRs with the sequences set forth in SEQ.I.D.NO: 4, 5 and 6 grafted onto a human light chain acceptor framework wherein said human light chain acceptor framework comprises SEQ.I.D.NO: 38 and wherein position 71 of the light chain is a tyrosine.

8. A humanised anti-interleukin-18 antibody comprising;

(a) a heavy chain comprising CDRs having sequences set forth in SEQ.I.D.NO: 1, 2 and 3 and;

(b) a light chain comprising CDRs having sequences set forth in SEQ.I.D.NO: 4, 5 and 6 grafted onto a human light chain acceptor framework wherein said light chain acceptor framework of said humanised anti-interleukin-18 antibody is a variant of the sequence set forth in SEQ.I.D.NO:38 wherein said variant comprises a tyrosine at position 71 and wherein said variant comprises 75% or greater identity to the framework having the sequence set forth in SEQ.I.D.NO:38.

9. A humanised anti-interleukin-18 antibody which antibody comprises;

(a) CDRs set forth in SEQ.I.D.NO: 1, 2, 3, 4, 5 and 6 derived from a donor antibody which donor antibody comprises a tyrosine at position 71 of the donor antibody light chain;

(b) a human acceptor framework which acceptor framework comprises a phenylalanine at position 71 of the human light chain;

wherein the anti-interleukin 18 antibody comprises a tyrosine at position 71 of the light chain.

10. A humanised anti-interleukin-18 antibody comprising;

(a) CDRs set forth in SEQ.I.D.NO: 1, 2, 3, 4, 5 and 6 derived from a donor antibody which donor antibody comprises an aromatic amino acid at position 71 of the donor antibody light chain;

(b) a human acceptor framework which acceptor framework comprises at position 71 of the light chain acceptor framework a different type of aromatic amino acid from the aromatic amino acid in part (a);

wherein the anti-interleukin-18 antibody comprises a light chain having at position 71 an aromatic amino acid derived from the antibody of part (a).

11. A humanised anti-interleukin-18 antibody which antibody displays a binding affinity (KD) of 90pM or greater with respect to human IL-18 when measured by surface plasmon resonance (e.g. Biacore™ T100) at 37°C.

12. A humanised anti-interleukin-18 antibody which antibody comprises CDRs as set forth in SEQ.I.D.NO: 1, 2, 3, 4, 5 and 6 and displays a binding affinity (KD) of 90pM or greater with respect to human IL-18 when measured by surface plasmon resonance (e.g. Biacore™ T100) at 37°C.

13. A humanised anti-interleukin-18 antibody which antibody displays an off-rate (*kd*) of 0.0002 (1/s) or less with respect to binding of human IL-18 when measured by surface plasmon resonance (e.g. Biacore™ T100) at 37°C.

14. A humanised anti-interleukin-18 antibody which antibody comprises;

(a) a heavy chain comprising CDRs derived from a donor antibody, which CDRs have sequences set forth in SEQ.I.D.NO: 1, 2 and 3 grafted onto a heavy chain acceptor framework which heavy chain acceptor framework has a sequence set forth in SEQ.I.D.NO: 37 wherein one or more residue/s of position/s 27, 28, 29, 93, 39, 40, 36, 71, 89, 91 of the heavy chain is identical to the corresponding residue in the donor antibody heavy chain;

(b) a light chain comprising CDRs derived from a donor antibody which CDRs have sequences set forth in SEQ.I.D.NO: 4, 5 and 6 grafted onto a light chain acceptor framework which light chain acceptor framework has a sequence set forth in SEQ.I.D.NO: 38 wherein position 71 and optionally one or more (e.g. all) residue/s of position/s 45, 83, 84, 85 of the light chain is identical to the corresponding residue in the donor antibody light chain.

15. A humanised anti-interleukin-18 antibody comprising;

(a) a heavy chain comprising CDRs derived from a donor antibody which CDRs have sequences set forth in SEQ.I.D.NO: 1, 2 and 3 grafted onto a human heavy chain acceptor framework which heavy chain acceptor framework has a sequence set forth in SEQ.I.D.NO: 37 wherein residues at

positions 27, 28, 29, 93 of the heavy chain are identical to the corresponding residues in the donor antibody heavy chain;

(b) a light chain comprising CDRs derived from a donor antibody which CDRs have sequences set forth in SEQ.I.D.NO: 4, 5 and 6 grafted onto a light chain acceptor framework which light chain acceptor framework has a sequence set forth in SEQ.I.D.NO: 38 wherein residue at position 71 of the light chain of said anti-interleukin-18 antibody is identical to the corresponding residue in the donor antibody light chain.

16. A humanised anti-interleukin-18 antibody comprising;

(a) a heavy chain comprising CDRs derived from a donor antibody which CDRs have sequences set forth in SEQ.I.D.NO: 1, 2 and 3 grafted onto a human heavy chain acceptor framework which heavy chain acceptor framework has the sequence set forth in SEQ.I.D.NO: 37 wherein residues at positions 27, 28, 29, 39, 40, 93 of the heavy chain are identical to the corresponding residues in the donor antibody heavy chain;

(b) a light chain comprising CDRs derived from a donor antibody which CDRs have sequences set forth in SEQ.I.D.NO: 4, 5 and 6 grafted onto a light chain acceptor framework which light chain acceptor framework has a sequence set forth in SEQ.I.D.NO: 38 wherein residue at position 71 of the light chain is identical to the corresponding residues in the donor antibody light chain

17. A humanised anti-interleukin-18 antibody comprising;

(a) a heavy chain comprising CDRs derived from a donor antibody which CDRs have sequences set forth in SEQ.I.D.NO: 1, 2 and 3 grafted onto a human heavy chain acceptor framework which acceptor framework comprises framework regions derived from the sequence set forth in SEQ.I.D.NO:37 wherein residues at positions 27, 28, 29, 36, 39, 40, 71, 89, 91, 93 of the heavy chain are identical to the corresponding residues in the donor antibody heavy chain;

(b) a light chain comprising CDRs derived from a donor antibody which CDRs have sequences set forth in SEQ.I.D.NO: 4, 5 and 6 grafted onto a light chain acceptor framework which light chain acceptor framework has a sequence set forth in SEQ.I.D.NO: 38 wherein residue at position 71 of the light chain is identical to the corresponding residues in the donor antibody light chain.

18. A humanised anti-interleukin-18 antibody comprising;

(a) a heavy chain comprising CDRs derived from a donor antibody which CDRs have sequences set forth in SEQ.I.D.NO:1, 2 and 3 grafted onto a human heavy chain acceptor framework which heavy chain acceptor framework has a sequence set forth in SEQ.I.D.NO:37 wherein residues at positions 27, 28, 29, 93 of the heavy chain are identical to the corresponding residues in the donor antibody heavy chain;

(b) a light chain comprising CDRs derived from a donor antibody which CDRs have sequences set forth in SEQ.I.D.NO: 4, 5 and 6 grafted onto a light chain acceptor framework which light chain acceptor framework has a sequence set forth in SEQ.I.D.NO: 38 wherein residues at positions 71, 45, 83, 84, 85 of the light chain are identical to the corresponding residues in the donor antibody light chain.

19. A humanised anti-interleukin-18 antibody comprising;

(a) a heavy chain comprising CDRs derived from a donor antibody which CDRs have sequences set forth in SEQ.I.D.NO: 1, 2 and 3 grafted onto a human heavy chain acceptor framework which heavy chain acceptor framework has a sequence set forth in SEQ.I.D.NO: 37 wherein residues at positions 27, 28, 29, 93, 39, 40 of the heavy chain are identical to the corresponding residues in the donor antibody heavy chain;

(b) a light chain comprising CDRs derived from a donor antibody which CDRs have sequences set forth in SEQ.I.D.NO: 4, 5 and 6 grafted onto a light chain acceptor framework which light chain acceptor framework has a sequence set forth in SEQ.I.D.NO: 38 wherein residues at positions 71, 45, 83, 84, 85 of the

light chain is identical to the corresponding residues in the donor antibody light chain.

20. A humanised anti-interleukin-18 antibody comprising;

(a) a heavy chain comprising CDRs derived from a donor antibody which CDRs have sequences set forth in SEQ.I.D.NO: 1, 2 and 3 grafted onto a human heavy chain acceptor framework which heavy chain acceptor framework has a sequence set forth in SEQ.I.D.NO: 37 wherein residues at positions 27, 28, 29, 93, 39, 40, 36, 71, 89, 91 of the heavy chain are identical to the corresponding residues in the donor antibody heavy chain;

(b) a light chain comprising CDRs derived from a donor antibody which CDRs have sequences set forth in SEQ.I.D.NO: 4, 5 and 6 grafted onto a light chain acceptor framework which light chain acceptor framework has a sequence set forth in SEQ.I.D.NO: 38 wherein residues at positions 71, 45, 83, 84, 85 of the light chain are identical to the corresponding residues in the donor antibody light chain.

21. A humanised anti-interleukin-18 antibody comprising a heavy chain selected from the group consisting of; SEQ.I.D.NO: 9, SEQ.I.D.NO: 17, SEQ.I.D.NO: 21; and a light chain selected from the group consisting of; SEQ.I.D.NO: 13, SEQ.I.D.NO: 29.

22. A humanised anti-interleukin-18 antibody comprising a heavy chain of SEQ.I.D.NO:9 and a light chain of SEQ.I.D.NO:13 or a heavy chain of SEQ.I.D.NO:9 and a light chain of SEQ.I.D.NO:29.

23. A humanised anti-interleukin-18 antibody comprising a heavy chain of SEQ.I.D.NO:17 and a light chain of SEQ.I.D.NO:13 or a heavy chain of SEQ.I.D.NO:17 and a light chain of SEQ.I.D.NO:29.

24. A humanised anti-interleukin-18 antibody comprising a heavy chain of SEQ.I.D.NO:21 and a light chain of SEQ.I.D.NO:13 or a heavy chain of SEQ.I.D.NO:21 and a light chain of SEQ.I.D.NO:29.

25. A humanised anti-interleukin-18 antibody comprising;

(a) a heavy chain having CDRs permissive of specific binding to human IL-18;

(b) a light chain comprising an acceptor framework having CDRs with the sequences set forth in SEQ.I.D.NO: 4, 5 and 6 and having a tyrosine residue at position 71.

26. A humanised anti-interleukin-18 antibody comprising a heavy chain and a light chain, wherein a ratio between off-rate (*kd*) of said antibody from binding to human IL-18 at 25℃ to off-rate (*kd*) of said antibody from binding to human IL-18 at 37℃ is 1:5 (or 1:less than 5), wherein said antibody comprises CDRs derived from a donor antibody and a human acceptor framework, and wherein a residue at position 71 of the light chain of the human acceptor framework is substituted by the corresponding residue from the donor antibody.

27. A humanised antibody according to claim 26, wherein the CDRs have sequences set forth in SEQ.I.D.NO: 1, 2, 3, 4, 5 and 6.

28. A humanised antibody according to claim 26 or 27, wherein the residue at position 71 of the light chain of the human acceptor framework is an aromatic amino acid, preferably phenylalanine, and the corresponding residue in the donor antibody is a different type of aromatic amino acid, preferably tyrosine.

29. A pharmaceutical composition comprising an anti-interleukin-18 antibody according to any one of claims 1 to 28 and a pharmaceutically acceptable carrier.

30. Use of an anti-interleukin-18 antibody according to any one of claims 1 to 28 in the manufacture of a medicament for the treatment of autoimmune diseases such as multiple sclerosis, arthritic diseases such as rheumatoid arthritis, Type 1 diabetes, inflammatory bowel disease (IBD) and psoriasis.

31. Use of claim 31 in the manufacture of a medicament for the treatment of rheumatoid arthritis.

32. An antibody of any one of claims 1 to 28 for the treatment of autoimmune diseases such as multiple sclerosis, arthritic diseases such as rheumatoid arthritis, Type 1 diabetes, inflammatory bowel disease (IBD) and psoriasis.

33. A method of treating a human patient afflicted with an autoimmune disease such as multiple sclerosis, arthritic diseases such as rheumatoid arthritis, Type 1 diabetes, inflammatory bowel disease (IBD) and psoriasis which method comprises administering to said patient a therapeutically effective amount of an antibody according to any one of claims 1 to 28.

34. A method for the production of an antibody according to any one of claims 1 to 28 which method comprises culturing a host cell transformed or transfected with a vector comprising a polynucleotide encoding said antibody under conditions permissive for the expression of said antibody.

35. The method of claim 34 wherein said conditions include culturing said host cell in serum-free culture media.

36. The method of claim 34 or 35 wherein said host cell is a mammalian cell.

37. The method of claim 36 wherein said host cell is CHO or NS0.

38. The method of claim 37 wherein the CHO cell is a DHFR$^-$ CHO cell prior to transfection or transformation with said polynucleotide.

39. A method of selecting an antibody (particularly an antibody that inhibits the interaction between a ligand and a receptor such as an anti-interleukin-18 antibody disclosed herein) for therapeutic use which method comprises;

(a) measuring the binding affinity (using e.g. surface plasmon resonance such as Biacore^{TM}) of the antibody for an antigen to which the antibody specifically binds at a temperature between 30 to 45°C (preferably 37°C);

(b) measuring the binding affinity (using e.g. surface plasmon resonance such as Biacore™) of the antibody for an antigen to which the antibody specifically binds at a temperature between 20 to 25°C (preferably 25°C);

(c) selecting said antibody for therapeutic use if the affinity of (a) is greater than the affinity of (b), preferably if said affinity of (a) is 2 fold or greater, more preferably 4 fold or greater than the affinity of step (b).

40. A method of selecting an antibody (particularly an antibody that inhibits the interaction between a ligand and a receptor such as an anti-interleukin-18 antibody disclosed herein) for therapeutic use which method comprises;

(a) measuring the off-rate (using e.g. surface plasmon resonance such as Biacore™) of the antibody from the antigen to which the antibody specifically binds, at a temperature between 30 to 45°C (preferably 37°C);

(b) measuring the off-rate (using e.g. surface plasmon resonance such as Biacore™) of the antibody from the antigen to which the antibody specifically binds at a temperature between 20 to 25°C (preferably 25°C);

(c) selecting said antibody for therapeutic use if the off-rate of (a) is slower than the off-rate of (b).

Claims

1. A humanised anti-interleukin-18 antibody comprising a heavy chain variable region as set forth in SEQ.I.D.NO:11 and a light chain variable region as set forth in SEQ.I.D.NO:15.

2. A humanised anti-interleukin-18 antibody as claimed in claim 1, comprising a heavy chain as set forth in SEQ.I.D.NO: 9 and a light chain as set forth in SEQ.I.D.NO: 13.

3. A pharmaceutical composition comprising an anti-interleukin-18 antibody according to claim 1 or claim 2 and a pharmaceutically acceptable carrier.

4. An antibody as claimed in claim 1 or claim 2 for use as a medicament.

5. An antibody as claimed in claim 4 wherein the medicament is for use in the treatment of an autoimmune disease.

6. An antibody as claimed in claim 5, wherein the autoimmune disease is selected from the group consisting of: multiple sclerosis, arthritic diseases such as rheumatoid arthritis, Type 1 diabetes, inflammatory bowel disease (IBD) and psoriasis.

7. Use of an antibody as claimed in claim 1 or claim 2 in the manufacture of a medicament for the treatment of an autoimmune disease.

8. A polynucleotide encoding an antibody heavy chain variable region and an antibody light chain variable region as defined in claim 1.

9. A polynucleotide encoding an antibody heavy chain and/or an antibody light chain as defined in claim 2.

10. A vector encoding the heavy chain and/or the light chain of an antibody as claimed in claim 1 or claim 2.

11. A stably transformed host cell comprising a vector as claimed in claim 10.

12. A stably transformed host cell comprising a first vector encoding the light chain and a second vector encoding the heavy chain of an antibody as claimed in claim 1 or claim 2.

13. A method for the production of an antibody according to claim 1 or claim 2 which method comprises culturing a host cell transformed or transfected with a vector or vectors encoding said antibody under conditions permissive for the expression of said antibody.

14. A method as claimed in claim 13 wherein polynucleotide encoding the light chain and polynucleotide encoding the heavy chain of the antibody are inserted into the same vector and introduced into the host cell.

15. A method as claimed in claim 13 wherein polynucleotide encoding the light chain and polynucleotide encoding the heavy chain of the antibody are inserted into separate vectors and introduced into the same host cell concurrently or sequentially.