CLAIMS:

1. A non-human vertebrate (optionally a mouse or a rat) or non-human vertebrate cell whose genome comprises an immunoglobulin heavy chain locus comprising unrearranged human gene segment JH6*02, one or more VH gene segments and one or more D gene segments upstream of a constant region; wherein the gene segments in the heavy chain locus are operably linked to the constant region thereof so that the vertebrate is capable of producing an antibody heavy chain produced by recombination of the human JH6*02 with a D segment and a VH segment, wherein the JH6*02 gene segment comprises the following nucleotide sequence: ATTACTA CTACTACTAC GGTATGGACG TCTGGGGCCA AGGGACCACG GTCACCGTCT CCTCAG.

2. The vertebrate of claim 1, wherein the vertebrate has been immunised with a target antigen and wherein the variable domain of the heavy chain is the product of recombination between a VH, D and JH6*02 and wherein the HCDR3 length is at least 20 amino acids.

3. A non-human vertebrate cell (optionally a mouse cell or a rat cell) whose genome comprises an immunoglobulin heavy chain locus comprising unrearranged human gene segment JH6*02, one or more VH gene segments and one or more D gene segments upstream of a constant region; wherein the gene segments in the heavy chain locus are operably linked to the constant region thereof for producing (e.g., in a subsequent progeny cell) an antibody heavy chain produced by recombination of the human JH6*02 with a D segment and a VH segment, wherein the JH6*02 gene segment comprises the following nucleotide sequence: ATTACTA CTACTACTAC GGTATGGACG TCTGGGGCCA AGGGACCACG GTCACCGTCT CCTCAG.

4. The cell of claim 3, which is an ES cell capable of differentiation into a progeny antibody-producing cell that expresses said heavy chain.

5. The vertebrate or cell of any preceding claim, wherein the heavy chain locus comprises a human JH6*02 recombination signal sequence (RSS) operably connected 5' to the JH6*02 gene segment.

6. The vertebrate or cell of claim 5, wherein the RSS is SEQ ID NO: 238 or a sequence having an identical 9mer and 7mer sequence flanking a sequence that is at least 70% identical to the 22mer sequence of SEQ ID NO: 238.

7. The vertebrate or cell of claim 6, wherein the RSS and JH6*02 are provided as SEQ ID NO: 237.

8. The vertebrate or cell of any preceding claim, wherein the JH6*02 is the only JH6-type gene segment in the genome.

9. The vertebrate or cell of any preceding claim, wherein the JH6*02 is the closest JH gene segment to the constant region in the locus.

10. The vertebrate or cell of any preceding claim, wherein the locus comprises one, more or all human D gene segments D3-9; D4-17; D3-10; D2-2; D5-24; D6-19; D3-22; D6-13; D5-12; D1- 26; D1-20; D5-18; D3-16; D2-21; D1-14; D7-27; D1-1; D6-25; D2-14; and D4-23.

11. The vertebrate or cell of claim 10, wherein the locus comprises one, more or all human D gene segments D3-9, D3-10, D6-19, D4-17, D6-13, D3-22, D2-2, D2-25 and D3-3.

AMENDED SHEET 014 17:48:33
Duration: 04.04.2014 17:47:10 - 04.04.2014 18:04:12. This page 5 of 5
Received at the EPO on Apr 04, 2014 18:04:12. Page 5 of 50

12. The vertebrate or cell of any preceding claim, wherein the locus comprises a plurality of human D gene segments and the JH6*02 is in human germline configuration with respect to the 3'-most human D gene segment.

13. The vertebrate or cell of any preceding claim, wherein the locus comprises one, more or all of IGHV gene segments selected from V3-21, V3-13, V3-7, V6-1, V1-8, V1-2, V7-4-1, V1-3, V1- 18, V4-4, V3-9, V3-23, V3-11 and V3-20.

14. The vertebrate or cell of any preceding claim, wherein the locus comprises one, more or all of human D3-9*01, D3-10*01, D6-19*01, D6-13*01, D1-26*01, IGHV1-8*01, IGHV4-61*01, IGHV6-1*01, IGHV4-4*02, IGHV1-3*01, IGHV3-66*03, IGHV3-7*01 and IGHV3-9*01.

15. An antibody-producing cell (e.g., a B-cell) that is a progeny of the cell of any one of claims 3 to 14, wherein the antibody-producing cell comprises a heavy chain locus comprising a rearranged variable region produced by recombination of human JH6*02 with a D segment and a VH segment.

16. The cell of claim 15, which is a B-cell or hybridoma that expresses a target antigen-specific antibody comprising a heavy chain that comprises a rearranged variable region produced by recombination of human JH6*02 with a D segment and a VH segment.

17. The vertebrate or cell of any preceding claim, wherein the antibody heavy chain specifically binds a target antigen.

18. The vertebrate or cell of any preceding claim, wherein the antibody heavy chain has a HCDR3 length of at least 20 amino acids.

19. The vertebrate or cell of any preceding claim, wherein the antibody heavy chain is a product of the recombination of JH6*02 with a human VH gene segment recited in claim 13 or 14 and/or a D gene segment recited in claim 10, 11 or 14.

20. The vertebrate or cell of any preceding claim, wherein all endogenous non-human vertebrate heavy chain variable region gene segments have been inactivated in the genome.

21. The vertebrate or cell of any preceding claim, wherein the genome is homozygous for said heavy chain locus.

22. A heavy chain (e.g., comprised by an antibody) isolated from a vertebrate of any one of claims 1, 2, 5 to 14 and 17 to 21 wherein the heavy chain comprises a HCDR3 of at least 20 amino acids and the HCDR3 is the product of recombination of human JH6*02 with a human VH gene segment and a human D gene segment.

23. The heavy chain of claim 22, wherein the human VH gene segment is as recited in claim 13 or 14 and/or a D gene segment as recited in claim 10, 11 or 14.

24. A heavy chain (e.g., comprised by an antibody) whose VH variable domain is identical to the VH variable domain of the heavy chain of claim 22 or 23, and which comprises a human constant region or a human-mouse chimaeric constant region.

25. The heavy chain of claim 22, 23 or 24, whose VH variable domain is specific for a target antigen.

Duration: 04.04.2014 17:47:10 - 04.04.2014 18:04:12. This page 6 of 5AMENDED SHEET014 17:48:52
Received at the EPO on Apr 04, 2014 18:04:12. Page 6 of 50

26. A method for producing a heavy chain, VH domain or an antibody specific to a target antigen, the method comprising immunizing a non-human vertebrate according to any one of claims 1, 2, 5 to 14 and 17 to 21 with the antigen and isolating the heavy chain, VH domain or an antibody specific to a target antigen or a cell producing the heavy chain, VH domain or an antibody, wherein the heavy chain, VH domain or an antibody comprises a HCDR3 that is derived from the recombination of human JH6*02 with a VH gene segment and a D gene segment.

27. A method for producing a human heavy chain or antibody comprising carrying out the method of claim 26, wherein the constant region of the locus is a non-human vertebrate (e.g., mouse or rat) constant region, and then replacing the non-human constant region of the isolated heavy chain or antibody with a human constant region.

28. A heavy chain, VH domain or an antibody produced by the method of claim 26 or 27, wherein the heavy chain, VH domain or antibody comprises a HCDR3 of at least 20 amino acids and the HCDR3 is the product of recombination of human JH6*02 with a human VH gene segment and/or a human D gene segment.

29. A non-human vertebrate B-cell or hybridoma expressing a heavy chain VH domain that is identical to the VH domain of the heavy chain of claim 22, 23 or 28.

30. A nucleic acid encoding the VH domain of the heavy chain of claim 22, 23 or 28, or encoding the heavy chain of claim 22, 23, 24, 25 or 28.

31. A vector (e.g., a CHO cell or HEK293 cell vector) comprising the nucleic acid of claim 30; optionally wherein the vector is in a host cell (e.g., a CHO cell or HEK293 cell).

32. A pharmaceutical composition comprising the antibody, heavy chain or VH domain (e.g., comprised by an antibody) of any one of claims 22 to 25 and 28, together with a pharmaceutically-acceptable excipient, diluent or a medicament (e.g., a further antigen-specific variable domain, heavy chain or antibody).

33. The antibody, heavy chain or VH domain (e.g., comprised by an antibody) of any one of claims 22 to 25 and 28 for use in medicine.

34. A non-human vertebrate (e.g., a mouse or rat) or a non-human vertebrate cell (e.g., an ES cell or a B-cell) having a genome comprising at least 3 human variable region gene segments of the same type (e.g., at least 3 human VH6-1 gene segments, at least 3 human JH6 gene segments, at least 3 human Vκ1-39 gene segments, at least 3 human D2-2 gene segments or at least 3 human Jκ1 gene segments), wherein at least two of the human gene segments are variants that are not identical to each other.

35. A non-human vertebrate (e.g., a mouse or rat) or a non-human vertebrate cell (e.g., an ES cell or a B-cell) having a genome comprising at least 2 different non-endogenous variable region gene segments of the same type (e.g., at least 2 human VH6-1 gene segments, at least 3 human JH6 gene segments, at least 2 human Vκ1-39 gene segments, at least 2 human D2-2 gene segments or at least 2 human Jκ1 gene segments) *cis* at the same Ig locus.

36 A non-human vertebrate (e.g., a mouse or rat) or a non-human vertebrate cell (e.g., an ES cell or a B-cell) having a genome comprising at least 2 different human variable region gene segments of the same type (e.g., at least 2 human VH6-1 gene segments, at least 2 human JH6 gene segments, at least 2 human Vκ1-39 gene segments, at least 2 human D2-2 gene segments or at least 2 human Jκ1 gene segments) *trans* at the same

AMENDED SHEET 014 17:49:15
Duration: 04.04.2014 17:47:10 - 04.04.2014 18:04:12. This page 7 of 50
Received at the EPO on Apr 04, 2014 18:04:12. Page 7 of 50

Ig locus; and optionally a third human gene segment of the same type, wherein the third gene segment is *cis* with one of said 2 different gene segments.

37. A population of non-human vertebrates (e.g., mice or rats) comprising a repertoire of human variable region gene segments, wherein the plurality comprises at least 2 human variable region gene segments of the same type (e.g., at least 2 human VH6-1 gene segments, at least 2 human JH6 gene segments, at least 2 human Vκ1-39 gene segments, at least 2 human D2-2 gene segments or at least 2 human Jκ1 gene segments), a first of said different gene segments is provided in the genome of a first vertebrate of the population, and a second of said different gene segments being provided in the genome of a second vertebrate of the population, wherein the genome of the first vertebrate does not comprise the second gene segment.

38. A non-human vertebrate (e.g., a mouse or rat) or a non-human vertebrate cell (e.g., an ES cell or a B-cell) having a genome comprising at least 2 different non-endogenous variable region gene segments of the same type (e.g., at least 2 human VH6-1 gene segments, at least 2 human JH6 gene segments, at least 2 human Vκ1-39 gene segments, at least 2 human D2-2 gene segments or at least 2 human Jκ1 gene segments), wherein the gene segments are derived from the genome sequence of different human individuals that are not genetically related over at least 3 generations.

39. A method of enhancing the human immunoglobulin gene diversity of a non-human vertebrate (e.g., a mouse or rat), the method comprising providing the vertebrate with a genome comprising at least 3 human variable region gene segments of the same type (e.g., at least 3 human VH6-1 gene segments, at least 3 human JH6 gene segments, at least 3 human Vκ1-39 gene segments, at least 3 human D2-2 gene segments or at least 3 human Jκ1 gene segments), wherein at least two of the human gene segments are variants that are not identical to each other.

40. A method of enhancing the immunoglobulin gene diversity of a non-human vertebrate (e.g., a mouse or rat), the method comprising providing the vertebrate with a genome comprising at least 2 different non-endogenous variable region gene segments of the same type (e.g., at least 2 human VH6-1 gene segments, at least 2 human JH6 gene segments, at least 2 human Vκ1-39 gene segments, at least 2 human D2-2 gene segments or at least 2 human Jκ1 gene segments) *cis* at the same Ig locus.

41. A method of enhancing the immunoglobulin gene diversity of a non-human vertebrate (e.g., a mouse or rat), the method comprising providing the vertebrate with a genome comprising at least 2 different human variable region gene segments of the same type (e.g., at least 2 human VH6-1 gene segments, at least 2 human JH6 gene segments, at least 2 human Vκ1-39 gene segments, at least 2 human D2-2 gene segments or at least 2 human Jκ1 gene segments) *trans* at the same Ig locus; and optionally a third human gene segment of the same type, wherein the third gene segment is *cis* with one of said 2 different gene segments.

42. A method of providing an enhanced human immunoglobulin variable region gene segment repertoire, the method comprising providing a population of non-human vertebrates (e.g., a mouse or rat) comprising a repertoire of human variable region gene segments, wherein the method comprises providing at least 2 different human variable region gene segments of the same type (e.g., at least 2 human VH6-1 gene segments, at least 2 human JH6 gene segments, at least 2 human Vκ1-39 gene segments, at least 2 human D2-2 gene segments or at least 2 human Jκ1 gene segments), wherein a first of said different gene segments is provided in the genome of a first vertebrate of the population, and a second of said different gene segments is provided in the genome of a

Duration: 04.04.2014 17:47:10 - 04.04.2014 18:04:12. This page 8 of 5AMENDED SHEET014 17:49:40
Received at the EPO on Apr 04, 2014 18:04:12. Page 8 of 50

second vertebrate of the population, wherein the genome of the first vertebrate does not comprise the second gene segment.

43. A method of enhancing the human immunoglobulin gene diversity of a non-human vertebrate (e.g., a mouse or rat), the method comprising providing the vertebrate with a genome comprising at least 2 different non-endogenous variable region gene segments of the same type (e.g., at least 2 human VH6-1 gene segments, at least 2 human JH6 gene segments, at least 2 human Vκ1-39 gene segments, at least 2 human D2-2 gene segments or at least 2 human Jκ1 gene segments), wherein the gene segments are derived from the genome sequence of different human individuals that are not genetically related over at least 3 generations.

44. The vertebrate, cell or method of any one of claims 34 to 43, wherein at least 2 or 3 of said different gene segments are provided *cis* at the same Ig locus in said genome.

45. The vertebrate, cell or method of any one of claims 34 to 44, wherein the gene segments are derived from the genome sequence of different human individuals that are not genetically related over at least 3 generations.

46. The vertebrate, cell or method of any one of claims 34 to 45, wherein the gene segments are derived from the genome sequence of two or more different human individuals; optionally wherein the different human individuals are from different human populations.

47. The vertebrate, cell or method of claim 46, wherein the individuals are not genetically related.

48. A method of enhancing the human immunoglobulin gene diversity of a non-human vertebrate (e.g., a mouse or rat), the method comprising providing the vertebrate with a genome comprising at least 2 human variable region gene segments of the same type (e.g., at least 2 human VH6-1 gene segments, at least 2 human JH6 gene segments, at least 2 human Vκ1-39 gene segments, at least 2 human D2-2 gene segments or at least 2 human Jκ1 gene segments), wherein the gene segments are derived from the genome sequence of different human individuals that are not genetically related over at least 3 generations; optionally wherein at least 2 or 3 of said different gene segments are provided at the same Ig locus in said genome.

49. The method of claim 48, wherein the different human individuals are from different human populations.

50. The method of claim 48, wherein the individuals are not genetically related.

51. The vertebrate, cell or method of preceding claim, wherein at least one of the different segments is a synthetic mutant of a human germline gene segment.

52. The vertebrate, cell or method of any one of claims 34 to 51, wherein each of said gene segments occurs in 10 or more different human populations.

53. The vertebrate, cell or method of preceding claim, wherein each of said gene segments has a human frequency of 5% or greater.

54. The vertebrate, cell or method of claim 53, wherein each of said gene segments occurs in 10 or more different human populations.

AMENDED SHEET 014 17:50:00
Duration: 04.04.2014 17:47:10 - 04.04.2014 18:04:12. This page 9 of 5
Received at the EPO on Apr 04, 2014 18:04:12. Page 9 of 50

55. The vertebrate, cell or method of any one of claims 34 to 54, wherein each of said gene segments occurs in the 1000 Genomes database in more than 50 individuals.

56. The vertebrate, cell or method of preceding claim, wherein each of said gene segments (i) has a human frequency of 5% or greater; and (ii) occurs in 10 or more different human populations.

57. A non-human vertebrate (e.g., a mouse or rat) or a non-human vertebrate cell (e.g., an ES cell or a B-cell) having a genome comprising first and second human JH6 gene segments, wherein the first gene segment is a gene segment selected from any one of Tables 1 to 7 and 9 to 14 (e.g., IGHJ6-a) and the second gene segment is the corresponding reference sequence (e.g., IGHJ6 ref; SEQ ID NO: 244).

58. The vertebrate or cell of claim 57, wherein the genome comprises a third human gene segment of said type, the third gene segment being different from the first and second gene segments.

59. The vertebrate or cell of claim 57 or 58, wherein the first and second gene segments are *cis* on the same chromosome; and optionally the third gene segment is also *cis* on said chromosome.

60. The vertebrate or cell of claim 59, wherein the gene segments are targeted insertions into an endogenous non-human Ig locus.

61. The vertebrate or cell of claim 57 or 58, wherein the first and second gene segments are trans on different chromosomes.

62. The vertebrate or cell of any one of claims 57 to 61, wherein the first gene segment is a gene segment selected any one of Tables 1 to 7 and 9 to 14 and the second gene segment is the corresponding reference sequence.

63. A population of non-human vertebrates (e.g., mice or rats) comprising first and second human JH6 gene segments, wherein the first gene segment is a gene segment selected from any one of Tables 1 to 7 and 9 to 14 (e.g., IGHJ6-a) and the second gene segment is the corresponding reference sequence (e.g., SEQ ID NO: 244), wherein the first gene segment is provided in the genome of a first vertebrate of the population, and the second gene segment is provided in the genome of a second vertebrate of the population.

64. The population of claim 63, wherein the genome of the first vertebrate does not comprise the second gene segment.

65. The population of claim 63 or 64, wherein the population comprises a third human gene segment of said type, the third gene segment being different from the first and second gene segments and optionally wherein the first and third gene segments are present in the genome of the first vertebrate.

66. The population of claim 63, 64 or 65, wherein the gene segments are targeted insertions into an endogenous non-human Ig locus in the respective genome.

67. The population of any one of claims 63 to 66, wherein the first gene segment is a gene segment selected from any one of Tables 1 to 7 and 9 to 14 and the second gene segment is the corresponding reference sequence.

Duration: 04.04.2014 17:47:10 - 04.04.2014 18:04:12. This page 10 of AMENDED SHEET 2014 17:50:20
Received at the EPO on Apr 04, 2014 18:04:12. Page 10 of 50

68. A method of enhancing the human immunoglobulin gene diversity of a non-human vertebrate (e.g., a mouse or rat), the method comprising providing the vertebrate with a genome comprising first and second human JH6 gene segments, wherein the first gene segment is a gene segment selected from any one of Tables 1 to 7 and 9 to 14 (e.g., IGHJ6-a) and the second gene segment is the corresponding reference sequence (e.g., SEQ ID NO: 244).

69. A method of providing an enhanced human immunoglobulin gene segment repertoire, the method comprising providing a population according to any one of claims 63 to 66.

70. A non-human vertebrate (e.g., a mouse or rat) or a non-human vertebrate cell (e.g., an ES cell or a B-cell) according to claim 34, having a genome comprising at least 3 human D gene segments of the same type (e.g., D2-2 gene segments), wherein at least two of the human D gene segments are variants that are not identical to each other (e.g., D2-2ref and D2-2a).

71. A non-human vertebrate (e.g., a mouse or rat) or a non-human vertebrate cell (e.g., an ES cell or a B-cell) according to claim 35, having a genome comprising at least 2 different non-endogenous D gene segments of the same type (e.g., D2-2ref and D2-2a) *cis* at the same Ig locus.

72. A non-human vertebrate (e.g., a mouse or rat) or a non-human vertebrate cell (e.g., an ES cell or a B-cell) according to claim 36, having a genome comprising at least 2 different human D gene segments of the same type (e.g., D2-2ref and D2-2a) trans at the same Ig locus; and optionally a third human D gene segment (e.g., D2-2ref, D2-2a or D2-2b) of the same type, wherein the third D is *cis* with one of said 2 different D gene segments.

73. A population of non-human vertebrates (e.g., mice or rats) according to claim 37, comprising a repertoire of human D gene segments, wherein the plurality comprises at least 2 different human D gene segments of the same type (e.g., D2-2 gene segments), a first of said different D gene segments (e.g., D2-2ref) is provided in the genome of a first vertebrate of the population, and a second of said different D gene segment (e.g., D2-2a) being provided in the genome of a second vertebrate of the population, wherein the genome of the first vertebrate does not comprise the second D gene segment.

74. A non-human vertebrate (e.g., a mouse or rat) or a non-human vertebrate cell (e.g., an ES cell or a B-cell) according to claim 38, having a genome comprising at least 2 different non-endogenous D gene segments of the same type (e.g., human D2-2 gene segments), wherein the D gene segments are derived from the genome sequence of different human individuals that are not genetically related over at least 3 generations.

75. A method of enhancing the human immunoglobulin gene diversity of a non-human vertebrate (e.g., a mouse or rat) according to claim 39, the method comprising providing the vertebrate with a genome comprising at least 3 human D gene segments of the same type (e.g., D2-2 gene segments), wherein at least two of the human D gene segments are variants that are not identical to each other (e.g., D2-2ref and D2-2a).

76. A method of enhancing the immunoglobulin gene diversity of a non-human vertebrate (e.g., a mouse or rat) according to claim 40, the method comprising providing the vertebrate with a genome comprising at least 2 different non-endogenous D gene segments of the same type (e.g., human D2-2 gene segments) *cis* at the same Ig locus.

77. A method of enhancing the immunoglobulin gene diversity of a non-human vertebrate (e.g., a mouse or rat) according to claim 41, the method comprising providing the

AMENDED SHEET 2014 17:50:44
Duration: 04.04.2014 17:47:10 - 04.04.2014 18:04:12. This page 11 of
Received at the EPO on Apr 04, 2014 18:04:12. Page 11 of 50

vertebrate with a genome comprising at least 2 different human D gene segments of the same type (e.g., D2-2ref and D2-2a) trans at the same Ig locus; and optionally a third human D gene segment (e.g., D2- 2ref, D2-2a or D2-2b) of the same type, wherein the third D is *cis* with one of said 2 different D gene segments.

78. A method of providing an enhanced human immunoglobulin D gene segment repertoire according to claim 42, the method comprising providing a population of non-human vertebrates (e.g., a mouse or rat) comprising a repertoire of human D gene segments, wherein the method comprises providing at least 2 different human D gene segments of the same type (e.g., D2-2ref and D2-2a), wherein a first of said different D gene segments is provided in the genome of a first vertebrate of the population, and a second of said different D gene segments is provided in the genome of a second vertebrate of the population, wherein the genome of the first vertebrate does not comprise the second D gene segment.

79. A method of enhancing the human immunoglobulin gene diversity of a non-human vertebrate (e.g., a mouse or rat) according to claim 43, the method comprising providing the vertebrate with a genome comprising at least 2 different non-endogenous D gene segments of the same type (e.g., D2-2ref and D2-2a), wherein the D gene segments are derived from the genome sequence of different human individuals that are not genetically related over at least 3 generations.

80. The vertebrate or cell of claim 70, 71 or 74, or the method of claim 75, 77 or 79, wherein at least 2 or 3 of said different gene segments are provided *cis* at the same Ig locus in said genome.

81. The vertebrate or cell of claim 70, 71 or 74, or the method of any one of claims 75 to 78 and 80, wherein the D gene segments are derived from the genome sequence of different human individuals that are not genetically related over at least 3 generations.

82. The vertebrate or cell of any one of claims 70 to 73, or the method of any one of claims 75 to 78 and 81, wherein the D gene segments are derived from the genome sequence of two or more different human individuals; optionally wherein the different human individuals are from different human populations.

83. The vertebrate, cell or method of claim 82, wherein the individuals are not genetically related.

84. The vertebrate, cell or method of any one of claims 70 to 83, wherein at least one of the different D segments is a synthetic mutant of a human germline D gene segment.

85. A method of enhancing the human immunoglobulin gene diversity of a non-human vertebrate (e.g., a mouse or rat) according to claim 48, the method comprising providing the vertebrate with a genome comprising at least 2 human D gene segments (e.g., D2-2ref and D2-2a), wherein the D gene segments are derived from the genome sequence of different human individuals that are not genetically related over at least 3 generations; optionally wherein at least 2 or 3 of said different gene segments are provided at the same IgH locus in said genome.

86. The vertebrate or cell of any one of claims 70 to 74 and 80 to 84, wherein the genome comprises a substantially complete functional repertoire of human D gene segment types supplemented with one, two or more variant human D gene segments, wherein said substantially complete functional repertoire and the supplementary D gene segments are not found together in the germline genome of a human individual.

AMENDED SHEET
Duration: 04.04.2014 17:47:10 - 04.04.2014 18:04:12. This page 12 of 2014 17:51:06
Received at the EPO on Apr 04, 2014 18:04:12. Page 12 of 50

87. The population of claim 73, wherein the population comprises a substantially complete functional repertoire of human D gene segment types supplemented with one, two or more variant human D gene segments, wherein said substantially complete functional repertoire and the supplementary D gene segments are not found together in the germline genome of a human individual.

88. A non-human vertebrate (e.g., a mouse or rat) or a non-human cell (e.g., an ES cell or a B-cell) having a genome comprising a substantially complete functional repertoire of human D gene segment types supplemented with one, two or more variant human D gene segments, wherein said substantially complete functional repertoire and the supplementary D gene segments are not found together in the germline genome of a human individual.

89. A population of non-human vertebrates (e.g., mice or rats) comprising a substantially complete functional repertoire of human JH gene segment types supplemented with one, two or more variant human D gene segments, wherein said substantially complete functional repertoire and the supplementary D gene segments are not found together in the germline genome of a human individual.

90. The vertebrate or cell of claim 88 or the population of claim 89, comprising first and second D gene segments selected from
D2-2ref and D2-2a; or
D2-21ref and D2-21a; or
D3-10ref and D3-10a; or
D3-16refand D3-16a; or
D2-8ref and D2-8a; or
D3-3ref and D3-3a; or
D4-23ref and D4-23a; or
D6-13ref and D6-13a; or
D3-9ref and D3-9a; or
D4-4ref and D4-4a; or
D7-27ref and D7-27a;

optionally wherein the first and/or second D gene segment is present in two or more copies.

91 The vertebrate, cell or population of claim 90, comprising human gene segments D2-2ref and D2-2a; and D3-3ref and D3-3a; and optionally also D2-15.

92. A non-human vertebrate or vertebrate cell according to claim 71, comprising a genome that comprises VH, D and JH gene repertoires comprising human gene segments, the D gene repertoire comprising one or more of

a plurality of D2-2 gene segments provided by at least 2 different D2-2 gene segments in *cis* at the same Ig locus in said genome;
a plurality of D2-21 gene segments provided by at least 2 different D2-21 gene segments in *cis* at the same Ig locus in said genome;
a plurality of D3-10 gene segments provided by at least 2 different D3-10 gene segments in *cis* at the same Ig locus in said genome;
a plurality of D3-16 gene segments provided by at least 2 different D3-16 gene segments in *cis* at the same Ig locus in said genome;
a plurality of D2-8 gene segments provided by at least 2 different D2-8 gene segments in *cis* at the same Ig locus in said genome;

Duration: 04.04.2014 17:47:10 - 04.04.2014 18:04:12. This page 13 of AMENDED SHEET 2014 17:51:25
Received at the EPO on Apr 04, 2014 18:04:12. Page 13 of 50

a plurality of D3-3 gene segments provided by at least 2 different D3-3 gene segments in *cis* at the same Ig locus in said genome;
a plurality of D4-23 gene segments provided by at least 2 different D4-23 gene segments in *cis* at the same Ig locus in said genome;
a plurality of D6-13 gene segments provided by at least 2 different D6-13 gene segments in *cis* at the same Ig locus in said genome;
a plurality of D3-9 gene segments provided by at least 2 different D3-9 gene segments in *cis* at the same Ig locus in said genome;
a plurality of D4-4 gene segments provided by at least 2 different D4-4 gene segments in *cis* at the same Ig locus in said genome; and
a plurality of D7-27 gene segments provided by at least 2 different D7-27 gene segments in *cis* at the same Ig locus in said genome;

optionally wherein the D gene segments are derived from the genome sequence of two or more different human individuals.

93. A non-human vertebrate or vertebrate cell according to claim 71, comprising a genome that comprises VH, D and JH gene repertoires comprising human gene segments, the D gene repertoire comprising one or more of
a plurality of D2-2 gene segments provided by at least 2 different D2-2 gene segments in *trans* in said genome;
a plurality of D2-21 gene segments provided by at least 2 different D2-21 gene segments in *trans* in said genome;
a plurality of D3-10 gene segments provided by at least 2 different D3-10 gene segments in *trans* in said genome;
a plurality of D3-16 gene segments provided by at least 2 different D3-16 gene segments in *trans* in said genome;
a plurality of D2-8 gene segments provided by at least 2 different D2-8 gene segments in *trans* in said genome;
a plurality of D3-3 gene segments provided by at least 2 different D3-3 gene segments in *trans* in said genome;
a plurality of D4-23 gene segments provided by at least 2 different D4-23 gene segments in *trans* in said genome;
a plurality of D6-13 gene segments provided by at least 2 different D6-13 gene segments in *trans* in said genome;
a plurality of D3-9 gene segments provided by at least 2 different D3-9 gene segments in *trans* in said genome;
a plurality of D4-4 gene segments provided by at least 2 different D4-4 gene segments in *trans* in said genome; and
a plurality of D7-27 gene segments provided by at least 2 different D7-27 gene segments in *trans* in said genome;

optionally wherein the D gene segments are derived from the genome sequence of two or more different human individuals.

94. A non-human vertebrate or vertebrate cell (optionally an ES cell or B-cell), according to claim 70, comprising a genome that comprises VH, D and JH gene repertoires comprising human gene segments, the D gene repertoire comprising one or more of
a plurality of D2-2 gene segments provided by at least 3 different D2-2 gene segments;
a plurality of D2-21 gene segments provided by at least 3 different D2-21 gene segments;
a plurality of D3-10 gene segments provided by at least 3 different D3-10 gene segments;
a plurality of D3-16 gene segments provided by at least 3 different D3-16 gene segments;
a plurality of D2-8 gene segments provided by at least 3 different D2-8 gene segments;
a plurality of D3-3 gene segments provided by at least 3 different D3-3 gene segments;

AMENDED SHEET 2014 17:51:47
Duration: 04.04.2014 17:47:10 - 04.04.2014 18:04:12. This page 14 of
Received at the EPO on Apr 04, 2014 18:04:12. Page 14 of 50

a plurality of D4-23 gene segments provided by at least 3 different D4-23 gene segments;
a plurality of D6-13 gene segments provided by at least 3 different D6-13 gene segments;
a plurality of D3-9 gene segments provided by at least 3 different D3-9 gene segments;
a plurality of D4-4 gene segments provided by at least 3 different D4-4 gene segments;
and a plurality of D7-27 gene segments provided by at least 3 different D7-27 gene segments;

optionally wherein the D gene segments are derived from the genome sequence of two or three different human individuals;

optionally wherein at least 2 or 3 of said different gene segments are provided in *cis* at the same Ig locus in said genome.

95. The vertebrate or cell of claim 92, 93 or 94, wherein the different human individuals are from different human populations.

96. The vertebrate or cell of any one of claims 92 to 95, wherein the individuals are not genetically related.

97. The vertebrate or cell of any one of claims 92 to 96, wherein at least one of the different D segments is a synthetic mutant of a human germline D gene segment.

98. A non-human vertebrate or vertebrate cell (optionally an ES cell or B-cell) according to claim 74, comprising a genome comprising human VH, D and JH gene repertoires, the D gene repertoire comprising of one or more of
a plurality of D2-2 gene segments provided by at least 2 different D2-2 gene; optionally in *cis* in said genome;
a plurality of D2-21 gene segments provided by at least 2 different D2-21 gene; optionally in *cis* in said genome;
a plurality of D3-10 gene segments provided by at least 2 different D3-10 gene; optionally in *cis* in said genome;
a plurality of D3-16 gene segments provided by at least 2 different D3-16 gene ; optionally in *cis* in said genome;
a plurality of D2-8 gene segments provided by at least 2 different D2-8 gene; optionally in *cis* in said genome;
a plurality of D3-3 gene segments provided by at least 2 different D3-3 gene; optionally in *cis* in said genome;
a plurality of D4-23 gene segments provided by at least 2 different D4-23 gene; optionally in *cis* in said genome;
a plurality of D6-13 gene segments provided by at least 2 different D6-13 gene; optionally in *cis* in said genome;
a plurality of D3-9 gene segments provided by at least 2 different D3-9 gene; optionally in *cis* in said genome;
a plurality of D4-4 gene segments provided by at least 2 different D4-4 gene; optionally in *cis* in said genome; and
a plurality of D7-27 gene segments provided by at least 2 different D7-27 gene; optionally in *cis* in said genome;

wherein the D gene segments are derived from the genome sequence of different human individuals that are not genetically related over at least 3 generations.

99. The vertebrate or cell of claim 98, wherein the human individuals are from different human populations.

AMENDED SHEET 2014 17:52:06
Duration: 04.04.2014 17:47:10 - 04.04.2014 18:04:12. This page 15 of
Received at the EPO on Apr 04, 2014 18:04:12. Page 15 of 50

100. The vertebrate, cell or population of any one of claims 70 to 99, wherein one or more of the D gene segments is a variant of a human germline D gene segment, wherein the variant gene segment encodes an amino acid sequence that differs by 1, 2 or 3 amino acids from the corresponding amino acid sequence encoded by the human germline D gene segment, provided in that said amino acid sequence encoded by the variant does not include a stop codon when said corresponding amino acid sequence does not include a stop codon.

101. The vertebrate, cell or population of claim 100, wherein said corresponding amino acid sequence encoded by the human germline D gene segment is a hydrophilic or hydrophobic sequence (according to J Mol Biol. 1997 Jul 25;270(4):587-97; Corbett SJ *et al*; Table 2).

102. The vertebrate, cell or population of claim 100 or 101, comprising said variant and said germline human D gene segments; optionally wherein the variant and germline human D gene segments are *cis* on the same chromosome.

103. The vertebrate, cell or population of any one of claims 100 to 102, wherein germline human D gene segment is a D2, D3, D5 or D6 family gene segment; optionally a D2-2, D2-15, D3-3, D3-9, D3-10, D3-22, D5-5, D6-18, D6-6, D6-13, D6-19 gene segment.

104. The vertebrate, cell or population of any one of claims 70 to 103, comprising a plurality of D2-2 gene segments, wherein the plurality comprises D2-2 gene segments that vary from each other at one or more nucleotide positions corresponding to positions

106,382,687 and
106,382,711
on human chromosome 14.

105. The vertebrate, cell or population of claim 104, wherein the plurality comprises a human D2- 2 gene segment comprising a thymine at a position corresponding to position 106,382,687 on human chromosome 14; and optionally no further mutation from the sequence of D2-2ref.

106. The vertebrate, cell or population of claim 104 or 105, wherein the plurality comprises a human D2-2 gene segment comprising a cytosine at a position corresponding to position 106,382,687 on human chromosome 14; and optionally no further mutation from the sequence of D2-2a.

107. The vertebrate, cell or population of any one of claims 104 to 106, wherein the plurality comprises a human D2-2 gene segment comprising an adenine at a position corresponding to position 106,382,711 on human chromosome 14; and optionally no further mutation from the sequence of D2-2b.

108. The vertebrate, cell or population of any one of claims 104 to 107, wherein the plurality comprises a human D2-2 gene segment comprising an thymine at a position corresponding to position 106,382,711 on human chromosome 14; and optionally no further mutation from the sequence of D2-2ref.

109. The vertebrate, cell or population of any one of claims 70 to 108, comprising a plurality of D7-27 gene segments, wherein the plurality comprises D7-27 gene segments that vary from each other at a nucleotide position corresponding to position 106,331,767 on human chromosome 14.

AMENDED SHEET 2014 17:52:26
Duration: 04.04.2014 17:47:10 - 04.04.2014 18:04:12. This page 16 of
Received at the EPO on Apr 04, 2014 18:04:12. Page 16 of 50

110. The vertebrate, cell or population of claim 109, wherein the plurality comprises a human D7- 27 gene segment comprising a cytosine at a position corresponding to position 106,331,767 on human chromosome 14; and optionally no further mutation from the sequence of D7-27ref.

111. The vertebrate, cell or population of claim 109 or 110, wherein the plurality comprises a human D7-27 gene segment comprising a guanine at a position corresponding to position 106,331,767 on human chromosome 14; and optionally no further mutation from the sequence of D7-27a.

112. The vertebrate, cell or population of any one of claims 70 to 111, comprising a plurality of D4-23 gene segments, wherein the plurality comprises D4-23 gene segments that vary from each other at a nucleotide position corresponding to position 106,350,740 on human chromosome 14.

113. The vertebrate, cell or population of claim 112, wherein the plurality comprises a human D4-23 gene segment comprising an adenine at a position corresponding to position 106,350,740 on human chromosome 14; and optionally no further mutation from the sequence of D4-23ref.

114. The vertebrate, cell or population of claim 112 or 113, wherein the plurality comprises a human D4-23 gene segment comprising an guanine at a position corresponding to position 106,350,740 on human chromosome 14; and optionally no further mutation from the sequence of D4-23a.

115. The vertebrate, cell or population of any one of claims 70 to 113, comprising a plurality of D2-21 gene segments, wherein the plurality comprises D2-21 gene segments that vary from each other at a nucleotide position corresponding to position 106,354,418 on human chromosome 14.

116. The vertebrate, cell or population of claim 115, wherein the plurality comprises a human D2-21 gene segment comprising an adenine at a position corresponding to position 106,354,418 on human chromosome 14; and optionally no further mutation from the sequence of D2-21ref.

117. The vertebrate, cell or population of claim 115 or 116, wherein the plurality comprises a human D2-21 gene segment comprising a guanine at a position corresponding to position 106,354,418 on human chromosome 14; and optionally no further mutation from the sequence of D2-21a.

118. The vertebrate, cell or population of any one of claims 70 to 117, comprising a plurality of D3-16 gene segments, wherein the plurality comprises D3-16 gene segments that vary from each other at a nucleotide position corresponding to position 106,354,418 on human chromosome 14.

119. The vertebrate, cell or population of claim 118, wherein the plurality comprises a human D3-16 gene segment comprising a thymine at a position corresponding to position 106,361,515 on human chromosome 14; and optionally no further mutation from the sequence of D3-16ref.

120. The vertebrate, cell or population of claim 118 or 119, wherein the plurality comprises a human D3-16 gene segment comprising a cytosine at a position corresponding to position 106,361,515 on human chromosome 14; and optionally no further mutation from the sequence of D3-16a.

AMENDED SHEET 2014 17:52:47
Duration: 04.04.2014 17:47:10 - 04.04.2014 18:04:12. This page 17 of
Received at the EPO on Apr 04, 2014 18:04:12. Page 17 of 50

121. The vertebrate, cell or population of any one of claims 70 to 120, comprising a plurality of D6-13 gene segments, wherein the plurality comprises D6-13 gene segments that vary from each other at a nucleotide position corresponding to position 106,367,013 on human chromosome 14.

122. The vertebrate, cell or population of claim 121, wherein the plurality comprises a human D6-13 gene segment comprising a thymine at a position corresponding to position 106,367,013 on human chromosome 14; and optionally no further mutation from the sequence of D6-13ref.

123. The vertebrate, cell or population of claim 121 or 122, wherein the plurality comprises a human D6-13 gene segment comprising a cytosine at a position corresponding to position 106,367,013 on human chromosome 14; and optionally no further mutation from the sequence of D6-13a.

124. The vertebrate, cell or population of any one of claims 70 to 123, comprising a plurality of D3-10 gene segments, wherein the plurality comprises D3-10 gene segments that vary from each other at one or more nucleotide positions corresponding to positions
106,370,370 and
106,370,371
on human chromosome 14.

125. The vertebrate, cell or population of claim 124, wherein the plurality comprises a human D3-10 gene segment comprising a thymine at a position corresponding to position 106,370,370 on human chromosome 14; and optionally no further mutation from the sequence of D3-10ref.

126. The vertebrate, cell or population of claim 124 or 125, wherein the plurality comprises a human D3-10 gene segment comprising a cytosine at a position corresponding to position 106,370,370 on human chromosome 14; and optionally no further mutation from the sequence of D3-10a.

127. The vertebrate, cell or population of claim 124, 125 or 126 wherein the plurality comprises a human D3-10 gene segment comprising an adenine at a position corresponding to position 106,370,371 on human chromosome 14; and optionally no further mutation from the sequence of D3-10ref.

128. The vertebrate, cell or population of any one of claims 124 to 127, wherein the plurality comprises a human D3-10 gene segment comprising a guanine at a position corresponding to position 106,370,371 on human chromosome 14; and optionally no further mutation from the sequence of D3-10b.

129. The vertebrate, cell or population of any one of claims 70 to 128, comprising a plurality of D3-9 gene segments, wherein the plurality comprises D3-9 gene segments that vary from each other at a nucleotide position corresponding to position 106,370,567 on human chromosome 14.

130. The vertebrate, cell or population of claim 129, wherein the plurality comprises a human D3-9 gene segment comprising an adenine at a position corresponding to position 106,370,567 on human chromosome 14; and optionally no further mutation from the sequence of D3-9ref.

Duration: 04.04.2014 17:47:10 - 04.04.2014 18:04:12. This page 18 of AMENDED SHEET 2014 17:53:06
Received at the EPO on Apr 04, 2014 18:04:12. Page 18 of 50

131. The vertebrate, cell or population of claim 129 or 130, wherein the plurality comprises a human D3-9 gene segment comprising a thymine at a position corresponding to position 106,370,567 on human chromosome 14; and optionally no further mutation from the sequence of D3-9a.

132. The vertebrate, cell or population of any one of claims 70 to 131, comprising a plurality of D2-8 gene segments, wherein the plurality comprises D2-8 gene segments that vary from each other at one or more nucleotide positions corresponding to positions
106,373,085;
106,373,086 and
106,373,089
on human chromosome 14.

133. The vertebrate, cell or population of claim 132, wherein the plurality comprises a human D2-8 gene segment comprising a cytosine at a position corresponding to position 106,373,085 on human chromosome 14.

134. The vertebrate, cell or population of claim 132 or 133, wherein the plurality comprises a human D2-8 gene segment comprising a thymine at a position corresponding to position 106,373,085 on human chromosome 14; and optionally no further mutation from the sequence of D2-8b.

135. The vertebrate, cell or population of claim 132, 133 or 134 wherein the plurality comprises a human D2-8 gene segment comprising a cytosine at a position corresponding to position 106,373,086 on human chromosome 14; and optionally no further mutation from the sequence of D2-8ref.

136. The vertebrate, cell or population of any one of claims 132 to 135, wherein the plurality comprises a human D2-8 gene segment comprising a thymine at a position corresponding to position 106,373,086 on human chromosome 14; and optionally no further mutation from the sequence of D2-8ref.

137. The vertebrate, cell or population of any one of claims 70 to 136, comprising a plurality of D4-4 gene segments, wherein the plurality comprises D4-4 gene segments that vary from each other at one or more nucleotide positions corresponding to positions
106,379,086; and
106,379,089
on human chromosome 14.

138. The vertebrate, cell or population of claim 137, wherein the plurality comprises a D4-4 gene segment comprising a cytosine at a position corresponding to position 106,379,086 on human chromosome 14; and optionally no further mutation from the sequence of D4-4ref.

139. The vertebrate, cell or population of claim 137 or 138, wherein the plurality comprises a human D4-4 gene segment comprising a thymine at a position corresponding to position 106,379,086 on human chromosome 14; and optionally no further mutation from the sequence of D4-4a.

140. The vertebrate, cell or population of claim 137, 138 or 139 wherein the plurality comprises a human D4-4 gene segment comprising a cytosine at a position corresponding to position 106,379,089 on human chromosome 14; and optionally no further mutation from the sequence of D4-4ref or a cytosine at a position corresponding to position 106,379,086 on human chromosome 14.

Duration: 04.04.2014 17:47:10 - 04.04.2014 18:04:12. This page 19 of AMENDED SHEET 2014 17:53:26
Received at the EPO on Apr 04, 2014 18:04:12. Page 19 of 50

141. The vertebrate, cell or population of any one of claims 137 to 140, wherein the plurality comprises a human D4-4 gene segment comprising a thymine at a position corresponding to position 106,373,089 on human chromosome 14; and optionally no further mutation from the sequence of D4-4a.

142. The vertebrate, cell or population of any one of claims 70 to 141, comprising a plurality of D3-3 gene segments, wherein the plurality comprises D3-3 gene segments that vary from each other at one or more nucleotide positions corresponding to positions
106,380,241; and
106,380,246
on human chromosome 14.

143. The vertebrate, cell or population of claim 142, wherein the plurality comprises a D3-3 gene segment comprising a thymine at a position corresponding to position 106,380,241 on human chromosome 14; and optionally no further mutation from the sequence of D3-3ref.

144. The vertebrate, cell or population of claim 142 or 143, wherein the plurality comprises a human D3-3 gene segment comprising a cytosine at a position corresponding to position 106,380,241 on human chromosome 14; and optionally no further mutation from the sequence of D3-3a.

145. The vertebrate, cell or population of claim 142, 143 or 144 wherein the plurality comprises a human D3-3 gene segment comprising an adenine at a position corresponding to position 106,380,246 on human chromosome 14; and optionally no further mutation from the sequence of D3-3ref.

146. The vertebrate, cell or population of any one of claims 142 to 145, wherein the plurality comprises a human D3-3 gene segment comprising a thymine at a position corresponding to position 106,380,246 on human chromosome 14; and optionally no further mutation from the sequence of D3-3a.

147. A non-human vertebrate (e.g., a mouse or rat) or a non-human vertebrate cell (e.g., an ES cell or a B-cell) according to claim 34, having a genome comprising at least 3 human JH gene segments of the same type (JH1, JH2, JH3, JH4, JH5 or JH6), wherein at least two of the human JH gene segments are variants that are not identical to each other.

148. A non-human vertebrate (e.g., a mouse or rat) or a non-human vertebrate cell (e.g., an ES cell or a B-cell) according to claim 35, having a genome comprising at least 2 different non-endogenous JH gene segments of the same type (JH1, JH2, JH3, JH4, JH5 or JH6) *cis* at the same Ig locus.

149. A non-human vertebrate (e.g., a mouse or rat) or a non-human vertebrate cell (e.g., an ES cell or a B-cell) according to claim 36, having a genome comprising at least 2 different human JH gene segments of the same type (JH1, JH2, JH3, JH4, JH5 or JH6) trans at the same Ig locus; and optionally a third human JH gene segments of the same type, wherein the third JH is *cis* with one of said 2 different JH gene segments.

150. A population of non-human vertebrates (e.g., mice or rats) comprising a repertoire of human JH gene segments according to claim 37, wherein the plurality comprises at least 2 different human JH gene segments of the same type (JH1, JH2, JH3, JH4, JH5 or JH6), a first of said different JH gene segments is provided in the genome of a first vertebrate of the population, and a second of said different JH gene segments being provided in the

Duration: 04.04.2014 17:47:10 - 04.04.2014 18:04:12. This page 20 of AMENDED SHEET 2014 17:53:47
Received at the EPO on Apr 04, 2014 18:04:12. Page 20 of 50

genome of a second vertebrate of the population, wherein the genome of the first vertebrate does not comprise the second JH gene segment.

151. A non-human vertebrate (e.g., a mouse or rat) or a non-human vertebrate cell (e.g., an ES cell or a B-cell) according to claim 38, having a genome comprising at least 2 different non- endogenous JH gene segments of the same type (JH1, JH2, JH3, JH4, JH5 or JH6), wherein the JH gene segments are derived from the genome sequence of different human individuals that are not genetically related over at least 3 generations.

152. A method of enhancing the human immunoglobulin gene diversity of a non-human vertebrate (e.g., a mouse or rat) according to claim 39, the method comprising providing the vertebrate with a genome comprising at least 3 human JH gene segments of the same type (JH1, JH2, JH3, JH4, JH5 or JH6), wherein at least two of the human JH gene segments are variants that are not identical to each other.

153. A method of enhancing the immunoglobulin gene diversity of a non-human vertebrate (e.g., a mouse or rat) according to claim 40, the method comprising providing the vertebrate with a genome comprising at least 2 different non-endogenous JH gene segments of the same type (JH1, JH2, JH3, JH4, JH5 or JH6) *cis* at the same Ig locus.

154. A method of enhancing the immunoglobulin gene diversity of a non-human vertebrate (e.g., a mouse or rat) according to claim 41, the method comprising providing the vertebrate with a genome comprising at least 2 different human JH gene segments of the same type (JH1, JH2, JH3, JH4, JH5 or JH6) trans at the same Ig locus; and optionally a third human JH gene segments of the same type, wherein the third JH is *cis* with one of said 2 different JH gene segments.

155. A method of providing an enhanced human immunoglobulin JH gene segment repertoire according to claim 42, the method comprising providing a population of non-human vertebrates (e.g., a mouse or rat) comprising a repertoire of human JH gene segments, wherein the method comprises providing at least 2 different human JH gene segments of the same type (JH1, JH2, JH3, JH4, JH5 or JH6), wherein a first of said different JH gene segments is provided in the genome of a first vertebrate of the population, and a second of said different JH gene segments is provided in the genome of a second vertebrate of the population, wherein the genome of the first vertebrate does not comprise the second JH gene segment.

156. A method of enhancing the human immunoglobulin gene diversity of a non-human vertebrate (e.g., a mouse or rat) according to claim 43, the method comprising providing the vertebrate with a genome comprising at least 2 different non-endogenous JH gene segments of the same type (JH1, JH2, JH3, JH4, JH5 or JH6), wherein the JH gene segments are derived from the genome sequence of different human individuals that are not genetically related over at least 3 generations.

157. The vertebrate or cell of claim 147, 149 or 151, or the method of claim 152, 154, 155 or 156, wherein at least 2 or 3 of said different gene segments are provided *cis* at the same Ig locus in said genome.

158. The vertebrate or cell of claim 147, 148 or 149, or the method of claim 152, 153, 154 or 155, wherein the JH gene segments are derived from the genome sequence of different human individuals that are not genetically related over at least 3 generations.

159. The vertebrate or cell of claim 147, 148 or 149, or the method of claim 152, 153, 154 or 155, wherein the JH gene segments are derived from the genome sequence of two or

AMENDED SHEET 2014 17:54:11
Duration: 04.04.2014 17:47:10 - 04.04.2014 18:04:12. This page 21 of
Received at the EPO on Apr 04, 2014 18:04:12. Page 21 of 50

more different human individuals; optionally wherein the different human individuals are from different human populations.

160. The vertebrate, cell or method of claim 159, wherein the individuals are not genetically related.

161. The vertebrate, cell or method of any one of claims 147 to 160, wherein at least one of the different JH segments is a synthetic mutant of a human germline JH gene segment.

162. A method of enhancing the human immunoglobulin gene diversity of a non-human vertebrate (e.g., a mouse or rat), the method comprising providing the vertebrate with a genome comprising at least 2 human JH gene segments of the same type (JH1, JH2, JH3, JH4, JH5 or JH6), wherein the JH gene segments are derived from the genome sequence of different human individuals that are not genetically related over at least 3 generations; optionally wherein at least 2 or 3 of said different gene segments are provided at the same IgH locus in said genome.

163. The vertebrate or cell of any one of claims 147 to 149 and 151, wherein the genome comprises a substantially complete functional repertoire of human JH gene segment types supplemented with one, two or more human JH gene segments, wherein said substantially complete functional repertoire and the supplementary JH gene segments are not found together in the germline genome of a human individual.

164. The population of claim 150, wherein the population comprises a substantially complete functional repertoire of human JH gene segment types supplemented with one, two or more human JH gene segments, wherein said substantially complete functional repertoire and the supplementary JH gene segments are not found together in the germline genome of a human individual.

165. A non-human vertebrate (e.g., a mouse or rat) or a non-human cell (e.g., an ES cell or a B-cell) having a genome comprising a substantially complete functional repertoire of human JH gene segment types supplemented with one, two or more human JH gene segments, wherein said substantially complete functional repertoire and the supplementary JH gene segments are not found together in the germline genome of a human individual.

166. The vertebrate of claim 165, wherein at least one of said JH gene segments is SEQ ID NO: 1, 2, 3 or 4.

167. The vertebrate or population of claim 166, wherein at least one of said JH gene segments is SEQ ID NO: 1 and at least one, two or more of said supplementary JH gene segments is a variant according to any one of claims 177 to 195.

168. The vertebrate or population of claim 166 or 167, wherein at least one of said JH gene segments is SEQ ID NO: 2 and at least one, two or more of said supplementary JH gene segments is a variant according to any one of claims 197 to 208.

169. The vertebrate or population of claim 166, 167 or 168, wherein at least one of said JH gene segments is SEQ ID NO: 2 and at least one, two or more of said supplementary JH gene segments is a variant according to any one of claims 211 to 216.

170. A non-human vertebrate or vertebrate cell according to claim 148, comprising a genome that comprises VH, D and JH gene repertoires comprising human gene segments, the JH gene repertoire comprising

Duration: 04.04.2014 17:47:10 - 04.04.2014 18:04:12. This page 22 of AMENDED SHEET 2014 17:54:32
Received at the EPO on Apr 04, 2014 18:04:12. Page 22 of 50

a plurality of JH1 gene segments provided by at least 2 different JH1 gene segments in *cis* at the same Ig locus in said genome;
a plurality of JH2 gene segments provided by at least 2 different JH2 gene segments in *cis* at the same Ig locus in said genome;
a plurality of JH3 gene segments provided by at least 2 different JH3 gene segments in *cis* at the same Ig locus in said genome;
a plurality of JH4 gene segments provided by at least 2 different JH4 gene segments in *cis* at the same Ig locus in said genome;
a plurality of JH5 gene segments provided by at least 2 different JH5 gene segments in *cis* at the same Ig locus in said genome; or
a plurality of JH6 gene segments provided by at least 2 different JH6 gene segments in *cis* at the same Ig locus in said genome;

optionally wherein the JH gene segments are derived from the genome sequence of two or more different human individuals.

171. A non-human vertebrate or vertebrate cell (optionally an ES cell or B-cell), according to claim 147, comprising a genome that comprises VH, D and JH gene repertoires comprising human gene segments, the JH gene repertoire comprising

a plurality of JH1 gene segments provided by at least 3 different JH1 gene segments; a plurality of JH2 gene segments provided by at least 3 different JH2 gene segments; a plurality of JH3 gene segments provided by at least 3 different JH3 gene segments; a plurality of JH4 gene segments provided by at least 3 different JH4 gene segments; a plurality of JH5 gene segments provided by at least 3 different JH5 gene segments; or a plurality of JH6 gene segments provided by at least 3 different JH6 gene segments;

optionally wherein the JH gene segments are derived from the genome sequence of two or three different human individuals;

optionally wherein at least 2 or 3 of said different gene segments are provided in *cis* at the same Ig locus in said genome.

172. The vertebrate or cell of claim 170 or 171, wherein the different human individuals are from different human populations.

173. The vertebrate or cell of any one of claims 170 to 172, wherein the individuals are not genetically related.

174. The vertebrate or cell of any one of claims 170 to 173, wherein at least one of the different JH segments is a synthetic mutant of a human germline JH gene segment.

175. A non-human vertebrate or vertebrate cell (optionally an ES cell or B-cell) according to claim 151, comprising a genome comprising human VH, D and JH gene repertoires, the JH gene repertoire comprising

a plurality of JH1 gene segments provided by at least 2 different human JH1 gene segments, optionally in *cis* at the same Ig locus in said genome;
a plurality of JH2 gene segments provided by at least 2 different human JH2 gene segments, optionally in *cis* at the same Ig locus in said genome;
a plurality of JH3 gene segments provided by at least 2 different human JH3 gene segments, optionally in *cis* at the same Ig locus in said genome;

Duration: 04.04.2014 17:47:10 - 04.04.2014 18:04:12. This page 23 of AMENDED SHEET 2014 17:54:52
Received at the EPO on Apr 04, 2014 18:04:12. Page 23 of 50

a plurality of JH4 gene segments provided by at least 2 different human JH4 gene segments, optionally in *cis* at the same Ig locus in said genome;
a plurality of JH5 gene segments provided by at least 2 different human JH5 gene segments, optionally in *cis* at the same Ig locus in said genome; or
a plurality of JH6 gene segments provided by at least 2 different human JH6 gene segments, optionally in *cis* at the same Ig locus in said genome;

wherein the JH gene segments are derived from the genome sequence of different human individuals that are not genetically related over at least 3 generations.

176. The vertebrate or cell of claim 175, wherein the human individuals are from different human populations.

177. The vertebrate, cell or population of any one of claims 147 to 151, 157 to 161 and 163 to 176, comprising a plurality of JH5 gene segments, wherein the plurality comprises a human JH5 gene variant of SEQ ID NO: 1, wherein the variant comprises a nucleotide mutation at one or more positions corresponding to positions

106,330,024
106,330,027
106,330,032
106,330,041
106,330,044
106,330,045
106,330,062
106,330,063
106,330,065
106,330,066
106,330,067
106,330,068 and
106,330,071

on human chromosome 14.

178. The vertebrate, cell or population of claim 177, wherein the plurality comprises a human JH5 gene variant of SEQ ID NO: 1, wherein the variant comprises a guanine at a position corresponding to position 106,330,067 on human chromosome 14; and optionally no further mutation from the sequence of SEQ ID NO: 1.

179. The vertebrate, cell or population of claim 178, wherein the variant comprises additionally a mutation at a position corresponding to (i) position 106,330,071 on human chromosome 14 (optionally the additional mutation being a guanine); (ii) position 106,330,066 on human chromosome 14 (optionally the additional mutation being a guanine); and/or (iii) position 106,330,068 on human chromosome 14 (optionally the additional mutation being a thymine).

180. The vertebrate, cell or population of claim 177, 178 or 179, wherein the plurality comprises a human JH5 gene variant of SEQ ID NO: 1, wherein the variant comprises a guanine at a position corresponding to position 106,330,071 on human chromosome 14; and optionally no further mutation from the sequence of SEQ ID NO: 1.

181. The vertebrate, cell or population of claim 180, wherein the variant comprises additionally a mutation at a position corresponding to (i) position 106,330,063 on human chromosome

Duration: 04.04.2014 17:47:10 - 04.04.2014 18:04:12. This page 24 of AMENDED SHEET 2014 17:55:09
Received at the EPO on Apr 04, 2014 18:04:12. Page 24 of 50

14 (optionally the additional mutation being an adenine); and/or (ii) position 106,330,067 on human chromosome 14 (optionally the additional mutation being a guanine).

182. The vertebrate, cell or population of claim 177 to 181, wherein the plurality comprises a human JH5 gene variant of SEQ ID NO: 1, wherein the variant comprises a cytosine at a position corresponding to position 106,330,045 on human chromosome 14; and optionally no further mutation from the sequence of SEQ ID NO: 1.

183. The vertebrate, cell or population of claim 177 to 182, wherein the plurality comprises a human JH5 gene variant of SEQ ID NO: 1, wherein the variant comprises an adenine at a position corresponding to position 106,330,044 on human chromosome 14; and optionally no further mutation from the sequence of SEQ ID NO: 1.

184. The vertebrate, cell or population of claim 183, wherein the variant comprises additionally a mutation at a position corresponding to (i) position 106,330,066 on human chromosome 14 (optionally the additional mutation being a guanine); and/or (ii) position 106,330,068 on human chromosome 14 (optionally the additional mutation being a thymine).

185. The vertebrate, cell or population of claim 177 to 184, wherein the plurality comprises a human JH5 gene variant of SEQ ID NO: 1, wherein the variant comprises a guanine at a position corresponding to position 106,330,066 on human chromosome 14; and optionally no further mutation from the sequence of SEQ ID NO: 1.

186. The vertebrate, cell or population of claim 185, wherein the variant comprises additionally a mutation at a position corresponding to (i) position 106,330,067 on human chromosome 14 (optionally the additional mutation being a guanine); and/or (ii) position 106,330,068 on human chromosome 14 (optionally the additional mutation being a thymine).

187. The vertebrate, cell or population of claim 177 to 184, wherein the plurality comprises a human JH5 gene variant of SEQ ID NO: 1, wherein the variant comprises a thymine at a position corresponding to position 106,330,068 on human chromosome 14; and optionally no further mutation from the sequence of SEQ ID NO: 1.

188. The vertebrate, cell or population of claim 187, wherein the variant comprises additionally a mutation at a position corresponding to (i) position 106,330,067 on human chromosome 14 (optionally the additional mutation being a guanine); and/or (ii) position 106,330,066 on human chromosome 14 (optionally the additional mutation being a guanine).

189. The vertebrate, cell or population of claim 177 to 188, wherein the plurality comprises a human JH5 gene variant of SEQ ID NO: 1, wherein the variant comprises a cytosine at a position corresponding to position 106,330,027 on human chromosome 14; and optionally no further mutation from the sequence of SEQ ID NO: 1.

190. The vertebrate, cell or population of claim 177 to 189, wherein the plurality comprises a human JH5 gene variant of SEQ ID NO: 1, wherein the variant comprises an adenine at a position corresponding to position 106,330,024 on human chromosome 14; and optionally no further mutation from the sequence of SEQ ID NO: 1.

191. The vertebrate, cell or population of claim 177 to 190, wherein the plurality comprises a human JH5 gene variant of SEQ ID NO: 1, wherein the variant comprises a thymine at a position corresponding to position 106,330,032 on human chromosome 14; and optionally no further mutation from the sequence of SEQ ID NO: 1.

Duration: 04.04.2014 17:47:10 - 04.04.2014 18:04:12. This page 25 of AMENDED SHEET 2014 17:55:32
Received at the EPO on Apr 04, 2014 18:04:12. Page 25 of 50

192. The vertebrate, cell or population of claim 177 to 191, wherein the plurality comprises a human JH5 gene variant of SEQ ID NO: 1, wherein the variant comprises a thymine at a position corresponding to position 106,330,041 on human chromosome 14; and optionally no further mutation from the sequence of SEQ ID NO: 1.

193. The vertebrate, cell or population of claim 177 to 192, wherein the plurality comprises a human JH5 gene variant of SEQ ID NO: 1, wherein the variant comprises an adenine or thymine at a position corresponding to position 106,330,063 on human chromosome 14; and optionally no further mutation from the sequence of SEQ ID NO: 1.

194. The vertebrate, cell or population of claim 193, wherein the variant comprises additionally a mutation at a position corresponding to position 106,330,071 on human chromosome 14 (optionally the additional mutation being a guanine).

195. The vertebrate, cell or population of claim 177 to 194, wherein the plurality comprises a human JH5 gene variant of SEQ ID NO: 1, wherein the variant comprises a cytosine at a position corresponding to position 106,330,062 on human chromosome 14; and optionally no further mutation from the sequence of SEQ ID NO: 1.

196. The vertebrate, cell or population of claim 177 to 195, wherein the genome comprises SEQ ID NO:1; optionally in *cis* at the same Ig locus as one, two or more of the variants.

197. The vertebrate, cell or population of any one of claims 147 to 151, 157 to 161 and 96 to 130, comprising a plurality of JH6 gene segments, wherein the plurality comprises a human JH6 gene variant of SEQ ID NO: 2, wherein the variant comprises a nucleotide mutation at one or more positions corresponding to positions

106,329,411
106,329,413
106,329,414
106,329,417
106,329,419
106,329,426
106,329,434
106,329,435, and
106,329,468

on human chromosome 14.

198. The vertebrate, cell or population of claim 197, comprising a plurality of JH6 gene segments, wherein the plurality comprises a human JH6 gene variant of SEQ ID NO: 2, wherein the variant comprises a guanine at a position corresponding to position 106,329,435 on human chromosome 14; and optionally no further mutation from the sequence of SEQ ID NO: 2.

199. The vertebrate, cell or population of claim 198, wherein the variant comprises additionally a mutation at a position corresponding to (i) position 106,329,468 on human chromosome 14 (optionally the additional mutation being a guanine); (ii) position 106,329,419 on human chromosome 14 (optionally the additional mutation being an adenine); (iii) position 106,329,434 on human chromosome 14 (optionally the additional mutation being a cytosine) and/or position 106,329,414 on human chromosome 14 (optionally the additional mutation being a guanine); (iv) position 106,329,426 on human chromosome 14 (optionally the additional mutation being an adenine); (v) position 106,329,413 on human chromosome 14 (optionally the additional mutation being an adenine); (vi)

Duration: 04.04.2014 17:47:10 - 04.04.2014 18:04:12. This page 26 of AMENDED SHEET 2014 17:55:52
Received at the EPO on Apr 04, 2014 18:04:12. Page 26 of 50

position 106,329,417 on human chromosome 14 (optionally the additional mutation being a thymine); (vii) position 106,329,411 on human chromosome 14 (optionally the additional mutation being a thymine); (viii) position 106,329,451 on human chromosome 14 (optionally the additional mutation being an adenine); (ix) position 106,329,452 on human chromosome 14 (optionally the additional mutation being a cytosine); and/or (x) position 106,329,453 on human chromosome 14 (optionally the additional mutation being a cytosine).

200. The vertebrate, cell or population of claim 199, wherein the variant comprises additionally mutations at positions corresponding to position 106,329,451 on human chromosome 14, the additional mutation being an adenine; position 106,329,452 on human chromosome 14, the additional mutation being a cytosine; and position 106,329,453 on human chromosome 14, the additional mutation being a cytosine.

201. The vertebrate, cell or population of any one of claims 147 to 151, 157 to 161 and 163 to 200, comprising a plurality of JH6 gene segments, wherein the plurality comprises a human JH6 gene variant of SEQ ID NO: 2, wherein the variant comprises a guanine at a position corresponding to position 106,329,468 on human chromosome 14; and optionally no further mutation from the sequence of SEQ ID NO: 2.

202. The vertebrate, cell or population of claim 201, wherein the variant comprises additionally a mutation at a position corresponding to position 106,329,435 on human chromosome 14 (optionally the additional mutation being a guanine).

203. The vertebrate, cell or population of any one of claims 147 to 151, 157 to 161 and 163 to 202, comprising a plurality of JH6 gene segments, wherein the plurality comprises a human JH6 gene variant of SEQ ID NO: 2, wherein the variant comprises a thymine at a position corresponding to position 106,329,417 on human chromosome 14; and optionally no further mutation from the sequence of SEQ ID NO: 2.

204. The vertebrate, cell or population of claim 203, wherein the variant comprises additionally a mutation at a position corresponding to position 106,329,435 on human chromosome 14 (optionally the additional mutation being a guanine).

205. The vertebrate, cell or population of any one of claims 147 to 151, 157 to 161 and 163 to 204, comprising a plurality of JH6 gene segments, wherein the plurality comprises a human JH6 gene variant of SEQ ID NO: 2, wherein the variant comprises a cytosine at a position corresponding to position 106,329,434 on human chromosome 14; and optionally no further mutation from the sequence of SEQ ID NO: 2.

206. The vertebrate, cell or population of claim 205, wherein the variant comprises additionally a mutation at a position corresponding to (i) position 106,329,414 on human chromosome 14 (optionally the additional mutation being a guanine); and/or (ii) position 106,329,435 on human chromosome 14 (optionally the additional mutation being a guanine).

207. The vertebrate, cell or population of any one of claims 147 to 151, 157 to 161 and 163 to 206, comprising a plurality of JH6 gene segments, wherein the plurality comprises a human JH6 gene variant of SEQ ID NO: 2, wherein the variant comprises a thymine at a position corresponding to position 106,329,411 on human chromosome 14; and optionally no further mutation from the sequence of SEQ ID NO: 2.

208. The vertebrate, cell or population of claim 207, wherein the variant comprises additionally a mutation at a position corresponding to position 106,329,435 on human chromosome 14 (optionally the additional mutation being a guanine).

AMENDED SHEET 2014 17:56:16
Duration: 04.04.2014 17:47:10 - 04.04.2014 18:04:12. This page 27 of
Received at the EPO on Apr 04, 2014 18:04:12. Page 27 of 50

209. The vertebrate, cell or population of any one of claims 147 to 151, 157 to 161 and 163 to 208, comprising a plurality of JH6 gene segments, wherein the plurality comprises a human JH6 gene variant that is an antisense sequence of the variant of any one of claims 107 to 118.

210. The vertebrate, cell or population of any one of claims 197 to 209, wherein the genome comprises SEQ ID NO:2; optionally *cis* at the same Ig locus as one, two or more of the JH6 variants.

211. The vertebrate, cell or population of any one of claims 147 to 151, 157 to 161 and 163 to 210, comprising a plurality of JH2 gene segments, wherein the plurality comprises a human JH2 gene variant of SEQ ID NO: 3, wherein the variant comprises a nucleotide mutation at one or more positions corresponding to positions

106,331,455
106,331,453, and
106,331,409

on human chromosome 14.

212. The vertebrate, cell or population of claim 211, comprising said plurality of JH2 gene segments, wherein the plurality comprises a human JH2 gene variant of SEQ ID NO: 3, wherein the variant comprises a guanine at a position corresponding to position 106,331,455 on human chromosome 14; and optionally no further mutation from the sequence of SEQ ID NO: 3.

213. The vertebrate, cell or population of claim 212, wherein the variant comprises additionally a mutation at a position corresponding to (i) position 106,331,453 on human chromosome 14 (optionally the additional mutation being an adenine); and/or (ii) position 106,331,409 on human chromosome 14 (optionally the additional mutation being an adenine); (iii) position 106,329,434 on human chromosome 14 (optionally the additional mutation being an adenine).

214. The vertebrate, cell or population of any one of claims 147 to 151, 157 to 161 and 163 to 213, comprising a plurality of JH2 gene segments, wherein the plurality comprises a human JH2 gene variant of SEQ ID NO: 3, wherein the variant comprises an adenine at a position corresponding to position 106,331,453 on human chromosome 14; and optionally no further mutation from the sequence of SEQ ID NO: 3.

215. The vertebrate, cell or population of claim 214, wherein the variant comprises additionally a mutation at a position corresponding to position 106,331,409 on human chromosome 14 (optionally the additional mutation being an adenine).

216. The vertebrate, cell or population of any one of claims 147 to 151, 157 to 161 and 163 to 215, comprising a plurality of JH2 gene segments, wherein the plurality comprises a human JH2 gene variant of SEQ ID NO: 3, wherein the variant comprises an adenine at a position corresponding to position 106,331,409 on human chromosome 14; and optionally no further mutation from the sequence of SEQ ID NO: 3.

217. The vertebrate, cell or population of any one of claims 147 to 151, 157 to 161 and 163 to 216, comprising a plurality of JH2 gene segments, wherein the plurality comprises a human JH2 gene variant that is an antisense sequence of the variant of any one of claims 187 to 192.

Duration: 04.04.2014 17:47:10 - 04.04.2014 18:04:12. This page 28 of AMENDED SHEET 2014 17:56:36
Received at the EPO on Apr 04, 2014 18:04:12. Page 28 of 50

218. The vertebrate, cell or population of any one of claims 211 to 217, wherein the genome comprises SEQ ID NO:3; optionally *cis* at the same Ig locus as one, two or more of the JH2 variants.

219. The vertebrate, cell or population of any one of claims 147 to 151, 157 to 161 and 163 to 218, wherein the genome comprises two or more different JH gene segments selected from SEQ ID NOs: 1 to 3 and variants according to any one of claims 177 to 218; optionally wherein said JH gene segments are *cis* at the same immunoglobulin Ig locus.

220. A non-human vertebrate (e.g., a mouse or rat) or a non-human vertebrate cell (e.g., an ES cell or a B-cell) according to claim 34, having a genome comprising at least 3 human JL gene segments of the same type (e.g., Jκ1), wherein at least two of the human JL gene segments are variants that are not identical to each other.

221. A non-human vertebrate (e.g., a mouse or rat) or a non-human vertebrate cell (e.g., an ES cell or a B-cell) according to claim 35, having a genome comprising at least 2 different non- endogenous JL gene segments of the same type (e.g., Jκ1) *cis* at the same Ig locus.

222. A non-human vertebrate (e.g., a mouse or rat) or a non-human vertebrate cell (e.g., an ES cell or a B-cell) according to claim 36, having a genome comprising at least 2 different human JL gene segments of the same type (e.g., Jκ1) trans at the same Ig locus; and optionally a third human JL gene segment of the same type, wherein the third JL is *cis* with one of said 2 different JL gene segments.

223. A population of non-human vertebrates (e.g., mice or rats) comprising a repertoire of human JL gene segments according to claim 37, wherein the plurality comprises at least 2 different human JL gene segments of the same type (e.g., Jκ1), a first of said different JL gene segments is provided in the genome of a first vertebrate of the population, and a second of said different JL gene segments being provided in the genome of a second vertebrate of the population, wherein the genome of the first vertebrate does not comprise the second JL gene segment.

224 A non-human vertebrate (e.g., a mouse or rat) or a non-human vertebrate cell (e.g., an ES cell or a B-cell) according to claim 38, having a genome comprising at least 2 different non-endogenous JL gene segments of the same type (e.g., Jκ1), wherein the JL gene segments are derived from the genome sequence of different human individuals that are not genetically related over at least 3 generations.

225. A method of enhancing the human immunoglobulin gene diversity of a non-human vertebrate (e.g., a mouse or rat) according to claim 39, the method comprising providing the vertebrate with a genome comprising at least 3 human JL gene segments of the same type (e.g., Jκ1), wherein at least two of the human JL gene segments are variants that are not identical to each other.

226. A method of enhancing the immunoglobulin gene diversity of a non-human vertebrate (e.g., a mouse or rat) according to claim 40, the method comprising providing the vertebrate with a genome comprising at least 2 different non-endogenous JL gene segments of the same type (e.g., Jκ1) *cis* at the same Ig locus.

227. A method of enhancing the immunoglobulin gene diversity of a non-human vertebrate (e.g., a mouse or rat) according to claim 41, the method comprising providing the vertebrate with a genome comprising at least 2 different human JL gene segments of the

Duration: 04.04.2014 17:47:10 - 04.04.2014 18:04:12. This page 29 of AMENDED SHEET 2014 17:56:58
Received at the EPO on Apr 04, 2014 18:04:12. Page 29 of 50

same type (e.g., Jκ1) trans at the same Ig locus; and optionally a third human JL gene segment of the same type, wherein the third JL is *cis* with one of said 2 different JL gene segments.

228. A method of providing an enhanced human immunoglobulin JL gene segment repertoire according to claim 42, the method comprising providing a population of non-human vertebrates (e.g., a mouse or rat) comprising a repertoire of human JL gene segments, wherein the method comprises providing at least 2 different human JL gene segments of the same type (e.g., Jκ1), wherein a first of said different JL gene segments is provided in the genome of a first vertebrate of the population, and a second of said different JL gene segments is provided in the genome of a second vertebrate of the population, wherein the genome of the first vertebrate does not comprise the second JL gene segment.

229. A method of enhancing the human immunoglobulin gene diversity of a non-human vertebrate (e.g., a mouse or rat) according to claim 43, the method comprising providing the vertebrate with a genome comprising at least 2 different non-endogenous JL gene segments of the same type (e.g., Jκ1), wherein the JL gene segments are derived from the genome sequence of different human individuals that are not genetically related over at least 3 generations.

230. The vertebrate or cell of claim 220, 222 or 224, or the method of claim 225, 227, 228 or 229, wherein at least 2 or 3 of said different gene segments are provided *cis* at the same Ig locus in said genome.

231. The vertebrate or cell of claim 220, 221 or 222, or the method of claim 225, 226, 227 or 228, wherein the JL gene segments are derived from the genome sequence of different human individuals that are not genetically related over at least 3 generations.

232. The vertebrate or cell of claim 220, 221 or 222, or the method of claim 225, 226, 227 or 228, wherein the JL gene segments are derived from the genome sequence of two or more different human individuals; optionally wherein the different human individuals are from different human populations.

233. The vertebrate, cell or method of claim 232, wherein the individuals are not genetically related.

234. The vertebrate, cell or method of any one of claims 220 to 233, wherein at least one of the different JL segments is a synthetic mutant of a human germline JL gene segment.

235. A method of enhancing the human immunoglobulin gene diversity of a non-human vertebrate (e.g., a mouse or rat), the method comprising providing the vertebrate with a genome comprising at least 2 human JL gene segments of the same type (e.g., Jκ1), wherein the JL gene segments are derived from the genome sequence of different human individuals that are not genetically related over at least 3 generations; optionally wherein at least 2 or 3 of said different gene segments are provided at the same IgL locus in said genome.

236. The vertebrate or cell of any one of claims claim 220 to 222 and 224, wherein the genome comprises a substantially complete functional repertoire of human Jκ and/or Jλ gene segment types supplemented with one, two or more human Jκ and/or Jλ gene segments respectively, wherein said substantially complete functional repertoire and the supplementary gene segments are not found together in the germline genome of a human individual.

Duration: 04.04.2014 17:47:10 - 04.04.2014 18:04:12. This page 30 of AMENDED SHEET 2014 17:57:21
Received at the EPO on Apr 04, 2014 18:04:12. Page 30 of 50

237. The population of claim 223, wherein the population comprises a substantially complete functional repertoire of human JL gene segment types supplemented with one, two or more human Jκ and/or Jλ gene segments respectively, wherein said substantially complete functional repertoire and the supplementary gene segments are not found together in the germline genome of a human individual.

238. A non-human vertebrate (e.g., a mouse or rat) or a non-human cell (e.g., an ES cell or a B-cell) having a genome comprising a substantially complete functional repertoire of human Jκ and/or Jλ gene segment types supplemented with one, two or more human Jκ and/or Jλ gene segments respectively, wherein said substantially complete functional repertoire and the supplementary gene segments are not found together in the germline genome of a human individual.

239. A population of non-human vertebrates (e.g., mice or rats) comprising a substantially complete functional repertoire of human Jκ and/or Jλ gene segment types supplemented with one, two or more human Jκ and/or Jλ gene segments respectively, wherein said substantially complete functional repertoire and the supplementary gene segments are not found together in the germline genome of a human individual.

240. A non-human vertebrate or vertebrate cell according to claim 221, comprising a genome that comprises VL and JL gene repertoires comprising human gene segments, the JL gene repertoire comprising

a plurality of human Jκ1 gene segments provided by at least 2 different human Jκ1 gene segments in *cis* at the same Ig locus in said genome;
a plurality of human Jκ2 gene segments provided by at least 2 different human Jκ1 gene segments in *cis* at the same Ig locus in said genome;
a plurality of human Jκ3 gene segments provided by at least 2 different human Jκ1 gene segments in *cis* at the same Ig locus in said genome;
a plurality of human Jκ4 gene segments provided by at least 2 different human Jκ1 gene segments in *cis* at the same Ig locus in said genome;
a plurality of human Jκ5 gene segments provided by at least 2 different human Jκ1 gene segments in *cis* at the same Ig locus in said genome;
a plurality of human Jλ1 gene segments provided by at least 2 different human Jλ1 gene segments in *cis* at the same Ig locus in said genome;
a plurality of human Jλ2 gene segments provided by at least 2 different human Jλ2 gene segments in *cis* at the same Ig locus in said genome;
a plurality of human Jλ3 gene segments provided by at least 2 different human Jλ3 gene segments in *cis* at the same Ig locus in said genome;
a plurality of human Jλ4 gene segments provided by at least 2 different human Jλ4 gene segments in *cis* at the same Ig locus in said genome;
a plurality of human Jλ5 gene segments provided by at least 2 different human Jλ5 gene segments in *cis* at the same Ig locus in said genome;
a plurality of human Jλ6 gene segments provided by at least 2 different human Jλ6 gene segments in *cis* at the same Ig locus in said genome; or
a plurality of human Jλ7 gene segments provided by at least 2 different human Jλ7 gene segments in *cis* at the same Ig locus in said genome;

optionally wherein the JL gene segments are derived from the genome sequence of two or more different human individuals.

241. A non-human vertebrate or vertebrate cell (optionally an ES cell or B-cell), according to claim 220, comprising a genome that comprises VL and JL gene repertoires comprising human gene segments, the JL gene repertoire comprising

AMENDED SHEET 2014 17:57:44
Duration: 04.04.2014 17:47:10 - 04.04.2014 18:04:12. This page 31 of
Received at the EPO on Apr 04, 2014 18:04:12. Page 31 of 50

a plurality of human Jκ1 gene segments provided by at least 3 different human Jκ1 gene segments;
a plurality of human Jκ2 gene segments provided by at least 3 different human Jκ1 gene segments;
a plurality of human Jκ3 gene segments provided by at least 3 different human Jκ1 gene segments;
a plurality of human Jκ4 gene segments provided by at least 3 different human Jκ1 gene segments;
a plurality of human Jκ5 gene segments provided by at least 3 different human Jκ1 gene segments;
a plurality of human Jλ1 gene segments provided by at least 3 different human Jλ1 gene segments;
a plurality of human Jλ2 gene segments provided by at least 3 different human Jλ2 gene segments;
a plurality of human Jλ3 gene segments provided by at least 3 different human Jλ3 gene segments;
a plurality of human Jλ4 gene segments provided by at least 3 different human Jλ4 gene segments;
a plurality of human Jλ5 gene segments provided by at least 3 different human Jλ5 gene segments;
a plurality of human Jλ6 gene segments provided by at least 3 different human Jλ6 gene segments; or
a plurality of human Jλ7 gene segments provided by at least 3 different human Jλ7 gene segments;

optionally wherein the JL gene segments are derived from the genome sequence of two or three different human individuals;

optionally wherein at least 2 or 3 of said different gene segments are provided in *cis* at the same Ig locus in said genome.

242. The vertebrate or cell of claim 240 or 241, wherein the different human individuals are from different human populations.

243. The vertebrate or cell of any one of claims 240 to 242, wherein the individuals are not genetically related.

244. The vertebrate or cell of any one of claims 240 to 243, wherein at least one of the different JL segments is a synthetic mutant of a human germline JL gene segment.

245. A non-human vertebrate or vertebrate cell (optionally an ES cell or B-cell) according to claim 228, comprising a genome comprising human VL and JL gene repertoires, the JL gene repertoire comprising

a plurality of human Jκ1 gene segments provided by at least 2 different human Jκ1 gene segments, optionally in *cis* at the same Ig locus in said genome;
a plurality of human Jκ2 gene segments provided by at least 2 different human Jκ1 gene segments, optionally in *cis* at the same Ig locus in said genome;
a plurality of human Jκ3 gene segments provided by at least 2 different human Jκ1 gene segments, optionally in *cis* at the same Ig locus in said genome;
a plurality of human Jκ4 gene segments provided by at least 2 different human Jκ1 gene segments, optionally in *cis* at the same Ig locus in said genome;

Duration: 04.04.2014 17:47:10 - 04.04.2014 18:04:12. This page 32 of AMENDED SHEET 2014 17:58:02
Received at the EPO on Apr 04, 2014 18:04:12. Page 32 of 50

a plurality of human Jκ5 gene segments provided by at least 2 different human Jκ1 gene segments, optionally in *cis* at the same Ig locus in said genome;
a plurality of human Jλ1 gene segments provided by at least 2 different human Jλ1 gene segments, optionally in *cis* at the same Ig locus in said genome;
a plurality of human Jλ2 gene segments provided by at least 2 different human Jλ2 gene segments, optionally in *cis* at the same Ig locus in said genome;
a plurality of human Jλ3 gene segments provided by at least 2 different human Jλ3 gene segments, optionally in *cis* at the same Ig locus in said genome;
a plurality of human Jλ4 gene segments provided by at least 2 different human Jλ4 gene segments, optionally in *cis* at the same Ig locus in said genome;
a plurality of human Jλ5 gene segments provided by at least 2 different human Jλ5 gene segments, optionally in *cis* at the same Ig locus in said genome;
a plurality of human Jλ6 gene segments provided by at least 2 different human Jλ6 gene segments, optionally in *cis* at the same Ig locus in said genome;
or a plurality of human Jλ7 gene segments provided by at least 2 different human Jλ7 gene segments, optionally in *cis* at the same Ig locus in said genome;

wherein the JL gene segments are derived from the genome sequence of different human individuals that are not genetically related over at least 3 generations.

246. The vertebrate or cell of claim 245, wherein the human individuals are from different human populations.

247. A non-human vertebrate or vertebrate cell (optionally an ES cell or antibody-producing cell) comprising a genome having a superhuman immunoglobulin heavy chain human VH and/or D and/or J gene repertoire, wherein the genome comprises a transgenic immunoglobulin heavy chain locus comprising a plurality of human immunoglobulin VH gene segments, one or more human D gene segments and one or more human J gene segments, wherein the plurality of VH gene segments consists of more than the natural human repertoire of functional VH gene segments; optionally wherein the genome is homozygous for said transgenic heavy chain locus.

248. The vertebrate or cell of claim 247, wherein VH gene repertoire consists of a plurality of VH gene segments derived from the genome sequence of a first human individual, supplemented with one or more different VH gene segments derived from the genome sequence of a second, different human individual; optionally wherein the individuals are not related; optionally wherein the D and J segments are derived from the genome sequence of the first human individual; and optionally wherein the VH gene segments from the genome sequence of the second individual are selected from the VH gene segments listed in Table 1.

249. The vertebrate or cell of claim 248, wherein the transgenic locus comprises more than 26 functional human VH gene segments; optionally wherein the locus comprises at least 27 or 28 functional human VH gene segments (e.g., wherein the locus comprises the full functional VH repertoire of said first individual supplemented with one or more VH gene segments derived from the genome sequence of the second human individual and optionally with one or more VH gene segments derived from the genome sequence of a third human individual).

250. The vertebrate of cell of claim 248 or 249, wherein the transgenic locus comprises a first VH gene segment derived from the genome sequence of the first individual and a second VH gene segment derived from the genome sequence of the second individual, wherein the second VH gene segment is a polymorphic variant of the first VH gene segment;

Duration: 04.04.2014 17:47:10 - 04.04.2014 18:04:12. This page 33 of AMENDED SHEET 2014 17:58:26
Received at the EPO on Apr 04, 2014 18:04:12. Page 33 of 50

optionally wherein the locus comprises a further polymorphic variant of the first VH gene segment (e.g., a variant derived from the genome sequence of a third human individual).

251. The vertebrate or cell of any one of claims 247 to 250, wherein the genome comprises a (or said) transgenic immunoglobulin heavy chain locus comprising a plurality of human immunoglobulin VH gene segments, a plurality of human D gene segments and one or more human J gene segments, wherein the plurality of D gene segments consists of more than the natural human repertoire of functional D gene segments; optionally wherein the genome is homozygous for said transgenic heavy chain locus.

252. The vertebrate or cell of claim 251, wherein D gene repertoire consists of a plurality of D gene segments derived from the genome sequence of a (or said) first human individual, supplemented with one or more different D gene segments derived from the genome sequence of a (or said) second, different human individual; optionally wherein the individuals are not related; optionally wherein J segments are derived from the genome sequence of the first human individual; and optionally wherein the D gene segments from the genome sequence of the second individual are selected from the D gene segments listed in Table 2.

253. The vertebrate or cell of claim 252, wherein the transgenic locus comprises more than 26 functional human D gene segments; optionally wherein the locus comprises at least 27 or 28 functional human D gene segments (e.g., wherein the locus comprises the full functional D repertoire of said first individual supplemented with one or more D gene segments derived from the genome sequence of the second human individual and optionally with one or more D gene segments derived from the genome sequence of a third human individual).

254. The vertebrate or cell of claim 252 or 253, wherein the transgenic locus comprises a first D gene segment derived from the genome sequence of the first individual and a second D gene segment derived from the genome sequence of the second individual, wherein the second D gene segment is a polymorphic variant of the first D gene segment; optionally wherein the locus comprises a further polymorphic variant of the first D gene segment (e.g., a variant derived from the genome sequence of a third human individual).

255. The vertebrate or cell of any one of claims 247 to 254, wherein the genome comprises a (or said) transgenic immunoglobulin heavy chain locus comprising a plurality of human immunoglobulin VH gene segments, one or more human D gene segments and a plurality of human JH gene segments, wherein the plurality of J gene segments consists of more than the natural human repertoire of functional J gene segments; optionally wherein the genome is homozygous for said transgenic heavy chain locus.

256. The vertebrate or cell of claim 255, wherein the J gene repertoire consists of a plurality of J gene segments derived from the genome sequence of a (or said) first human individual, supplemented with one or more different J gene segments derived from the genome sequence of a (or said) second, different human individual; optionally wherein the individuals are not related; optionally wherein D segments are derived from the genome sequence of the first human individual; and optionally wherein the J gene segments from the genome sequence of the second individual are selected from the J gene segments listed in Table 3.

257. The vertebrate or cell of claim 256, wherein the transgenic locus comprises more than 26 functional human J gene segments; optionally wherein the locus comprises at least 27 or 28 functional human J gene segments (e.g., wherein the locus comprises the full functional J repertoire of said first individual supplemented with one or more J gene

Duration: 04.04.2014 17:47:10 - 04.04.2014 18:04:12. This page 34 of AMENDED SHEET 2014 17:58:51
Received at the EPO on Apr 04, 2014 18:04:12. Page 34 of 50

segments derived from the genome sequence of the second human individual and optionally with one or more J gene segments derived from the genome sequence of a third human individual).

258. The vertebrate of cell of claim 256 or 257, wherein the transgenic locus comprises a first J gene segment derived from the genome sequence of the first individual and a second J gene segment derived from the genome sequence of the second individual, wherein the second J gene segment is a polymorphic variant of the first J gene segment; optionally wherein the locus comprises a further polymorphic variant of the first J gene segment (e.g., a variant derived from the genome sequence of a third human individual).

259. A non-human vertebrate or vertebrate cell (optionally an ES cell or antibody-producing cell) comprising a genome having a superhuman immunoglobulin light chain human VL gene repertoire; optionally wherein the vertebrate or cell is according to any one of claims 247 to 258.

260. The vertebrate or cell of claim 259, wherein the genome comprises

(i) a transgenic immunoglobulin kappa light chain locus comprising a plurality of human immunoglobulin Vκ gene segments and one or more human J gene segments, wherein the plurality of Vκ gene segments consists of more than the natural human repertoire of functional Vκ gene segments; optionally wherein the genome is homozygous for said transgenic kappa light chain locus; and/or

(ii) a transgenic immunoglobulin lambda light chain locus comprising a plurality of human immunoglobulin Vλ gene segments and one or more human J gene segments, wherein the plurality of Vλ gene segments consists of more than the natural human repertoire of functional Vλ gene segments; optionally wherein the genome is homozygous for said transgenic lambda light chain locus.

261. The vertebrate or cell of claim 260, wherein

(i) the Vκ gene repertoire consists of a plurality of Vκ gene segments derived from the genome sequence of a first human individual, supplemented with one or more Vκ gene segments derived from the genome sequence of a second, different human individual; optionally wherein the individuals are not related; optionally wherein the J segments are derived from the genome sequence of the first human individual; and optionally wherein the Vκ gene segments from the genome sequence of the second individual are selected from the Vκ gene segments listed in Table 4; and

(ii) the Vλ gene repertoire consists of a plurality of Vλ gene segments derived from the genome sequence of a first human individual, supplemented with one or more Vλ gene segments derived from the genome sequence of a second, different human individual; optionally wherein the individuals are not related; optionally wherein the J segments are derived from the genome sequence of the first human individual; and optionally wherein the Vλ gene segments from the genome sequence of the second individual are selected from the Vλ gene segments listed in Table 5.

262. The vertebrate or cell of claim 261, wherein

the kappa light transgenic locus comprises more than 26 functional human Vκ gene segments; optionally wherein the locus comprises at least 27 or 28 functional human Vκ gene segments (e.g., wherein the locus comprises the full functional Vκ repertoire of said first individual supplemented with one or more Vκ gene segments derived from the

AMENDED SHEET 2014 17:59:13
Duration: 04.04.2014 17:47:10 - 04.04.2014 18:04:12. This page 35 of
Received at the EPO on Apr 04, 2014 18:04:12. Page 35 of 50

genome sequence of the second human individual and optionally with one or more Vκ gene segments derived from the genome sequence of a third human individual); and

the lambda light transgenic locus comprises more than 26 functional human Vλ gene segments; optionally wherein the locus comprises at least 27 or 28 functional human Vλ gene segments (e.g., wherein the locus comprises the full functional Vλ repertoire of said first individual supplemented with one or more Vλ gene segments derived from the genome sequence of the second human individual and optionally with one or more Vλ gene segments derived from the genome sequence of a third human individual).

263. The vertebrate of cell of claim 261 or 262, wherein

the kappa light transgenic locus comprises a first Vκ gene segment derived from the genome sequence of the first individual and a second Vκ gene segment derived from the genome sequence of the second individual, wherein the second Vκ gene segment is a polymorphic variant of the first Vκ gene segment; optionally wherein the locus comprises a further polymorphic variant of the first Vκ gene segment (e.g., a variant derived from the genome sequence of a third human individual); and

the lambda light transgenic locus comprises a first Vλ gene segment derived from the genome sequence of the first individual and a second Vλ gene segment derived from the genome sequence of the second individual, wherein the second Vλ gene segment is a polymorphic variant of the first Vλ gene segment; optionally wherein the locus comprises a further polymorphic variant of the first Vλ gene segment (e.g., a variant derived from the genome sequence of a third human individual).

264. The vertebrate or cell of any one of claims 259 to 263, wherein the genome comprises a (or said) transgenic immunoglobulin light chain locus comprising a plurality of human immunoglobulin VL gene segments and a plurality of human JL gene segments, wherein the plurality of J gene segments consists of more than the natural human repertoire of functional J gene segments; optionally wherein the genome is homozygous for said transgenic heavy chain locus.

265. The vertebrate or cell of claim 264, wherein

(i) the Jκ gene repertoire consists of a plurality of Jκ gene segments derived from the genome sequence of a (or said) first human individual, supplemented with one or more Jκ gene segments derived from the genome sequence of a (or said) second, different human individual; optionally wherein the individuals are not related; optionally wherein the Vκ segments are derived from the genome sequence of the first human individual; optionally wherein the Jκ gene segments from the genome sequence of the second individual are selected from the Jκ gene segments listed in Table 6; and

(ii) the Jκ gene repertoire consists of a plurality of Jλ gene segments derived from the genome sequence of a (or said) first human individual, supplemented with one or more Jλ gene segments derived from the genome sequence of a (or said) second, different human individual; optionally wherein the individuals are not related; optionally wherein the Vλ segments are derived from the genome sequence of the first human individual; optionally wherein the Jλ gene segments from the genome sequence of the second individual are selected from the Jλ gene segments listed in Table 7.

266. The vertebrate or cell of claim 265, wherein

Duration: 04.04.2014 17:47:10 - 04.04.2014 18:04:12. This page 36 of AMENDED SHEET 2014 17:59:36
Received at the EPO on Apr 04, 2014 18:04:12. Page 36 of 50

(i) the transgenic light chain locus comprises more than 26 functional human Jκ gene segments; optionally wherein the locus comprises at least 27 or 28 functional human Jκ gene segments (e.g., wherein the locus comprises the full functional Jκ repertoire of said first individual supplemented with one or more Jκ gene segments derived from the genome sequence of the second human individual and optionally with one or more Jκ gene segments derived from the genome sequence of a third human individual); and/or

(ii) the transgenic light chain locus comprises more than 26 functional human Jλ gene segments; optionally wherein the locus comprises at least 27 or 28 functional human Jλ gene segments (e.g., wherein the locus comprises the full functional Jλ repertoire of said first individual supplemented with one or more Jλ gene segments derived from the genome sequence of the second human individual and optionally with one or more Jλ gene segments derived from the genome sequence of a third human individual).

267. The vertebrate or cell of claim 265 or 266, wherein

(i) the kappa light transgenic locus comprises a first Jκ gene segment derived from the genome sequence of the first individual and a second Jκ gene segment derived from the genome sequence of the second individual, wherein the second Jκ gene segment is a polymorphic variant of the first Jκ gene segment; optionally wherein the locus comprises a further polymorphic variant of the first Jκ gene segment (e.g., a variant derived from the genome sequence of a third human individual); and

(ii) the lambda light transgenic locus comprises a first Jλ gene segment derived from the genome sequence of the first individual and a second Jλ gene segment derived from the genome sequence of the second individual, wherein the second Jκ gene segment is a polymorphic variant of the first Jλ gene segment; optionally wherein the locus comprises a further polymorphic variant of the first Jλ gene segment (e.g., a variant derived from the genome sequence of a third human individual).

268. A library of antibody-producing transgenic cells whose genomes collectively encode a repertoire of antibodies, wherein

(a) a first transgenic cell expresses a first antibody having a chain encoded by a first immunoglobulin gene, the gene comprising a first variable domain nucleotide sequence produced following recombination of a first human unrearranged immunoglobulin gene segment;

(b) a second transgenic cell expresses a second antibody having a chain encoded by a second immunoglobulin gene, the second gene comprising a second variable domain nucleotide sequence produced following recombination of a second human unrearranged immunoglobulin gene segment, the first and second antibodies being non-identical;

(c) the first and second gene segments are different and derived from the genome sequences of first and second human individuals respectively, wherein the individuals are different; and optionally not related;

(d) wherein the cells are non-human vertebrate (e.g., mouse or rat) cells.

AMENDED SHEET 2014 17:59:57
Duration: 04.04.2014 17:47:10 - 04.04.2014 18:04:12. This page 37 of
Received at the EPO on Apr 04, 2014 18:04:12. Page 37 of 50

269. The library of claim 268, wherein in step (c) the individuals or not related.

270. The vertebrate, cell or library of any one of claims 247 to 269, wherein the first and second human individuals are members of first and second ethnic populations respectively, wherein the populations are different; optionally wherein the ethnic populations are selected from those identified in the 1000 genomes database.

271. The vertebrate, cell or library of claim 270, wherein the human immunoglobulin gene segment derived from the genome sequence of the second individual is low-frequency (optionally rare) within the second ethnic population.

272. The library of claim 270 or 271, wherein the first variable region nucleotide sequence is produced by recombination of the first human immunoglobulin gene segment with a first J gene segment and optionally a first D gene segment, wherein the first human immunoglobulin gene segment is a V gene segment and the V, D and J segments are derived from the first human population, optionally from the genome of one individual of the first human population.

273. The library of claim 272, wherein the second variable region nucleotide sequence is produced by recombination of the second human immunoglobulin gene segment with a second J gene segment and optionally a second D gene segment, wherein the second human immunoglobulin gene segment is a V gene segment derived from the second population and the D and/or J segments are derived from the first human population, optionally the D and J gene segments being from the genome of one individual of the first human population.

274. The library of claim 273, wherein all of the D and J segments that have been recombined with the first and second V gene segments are D and J segments derived from the first human population, optionally the D and J gene segments being from the genome of one individual of the first human population.

275. The vertebrate, cell or library of any one of claims 270 to 274, wherein the first and second ethnic populations are selected from the group consisting of an ethnic population with European ancestry, an ethnic population with East Asian, an ethnic population with West African ancestry, an ethnic population with Americas ancestry and an ethnic population with South Asian ancestry.

276. The vertebrate, cell or library of claim 275, wherein the first and second ethnic populations are selected from the group consisting of an ethnic population with Northern European ancestry; or an ethnic population with Western European ancestry; or an ethnic population with Toscani ancestry; or an ethnic population with British ancestry; or an ethnic population with Icelandic ancestry; or an ethnic population with Finnish ancestry; or an ethnic population with Iberian ancestry; or an ethnic population with Japanese ancestry; or an ethnic population with Chinese ancestry; or an ethnic population Vietnamese ancestry; or an ethnic population with Yoruba ancestry; or an ethnic population with Luhya ancestry; or an ethnic population with Gambian ancestry; or an ethnic population with Malawian ancestry; or an ethnic population with Native American ancestry; or an ethnic population with Afro-Caribbean ancestry; or an ethnic population with Mexican ancestry; or an ethnic population with Puerto Rican ancestry; or an ethnic population with Columbian ancestry; or an ethnic population with Peruvian ancestry; or an ethnic population with Ahom ancestry; or an ethnic population with Kayadtha ancestry; or an ethnic population with Reddy ancestry; or an ethnic population with Maratha; or an ethnic population with Punjabi ancestry.

Duration: 04.04.2014 17:47:10 - 04.04.2014 18:04:12. This page 38 of AMENDED SHEET 2014 18:00:20
Received at the EPO on Apr 04, 2014 18:04:12. Page 38 of 50

277. The library of claim 268, wherein the second human immunoglobulin gene segment is a polymorphic variant of the first human immunoglobulin gene segment; optionally wherein the second gene segment is selected from the group consisting of a gene segment in any of Tables 1 to 7 and 9 to 14, e.g., the second gene segment is a polymorphic variant of VH1-69.

278. The library of any one of claims 268 to 277, wherein the first and second human immunoglobulin gene segments are both (i) V_H gene segments; (ii) D segments; (iii) J segments (optionally both J_H segments, both J_κ segments or both J_λ segments); (iv) constant regions (optionally both a gamma constant region, optionally both a C gamma-1 constant region); (v) CH1 regions; (vi) CH2 regions; or (vii) CH3 regions.

279. The library of any one of claims 268 to 277, wherein the library is naive and optionally has a library size of from 10^2 to 10^9 cells.

280. The library of any one of claims 268 to 279, wherein the library has been selected against a predetermined antigen optionally has a library size of from 10^2 to 10^9 cells.

281. The library of any one of claims 268 to 280, wherein said first and second cells are progeny of first and second ancestor non-human vertebrate cells respectively, wherein the first ancestor cell comprises a genome comprising said first human immunoglobulin gene segment; and the second ancestor cell comprises a genome comprising said second human immunoglobulin gene segment.

282. A library of antibody-producing transgenic cells whose genomes collectively encode a repertoire of antibodies, wherein the library comprises the first and second ancestor cells recited in claim 281.

283. A library of hybridoma cells produced by fusion of the library of any one of claims 247 to 282 with fusion partner cells; and optionally the hybridoma library has a size of from 10^2 to 10^9 cells.

284. An isolated antibody having

(a) a heavy chain encoded by a nucleotide sequence produced following recombination in a transgenic non-human vertebrate cell of an unrearranged human immunoglobulin V gene segment with a human D and human J segment, optionally with affinity maturation in said cell, wherein one of the gene segments is derived from the genome of an individual from a first human ethnic population; and the other two gene segments are derived from the genome of an individual from a second, different, human ethnic population, and wherein the antibody comprises heavy chain constant regions of said non-human vertebrate (e.g., rodent, mouse or rat heavy chain constant regions); and/or

(b) a light chain encoded by a nucleotide sequence produced following recombination in a transgenic non-human vertebrate cell of an unrearranged human immunoglobulin V gene segment with a human J segment, optionally with affinity maturation in said cell, wherein one of the gene segments is derived from the genome of an individual from a first human ethnic population (optionally the same as the first population in (a)); and the other gene segment is derived from the genome of an individual from a second, different, human ethnic population (optionally the same as the second population in (a)), and wherein the antibody

Duration: 04.04.2014 17:47:10 - 04.04.2014 18:04:12. This page 39 of AMENDED SHEET 2014 18:00:42
Received at the EPO on Apr 04, 2014 18:04:12. Page 39 of 50

comprises light chain constant regions of said non-human vertebrate (e.g., rodent, mouse or rat heavy light constant regions);

(c) Optionally wherein each variable domain of the antibody is a human variable domain and

(d) Optionally wherein the heavy chain constant regions are gamma-type constant regions.

285. An isolated nucleotide sequence encoding the antibody of claim284, optionally wherein the sequence is provided in an antibody expression vector, optionally in a host cell.

286. A method of producing a human antibody, the method comprising replacing the non-human vertebrate constant regions of the antibody of claim 284 with human antibody constant regions.

287. A pharmaceutical composition comprising an antibody according to claim 284, or an antibody produced according to the method of claim 286 and a diluent, excipient or carrier; optionally wherein the composition is provided in a container connected to an IV needle or syringe or in an IV bag.

288. An antibody-producing cell that expresses the second antibody recited in any one of claims 268 to 284 or the isolated antibody of claim 284.

289. A non-human vertebrate or vertebrate cell (optionally an ES cell or antibody-producing cell) whose genome comprises a transgenic immunoglobulin locus (e.g., a heavy chain locus or a light chain locus), said locus comprising immunoglobulin gene segments according to the first and second human immunoglobulin gene segments (optionally V segments) recited in any one of claims 268 to 284 operably connected upstream of an immunoglobulin constant region; optionally wherein the genome is homozygous for said transgenic immunoglobulin locus;

optionally wherein the immunoglobulin locus comprises more than the natural human complement of functional V gene segments; and/or

optionally wherein the immunoglobulin locus comprises more than the natural human complement of functional D gene segments; and/or

optionally wherein the immunoglobulin locus comprises more than the natural human complement of functional J gene segments.

290. A transgenic non-human vertebrate (e.g., a mouse or rat) or vertebrate cell (optionally an ES cell or antibody-producing cell) whose genome comprises a transgenic immunoglobulin locus comprising a plurality of human immunoglobulin gene segments operably connected upstream of a non-human vertebrate constant region for the production of a repertoire of chimaeric antibodies, or chimaeric light or heavy chains, having a non-human vertebrate constant region and a human variable region;

wherein the transgenic locus comprises one or more human immunoglobulin V gene segments, one or more human J gene segments and optionally one or more human D gene segments, a first (optionally a V segment) of said gene segments and a second (optionally a V segment) of said gene segments being different and derived from the genomes of first and second human individuals respectively, wherein the individuals are different; and optionally not related;

Duration: 04.04.2014 17:47:10 - 04.04.2014 18:04:12. This page 40 of AMENDED SHEET 2014 18:01:02
Received at the EPO on Apr 04, 2014 18:04:12. Page 40 of 50

optionally wherein the immunoglobulin locus comprises more than the natural human complement of functional V gene segments; and/or

optionally wherein the immunoglobulin locus comprises more than the natural human complement of functional D gene segments; and/or

optionally wherein the immunoglobulin locus comprises more than the natural human complement of functional J gene segments.

291. A transgenic non-human vertebrate (e.g., a mouse or rat) or vertebrate cell (optionally an ES cell or antibody-producing cell) whose genome comprises first and second transgenic immunoglobulin loci, each locus comprising a plurality of human immunoglobulin gene segments operably connected upstream of a non-human vertebrate constant region for the production of a repertoire of chimaeric antibodies, or chimaeric light or heavy chains, having a non-human vertebrate constant region and a human variable region;

wherein (i) the first transgenic locus comprises one or more human immunoglobulin V gene segments, one or more human J gene segments and optionally one or more human D gene segments, (ii) the second transgenic locus comprises one or more human immunoglobulin V gene segments, one or more human J gene segments and optionally one or more human D gene segments; and (iii) wherein a first (optionally a V) gene segment of said first locus and a second (optionally a V) gene segment of said second gene locus are different and derived from the genomes of first and second human individuals respectively, wherein the individuals are different; and optionally not related

optionally wherein the first and second loci are on different chromosomes (optionally chromosomes with the same chromosome number) in said genome;

optionally wherein each immunoglobulin locus comprises more than the natural human complement of functional V gene segments; and/or

optionally wherein each immunoglobulin locus comprises more than the natural human complement of functional D gene segments; and/or

optionally wherein each immunoglobulin locus comprises more than the natural human complement of functional J gene segments.

292. The non-human vertebrate or cell of claim 290 or 291, wherein the immunoglobulin gene segments are as recited in any one of claims 23 to 37.

293. The non-human vertebrate or cell of claim 289, 290, 291 or 292, wherein the genome comprises a third immunoglobulin gene segment (optionally a V segment), the third gene segment being derived from a human individual that is different from the individual from which the first (and optionally also the second) gene segment is derived; optionally wherein the first, second and third gene segments are polymorphic variants of a human immunoglobulin gene segment.

294. The non-human vertebrate or cell of any one of claims 289 to 293, wherein the genome of the vertebrate or cell is homozygous for the first, second and optional third gene segment, wherein a copy of the first, second and optional third gene segments are provided together on the same chromosome operably connected upstream of a common non-human vertebrate constant region.

AMENDED SHEET 2014 18:01:23
Duration: 04.04.2014 17:47:10 - 04.04.2014 18:04:12. This page 41 of
Received at the EPO on Apr 04, 2014 18:04:12. Page 41 of 50

295. The non-human vertebrate or cell of any one of claims 289 to 294, wherein each first, second and optional third gene segment is a V gene segment.

296. The library of any one of claims 268 to 283, wherein the library is provided by a collection of non-human vertebrates (optionally a collection of rodents, mice or rats); optionally, wherein a first member of said collection produces said first antibody but not said second antibody, and a second member of the collection produces said second antibody (but optionally not said first antibody).

297. A repertoire of antibodies expressed from a library of cells according to any one of claims 268 to 283 and 296.

298. A method of constructing a cell (eg, an ES cell) according to any one of claims 247 to 267, the method comprising
(a) identifying functional V and J (and optionally D) gene segments of the genome sequence of a (or said) first human individual;
(b) identifying one or more functional V and/or D and/or J gene segments of the genome sequence of a (or said) second human individual, wherein these additional gene segments are not found in the genome sequence of the first individual;
(c) and constructing a transgenic immunoglobulin locus in the cell, wherein the gene segments of (a) and (b) are provided in the locus operably connected upstream of a constant region.

299. The method of claim 298, wherein the cell comprises a heavy chain locus constructed according to steps (a) to (c) and/or a light chain locus (kappa and/or lambda loci) constructed according to steps (a) to (c).

300. The method of claim 298 or 299, wherein the cell is homozygous for the or each transgenic locus; optionally wherein antibody expression from loci endogenous to said cell has been inactivated.

301. The method of any one of claims 298 to 300, wherein the gene segment(s) in step (b) are identified from an immunoglobulin gene database selected from the 1000 genomes, Ensembl, Genbank and IMGT databases.

302. The method of any one of claims 298 to 301, wherein the first and second human individuals are members of first and second ethnic populations respectively, wherein the populations are different, optionally wherein the human immunoglobulin gene segment derived from the genome sequence of the second individual is low-frequency (optionally rare) within the second ethnic population.

303. A method of making a transgenic non-human vertebrate (e.g., a mouse or rat), the method comprising
(a) constructing an ES cell (e.g., a mouse C57BL/6N, C57BL/6J, 129S5 or 129Sv strain ES cell) by carrying out the method of any one of claims 298 to 302;
(b) injecting the ES cell into a donor non-human vertebrate blastocyst (e.g., a mouse C57BL/6N, C57BL/6J, 129S5 or 129Sv strain blastocyst);
(c) implanting the blastocyst into a foster non-human vertebrate mother (e.g., a C57BL/6N, C57BL/6J, 129S5 or 129Sv strain mouse); and
(d) obtaining a child from said mother, wherein the child genome comprises a transgenic immunoglobulin locus.

Duration: 04.04.2014 17:47:10 - 04.04.2014 18:04:12. This page 42 of AMENDED SHEET 2014 18:01:44
Received at the EPO on Apr 04, 2014 18:04:12. Page 42 of 50

304. A transgenic non-human vertebrate (e.g., a mouse or rat) made by the method of claim 303 or a progeny thereof.

305. A population of non-human vertebrates according to claim 304.

306. A method of isolating an antibody that binds a predetermined antigen (e.g., a bacterial or viral pathogen antigen), the method comprising
(a) providing a vertebrate (optionally a mouse or rat) according to any one of claims 247 to 267, 270, 271, 275, 276, 289 to 295 and 304;
(b) immunising (eg, using a standard prime-boost method) said vertebrate with said antigen (optionally wherein the antigen is an antigen of an infectious disease pathogen);
(c) removing B lymphocytes from the vertebrate and selecting one or more B lymphocytes expressing antibodies that bind to the antigen;
(d) optionally immortalising said selected B lymphocytes or progeny thereof, optionally by producing hybridomas therefrom; and
(e) isolating an antibody (e.g., and IgG-type antibody) expressed by the B lymphocytes; and
(f) optionally producing a derivative or variant of the antibody.

307. The method of claim 306, further comprising after step (e) the step of isolating from said B lymphocytes nucleic acid encoding said antibody that binds said antigen; optionally exchanging the heavy chain constant region nucleotide sequence of the antibody with a nucleotide sequence encoding a human or humanised heavy chain constant region and optionally affinity maturing the variable region of said antibody; and optionally inserting said nucleic acid into an expression vector and optionally a host.

308. A non-human vertebrate (e.g., a mouse or rat) or cell (e.g., a mouse cell or rat cell) comprising a genome that comprises a transgenic heavy chain immunoglobulin locus, wherein the locus comprises a full human repertoire of functional VH, D and JH segments derived from the genome sequence of the same human individual, supplemented with one or more additional functional human VH, D and/or JH gene segment that is not found in the genome sequence of said human individual.

309. The vertebrate or cell of claim 308, wherein each additional VH, D and JH segment is selected from the group consisting of (i) a gene segment derived from a second, different individual, optionally wherein the first and second individuals are members of different ethnic populations; (ii) a mutant of a human gene segment (optionally a human germline gene segment having up to 5, 10 or 15 mutations); and (iii) a hybrid human gene segment comprising a first and second nucleotide sequences derived from genome sequences of different human individuals or different polymorphic variants of a human immunoglobulin gene segment (e.g., variants of a germline human VH, D or JH gene segment).

310. The vertebrate or cell of any one of claims 308 to 309, wherein the genome is homozygous for said heavy chain transgene and optionally endogenous immunoglobulin heavy chain expression has been inactivated.

311. A non-human vertebrate (e.g., a mouse or rat) or cell (e.g., a mouse cell or rat cell) comprising a genome that comprises a transgenic kappa light chain immunoglobulin locus, wherein the locus comprises a full human repertoire of functional Vκ and Jκ segments derived from the genome sequence of the same human individual, supplemented with one or more additional functional human Vκ and/or Jκ gene segment that is not found in the genome sequence of said human individual.

Duration: 04.04.2014 17:47:10 - 04.04.2014 18:04:12. This page 43 of AMENDED SHEET 2014 18:02:06
Received at the EPO on Apr 04, 2014 18:04:12. Page 43 of 50

312. The vertebrate or cell of claim 311, wherein each additional Vκ and Jκ segment is selected from the group consisting of (i) a gene segment derived from a second, different individual, optionally wherein the first and second individuals are members of different ethnic populations; (ii) a mutant of a human gene segment (optionally a human germline gene segment having up to 5, 10 or 15 mutations); and (iii) a hybrid human gene segment comprising a first and second nucleotide sequences derived from: genome sequences of different human individuals or different polymorphic variants of a human immunoglobulin gene segment (e.g., variants of a germline human Vκ or Jκ gene segment).

313. The vertebrate or cell of any one of claims 311 to 312, wherein the genome is homozygous for said kappa light chain transgene and optionally endogenous immunoglobulin kappa light chain expression has been inactivated.

314. A non-human vertebrate (e.g., a mouse or rat) or cell (e.g., a mouse cell or rat cell) comprising a genome that comprises a transgenic lambda light chain immunoglobulin locus, wherein the locus comprises a full human repertoire of functional V lambda and J lambda segments derived from the genome sequence of the same human individual, supplemented with one or more additional functional human V lambda and/or J lambda gene segment that is not found in the genome sequence of said human individual.

315. The vertebrate or cell of claim 314, wherein each additional V lambda and J lambda segment is selected from the group consisting of (i) a gene segment derived from a second, different individual, optionally wherein the first and second individuals are members of different ethnic populations; (ii) a mutant of a human gene segment (optionally a human germline gene segment having up to 5, 10 or 15 mutations); and (iii) a hybrid human gene segment comprising a first and second nucleotide sequences derived from genome sequences of different human individuals or different polymorphic variants of a human immunoglobulin gene segment (e.g., variants of a germline human V lambda or J lambda gene segment).

316. The vertebrate or cell of any one of claims 314 to 315, wherein the genome is homozygous for said lambda light chain transgene and optionally endogenous immunoglobulin lambda light chain expression has been inactivated.

317. A transgenic immunoglobulin locus comprising a synthetic immunoglobulin gene haplotype, the haplotype comprising first and second human gene segments (each being a V, D or J), a switch region and a constant region, wherein

a) the second gene segment is a polymorphic variant of the first gene segment; or
b) the first and second gene segments are derived respectively from genome sequence of individuals from different, first and second, ethnic populations (e.g., according to the 1000 Genomes database) and the second gene segment is not found in the first population (e.g., according to the 1000 Genomes database), optionally wherein the second gene segment occurs at low-frequency (or is rare) in the second population; and

wherein the constant region, and optionally the switch region, are non-human vertebrate (e.g., mouse or rat) constant and switch regions (e.g., mouse or rat Cmu; mouse or rat Smu; mouse or rat C gamma; or mouse or rat S gamma).

318. The transgenic immunoglobulin locus of claim 317 wherein the transgene comprises a third human immunoglobulin gene segment (a V, D or J) which is (a) a polymorphic

Duration: 04.04.2014 17:47:10 - 04.04.2014 18:04:12. This page 44 of AMENDED SHEET 2014 18:02:29
Received at the EPO on Apr 04, 2014 18:04:12. Page 44 of 50

variant of the first and second gene segments; or (b) derived from a genome sequence of the second population (and optionally is a low-frequency or rare gene in that population) or is from a third human ethnic population, wherein the third gene segment is not found in the first population (e.g., according to the 1000 Genomes database).

319. A non-human vertebrate or cell comprising the transgene of claim 317 or 318; optionally wherein the vertebrate or cell is homozygous for said transgene.

320. The vertebrate or cell of any one of claims 1-21 or the heavy chain, VH domain or antibody of any one of claims 22-23, 25 or 28-33,, wherein the constant region is a non-human vertebrate constant region.

321. The antibody, heavy chain or VH domain (e.g., comprised by an antibody) of any one of claims 22 to 25 and 28 for use in treating and/or preventing a disease or medical condition in a human.

322. A method of treating and/or preventing a disease or medical condition in a human, the method comprising administering to the human a therapeutically or prophylactically effective amount of the antibody, heavy chain or VH domain (e.g., comprised by an antibody) of any one of claims 22 to 25 and 28.

323. The vertebrate, cell, or method of any one of claims 34 to 66, wherein the at least two or at least three gene segments are human VH1-69 gene segments.

324. A method for producing a heavy chain, VH domain or an antibody specific to a target antigen, the method comprising immunizing a non-human vertebrate according to claims 13 or 14 with the antigen and isolating the heavy chain, VH domain or an antibody specific to a target antigen or a cell producing the heavy chain, VH domain or an antibody, wherein the heavy chain, VH domain or an antibody comprises a HCDR3 that is derived from the recombination of human JH6*02 with a VH gene segment and a D gene segment.

325. A method for producing a human heavy chain or antibody comprising carrying out the method of claim 324, wherein the constant region of the locus is a non-human vertebrate (e.g., mouse or rat) constant region, and then replacing the non-human constant region of the isolated heavy chain or antibody with a human constant region.

326. The method of claim 26, claim 27, claim 324 or claim 325, wherein the HCDR3 is at least 20 amino acids in length.

327. Use of human JH6*02 for generating a HCDR3 of more than 20 amino acids in a non-human vertebrate whose genome comprises an immunoglobulin heavy chain locus comprising human gene segment JH6*02, one or more VH gene segments and one or more D gene segments upstream of a constant region; wherein the gene segments in the heavy chain locus are operably linked to the constant region thereof so that the vertebrate is capable of producing an antibody heavy chain produced by recombination of the human JH6*02 with a D segment and a VH segment and wherein the JH6*02 gene segment comprises the following nucleotide sequence: ATTACTA CTACTACTAC GGTATGGACG TCTGGGGCCA AGGGACCACG GTCACCGTCT CCTCAG.

328. A heavy chain (e.g., comprised by an antibody) isolated from a vertebrate of claim 13 or claim 14 wherein the heavy chain comprises a HCDR3 of at least 20 amino acids and the HCDR3 is the product of recombination of human JH6*02 with a human VH gene segment and a human D gene segment.

Duration: 04.04.2014 17:47:10 - 04.04.2014 18:04:12. This page 45 of AMENDED SHEET 2014 18:02:51
Received at the EPO on Apr 04, 2014 18:04:12. Page 45 of 50

329. A heavy chain, VH domain or an antibody produced by the method of claim 325 or 326, wherein the heavy chain, VH domain or antibody comprises a HCDR3 of at least 20 amino acids and the HCDR3 is the product of recombination of human JH6*02 with a human VH gene segment of claim 13 and/or a human D gene segment of claim 14.

Duration: 04.04.2014 17:47:10 - 04.04.2014 18:04:12. This page 46 of AMENDED SHEET 2014 18:02:57
Received at the EPO on Apr 04, 2014 18:04:12. Page 46 of 50

CLAIMS

1. A non-human vertebrate whose genome comprises an immunoglobulin heavy chain locus comprising unrearranged human gene segment JH6*02, one or more human VH gene segments and one or more human D gene segments upstream of a constant region; in which the gene segments in the heavy chain locus are operably linked to the constant region thereof so that the vertebrate is capable of producing an antibody heavy chain produced by recombination of the human JH6*02 with a human D segment and a human VH segment, in which the JH6*02 gene segment comprises the following nucleotide sequence: ATTACTA CTACTACTAC GGTATGGACG TCTGGGGCCA AGGGACCACG GTCACCGTCT CCTCAG,

in which the vertebrate has been immunised with a target antigen and produces an antibody heavy chain specific for a target antigen in which the variable domain of the heavy chain is the product of recombination between a human VH, D and JH6*02 and in which the HCDR3 length is at least 20 amino acids.

2. A vertebrate according to Claim 1, in which the vertebrate is a mouse or a rat.

3. An antibody-producing cell that is a progeny of a non-human vertebrate cell whose genome comprises an immunoglobulin heavy chain locus comprising human gene segment JH6*02, one or more human VH gene segments and one or more human D gene segments upstream of a constant region; in which the gene segments in the heavy chain locus are operably linked to the constant region thereof for producing an antibody heavy chain produced by recombination of the human JH6*02 with a human D segment and a human VH segment,

in which the JH6*02 gene segment comprises the following nucleotide sequence: ATTACTA CTACTACTAC GGTATGGACG TCTGGGGCCA AGGGACCACG GTCACCGTCT CCTCAG

in which the antibody-producing cell comprises a heavy chain locus comprising a rearranged variable region produced by recombination of human JH6*02 with a human D segment and a human VH segment,

in which the antibody-producing cell produces an antibody heavy chain specific for a target antigen and in which the variable domain of the heavy chain is the product of

recombination between a human VH, human D and human JH6*02 and in which the HCDR3 length is at least 20 amino acids.

4. A cell according to Claim 3, in which the cell is a B-cell.

5. A cell according to Claim 3 or 4, in which the non-human vertebrate cell is a mouse cell or a rat cell.

6. A cell according to any of Claims 3 to 5, which is a B-cell or hybridoma that expresses a target antigen-specific antibody comprising a heavy chain that comprises a rearranged variable region produced by recombination of human JH6*02 with a human D segment and a human VH segment selected from

VH3-11 and D3-9;

VH3-20 and D3-10;

VH4-4 and D3-10;

VH3-9 and D3-10; or

VH1-8 and D310.

7. A cell according to Claim 6, in which the VH3-11 is VH3-11*01.

8. A cell according to Claim 6, in which the VH3-20 is VH3-20*01.

9. A cell according to Claim 6, in which the VH4-4 is VH4-4*02.

10. A cell according to Claim 6, in which the VH3-9 is VH3-9*01.

11. A cell according to Claim 6, in which the VH1-8 is VH1-8*01.

12. A cell or vertebrate according to any preceding claim in which the HCDR3 length is at least 21, 22, 23, 24, 25, 26, 27, 28, 29 or 30 amino acids.

13. A cell or vertebrate according to any preceding claim in which the HCDR3 length is no more than 35, no more than 34, no more than 33, no more than 32 or no more than 31 amino acids.

14. A cell or vertebrate according to any of Claims 1 to 11 and 13 in which the HCDR3 length is 20, 21, 22, 23 or 24 amino acids.

15. A vertebrate or cell according to any preceding claim, in which the heavy chain locus comprises a human JH6*02 recombination signal sequence (RSS) operably connected 5' to the JH6*02 gene segment.

16. A vertebrate or cell according to Claim 15, in which the RSS is SEQ ID NO: 238 or a sequence having an identical 9mer and 7mer sequence flanking a sequence that is at least 70% identical to the 22mer sequence of SEQ ID NO: 238.

17. A vertebrate or cell according to Claim 16, in which the RSS and JH6*02 are provided as SEQ ID NO: 237.

18. A vertebrate according to Claim 1 or 2, in which the locus comprises one, more or all human D gene segments D3-9; D4-17; D3-10; D2-2; D5-24; D6-19; D3-22; D6-13; D5-12; D1- 26; D1-20; D5-18; D3-16; D2-21; D1-14; D7-27; D1-1; D6-25; D2-14; and D4-23.

19. A vertebrate or cell according to Claim 18, in which the locus comprises one, more or all human D gene segments D3-9, D3-10, D6-19, D4-17, D6-13, D3-22, D2-2, D2-25 and D3-3.

20. A vertebrate or cell according to any preceding claim, in which i) the JH6*02 is the only JH6-type gene segment in the genome or ii) the JH6*02 is the closest JH gene segment to the constant region in the locus.

21. A vertebrate according to Claim 1 or 2 in which the locus comprises a plurality of human D gene segments and the JH6*02 is in human germline configuration with respect to the 3'-most human D gene segment.

22. A vertebrate according to Claim 1 or 2, in which the locus comprises one, more or all of human gene segments selected from V3-21, V3-13, V3-7, V6-1, V1-8, V1-2, V7-4-1, V1-3, V1-18, V4-4, V3-9, V3-23, V3-11, V3-20, D3-9*01, D3-10*01, D6-19*01, D6-13*01, D1-26*01, IGHV1-8*01, IGHV4-61*01, IGHV6-1*01, IGHV4-4*02, IGHV1-3*01, IGHV3-66*03, IGHV3-7*01 and IGHV3-9*01.

23. A vertebrate or cell according to any preceding claim, in which the antibody heavy chain is a product of the recombination of JH6*02 with a human VH gene segment recited in Claim 22 and/or a D gene segment recited in Claim 18.

24. A vertebrate or cell according to any preceding claim, in which all endogenous non-human vertebrate heavy chain variable region gene segments have been inactivated in the genome and/or in which the genome is homozygous for said heavy chain locus.

25. A method for producing a heavy chain, VH domain or an antibody specific to a target antigen, the method comprising immunizing a non-human vertebrate according to any of Claims 1, 2 and 12 to 24 with the antigen and isolating the heavy chain, VH domain or an antibody specific to a target antigen or a cell producing the heavy chain, VH domain or an antibody, in which the heavy chain, VH domain or an antibody comprises a HCDR3 that is derived from the recombination of human JH6*02 with a human VH gene segment and a human D gene segment

in which the JH6*02 gene segment comprises the following nucleotide sequence: ATTACTA CTACTACTAC GGTATGGACG TCTGGGGCCA AGGGACCACG GTCACCGTCT CCTCAG,

in which the immunised vertebrate produces an antibody heavy chain specific for a target antigen, in which the variable domain of the heavy chain is the product of recombination between a human VH, human D and JH6*02, and in which the HCDR3 length is at least 20 amino acids.

26. A method according to Claim 25, in which the constant region of the locus is a non-human vertebrate constant region, and the non-human constant region of the isolated heavy chain or antibody is replaced with a human constant region.

27. A method according to Claim 26, in which the non-human vertebrate is mouse or rat.

28. A heavy chain, VH domain or an antibody produced by the method according to any of Claims 25 to 27, in which the HCDR3 length is at least 20 amino acids.

29. A B-cell or hybridoma expressing a heavy chain VH domain that is identical to the VH domain of the heavy chain according to Claim 28.

30. A nucleic acid encoding a VH domain of the heavy chain according to Claim 28, or encoding the heavy chain according to Claim 28.

31. A vector comprising the nucleic acid according to Claim 30.

32. A vector according to Claim 31, which is a CHO cell or HEK293 cell vector.

33. A vector according to Claim 31 or 32, in which the vector is in a host cell.

34. A vector according to Claim 33, in which the host cell is a CHO cell or HEK293 cell.

35. A heavy chain or antibody, or B cell or hybridoma, according to Claim 28 or 29 in which the constant region is mouse or rat.

36. A nucleic acid according to Claim 30 or vector according to any of Claims 31 to 34 in which the nucleic acid encodes the heavy chain according to Claim 28 and the constant region is mouse or rat.

37. A heavy chain or an antibody obtainable by a method according to any of Claims 25 to 27, in which the HCDR3 length is at least 20 amino acids and the constant region is mouse or rat.

38. A non-human vertebrate or a non-human vertebrate cell having a genome comprising first and second human JH6 gene segments, in which the first gene segment is the JH6*02 gene segment comprising the following nucleotide sequence: ATTACTA CTACTACTAC GGTATGGACG TCTGGGGCCA AGGGACCACG GTCACCGTCT CCTCAG and the second gene segment is SEQ ID NO: 244 and in which the vertebrate or cell genome comprises one or more human VH gene segments and one or more human D gene segments upstream of a constant region; in which the gene segments in the heavy chain locus are operably linked to the constant region thereof so that the vertebrate is capable of producing an antibody heavy chain produced by recombination of the human JH6*02 with a human D segment and a human VH segment.

39. A vertebrate or cell according to Claim 38, in which the vertebrate is a mouse or rat.

40. A cell according to Claim 38, which is an ES cell or a B-cell.

41. A vertebrate or cell according to any of Claims 38 to 40 in which the constant region is an endogenous constant region of said vertebrate.

42. A vertebrate or cell or method according to Claim 41 in which the constant region is an endogenous mouse or rat constant region.

43. A vertebrate or cell according to Claim 38, in which (i) the genome comprises a third human gene segment of said type, the third gene segment being different from the first and

second gene segments and/or (ii) the first and second gene segments are cis on the same chromosome.

44. A vertebrate or cell according to Claim 43, in which the third gene segment is also cis on said chromosome.

45. A vertebrate or cell according to Claim 44, in which the gene segments are targeted insertions into an endogenous non-human Ig locus.

46. A vertebrate or cell according to any of Claims 38 to 40, in which the first and second gene segments are trans on different chromosome.

47. A population of non-human vertebrates comprising first and second human JH6 gene segments, in which the first gene segment is the JH6*02 gene segment comprising the following nucleotide sequence: ATTACTA CTACTACTAC GGTATGGACG TCTGGGGCCA AGGGACCACG GTCACCGTCT CCTCAG and the second gene segment is SEQ lD NO: 244, in which the first gene segment is provided in the genome of a first vertebrate of the population, and the second gene segment is provided in the genome of a second vertebrate of the population

and in which each vertebrate genome comprises one or more human VH gene segments and one or more D gene segments upstream of a constant region; in which the gene segments in the heavy chain locus are operably linked to the constant region thereof so that the vertebrate is capable of producing an antibody heavy chain produced by recombination of a human JH6 with a human D segment and a human VH segment.

48. A population according to Claim 47 in which the non-human vertebrates are mice or rats.

49. A population according to Claim 47 or 48, in which the genome of the first vertebrate does not comprise the second gene segment and/or the population comprises a third human gene segment of said type, the third gene segment being different from the first and second gene segments.

50. A population according to any of Claims 47 to 49, in which the first and third gene segments are present in the genome of the first vertebrate.

51. A population according to any of Claims 47 to 50, in which the gene segments are targeted insertions into an endogenous non-human Ig locus in the respective genome.

52. A method of enhancing the human immunoglobulin gene diversity of a non-human vertebrate, the method comprising providing the vertebrate with a genome comprising first and second human JH6 gene segments, in which the first gene segment is the JH6*02 gene segment comprising the following nucleotide sequence: ATTACTA CTACTACTAC GGTATGGACG TCTGGGGCCA AGGGACCACG GTCACCGTCT CCTCAG and the second gene segment is SEQ ID NO: 244,

in which the vertebrate genome comprises one or more human VH gene segments and one or more human D gene segments upstream of a constant region; in which the gene segments in the heavy chain locus are operably linked to the constant region thereof so that the vertebrate is capable of producing an antibody heavy chain produced by recombination of the human JH6*02 with a human D segment and a human VH segment.

53. A method according to Claim 52, in which the vertebrate is a mouse or rat.

54. A method of providing an enhanced human immunoglobulin gene segment repertoire, the method comprising providing a population according to any of Claims 47 to 51.

55. The vertebrate or cell according to any of Claims 1 to 24, in which the constant region is a mouse or rat constant region.

56. A vertebrate or cell according to Claim 55, in which the constant region is an endogenous constant region of said vertebrate or cell.

57. Use of human JH6*02 for generating a HCDR3 of at least 20 amino acids in a non-human vertebrate whose genome comprises an immunoglobulin heavy chain locus comprising human gene segment JH6*02, one or more human VH gene segments and one or more human D gene segments upstream of a constant region; in which the gene segments in the heavy chain locus are operably linked to the constant region thereof so that the vertebrate is capable of producing an antibody heavy chain produced by recombination of the human JH6*02 with a human D segment and a human VH segment and in which the JH6*02 gene segment comprises the following nucleotide sequence: ATTACTA CTACTACTAC GGTATGGACG TCTGGGGCCA AGGGACCACG GTCACCGTCT CCTCAG.

58. Use according to Claim 57 in which the antibody heavy chain specifically binds a target antigen.

59. Use according to Claim 57 or 58, in which the vertebrate is according to any of Claims 1, 2 and 12 to 24.