CLAIM

1. A genetically modified non-human animal comprising a modified immunoglobulin heavy chain locus, wherein the modified immunoglobulin heavy chain locus comprises an IgG constant region gene, wherein the IgG constant region gene encodes an IgG heavy chain constant region lacking a CH1 domain, wherein the genetically modified non-human animal expresses a heavy-chain antibody;
   preferably, the animal comprises exactly one IgG constant region gene;
   preferably, the IgG heavy chain constant region gene is IGHG1;
   preferably, the IgG heavy chain constant region comprises or consists of a CH2 domain and a CH3 domain, and optionally a hinge region.

2. A genetically modified non-human animal whose genome comprises a germline genetic modification comprising a deletion of IGHG3, IGHG2b, and IGHG2c genes and a deletion of the CH1 exon of IGHG1 gene at an endogenous immunoglobulin heavy chain gene locus.

3. The animal of claim 2, wherein the germline genetic modification further comprises a deletion of endogenous IGHE gene at the endogenous immunoglobulin heavy chain gene locus.

4. The animal of claim 2 or 3, wherein the genetic modification further comprises a deletion of endogenous Sγ2b, Sγ2c, and Sε switch regions at the endogenous immunoglobulin heavy chain gene locus.

5. The animal of any one of claims 2-4, wherein the modified immunoglobulin heavy chain gene locus comprises a modified IGHG1 gene lacking a sequence encoding a CH1 domain, wherein the modified IGHG1 gene comprises a sequence that is at least 80%, 90%, 95% or 99% identical to SEQ ID NO: 1.

6. The animal of any one of claims 2-5, wherein the genetic modification further comprises a deletion of endogenous Sγ3 switch region at the endogenous immunoglobulin heavy chain gene locus.

7. The animal of any one of claims 2-6, wherein:

   (i) the animal's genome comprises endogenous Sμ, Sγ1, Sα switch regions, the modified rodent IGHG1 gene lacking a sequence encoding a CH1 domain, and endogenous IGHM, IGHδ, IGHA genes;
   (ii) the genetic modification further comprises a deletion of endogenous IGHM and IGHδ genes at the endogenous immunoglobulin heavy chain gene locus; preferably, the animal genome comprises endogenous Sμ, Sγ1, Sα switch regions, the modified IGHG1 gene lacking a sequence encoding a CH1 domain, and the endogenous IGHA gene; preferably, the Sμ and Sγ1 switch regions are linked with a sequence that is at least 80%, 90%, 95% or 99% identical to SEQ ID NO: 8;

(iii) the genetic modification further comprises a deletion of the CH1 coding sequence of IGHM gene at the endogenous immunoglobulin heavy chain gene locus; preferably, the animal's genome comprises endogenous Sμ, Sγ1, Sα switch regions, a modified endogenous IGHM gene lacking a sequence encoding a CH1 domain, the modified IGHG1 gene lacking a sequence encoding a CH1 domain, and endogenous IGHδ, IGHA genes; preferably, the Sμ switch region and the modified IGHM gene are linked with a sequence that is at least 80%, 90%, 95% or 99% identical to SEQ ID NO: 10;

(iv) wherein the genetic modification further comprises a deletion of the CH1 exon of IGHM gene and a deletion of IGHδ gene at the endogenous immunoglobulin heavy chain gene locus; preferably, the animal's genome comprises endogenous Sμ, Sγ1, Sα switch regions, a modified IGHM gene lacking a sequence encoding a CH1 domain, the modified IGHG1 gene lacking a sequence encoding a CH1 domain, and an endogenous IGHA gene; or,

(v) the genetic modification further comprises a deletion of the CH1 exon of IGHM gene and a deletion of the CH1 coding sequence of IGHδ gene at the endogenous immunoglobulin heavy chain gene locus; preferably, the animal's genome comprises endogenous Sμ, Sγ1, Sα switch regions, a modified IGHM gene lacking a sequence encoding a CH1 domain, a modified IGHδ gene lacking a sequence encoding a CH1 domain, the modified IGHG1 gene lacking a sequence encoding a CH1 domain, and an endogenous IGHA gene; preferably, the modified IGHM gene are linked with a sequence that is at least 80%, 90%, 95% or 99% identical to SEQ ID NO: 10, and the modified IGHδ gene comprises a sequence that is at least 80%, 90%, 95%, or 99% identical to SEQ ID NO: 41.

8. The animal of any one of claims 2-5, wherein the genetic modification further comprises a deletion of endogenous Sγ1 switch region at the endogenous immunoglobulin heavy chain gene locus.

9. The animal of claim 8, wherein:

(i) the animal's genome comprises endogenous Sμ, Sγ3, Sα switch regions, the modified IGHG1 gene lacking a sequence encoding a CH1 domain, and endogenous IGHM, IGHδ, IGHA genes;

(ii) the genetic modification further comprises a deletion of endogenous Sγ3 switch region at the endogenous immunoglobulin heavy chain gene locus;

(iii) the genetic modification further comprises a deletion of endogenous IGHM and IGHδ genes at the endogenous immunoglobulin heavy chain gene locus; or,

(iv) the animal's genome comprises endogenous Sμ, Sα switch regions, the modified IGHG1 gene lacking a sequence encoding a CH1 domain, and the endogenous IGHA gene; preferably, the Sμ switch region and the modified IGHG1 gene are linked with a sequence that is at least 80%, 90%, 95%, or 99% identical to SEQ ID NO: 9.

10. The animal of any one of claims 2-6 and 8, wherein the modified genome comprises a functional IGHM gene.

11. A genetically-modified non-human animal, wherein:

(i) whose genome comprises the following elements, at an endogenous immunoglobulin heavy chain gene locus in a 5' to 3' order: Sμ switch region, IGHM gene, IGHδ gene, Sγ1 switch region, IGHG1 gene lacking a sequence encoding a CH1 domain, Sα switch region, and IGHA gene; wherein the elements are operably linked; preferably, the endogenous immunoglobulin heavy chain constant region gene locus consists of the following functional genes and switch regions: Sμ switch region, IGHM gene, IGHδ gene, Sγ1 switch region, IGHG1 gene lacking a sequence encoding a CH1 domain, Sα switch region, and IGHA gene;

(ii) whose genome comprises the following elements, at an endogenous immunoglobulin heavy chain gene locus in a 5' to 3' order: Sμ switch region, IGHM gene, IGHδ gene, Sγ3 switch region, IGHG1 gene lacking a sequence encoding a CH1 domain, Sα switch region, and IGHA gene; wherein the elements are operably linked; preferably, the endogenous immunoglobulin heavy chain constant region gene locus consists of the following functional genes and switch regions: Sμ switch region, IGHM gene, IGHδ gene, Sγ3 switch region, IGHG1 gene lacking a sequence encoding a CH1 domain, Sα switch region, and IGHA gene;

(iii) whose genome comprises the following elements, at an endogenous immunoglobulin heavy chain gene locus in a 5' to 3' order: Sμ switch region, Sγ1 switch region, IGHG1 gene lacking a sequence encoding a CH1 domain, Sα switch region, and IGHA gene; wherein the elements are operably linked; preferably, the endogenous immunoglobulin heavy chain constant region gene locus consists of the following functional genes and switch regions: Sμ switch region, Sγ1 switch region, IGHG1 gene lacking a sequence encoding a CH1 domain, Sα switch region, and IGHA gene;

(iv) whose genome comprises the following elements, at an endogenous immunoglobulin heavy chain gene locus in a 5' to 3' order: Sμ switch region, IGHG1 gene lacking a sequence encoding a CH1 domain, Sα switch region, and IGHA gene; wherein the elements are operably linked; preferably, the endogenous immunoglobulin heavy chain constant region gene locus consists of the following functional genes and switch regions: Sμ switch region, IGHG1 gene lacking a sequence encoding a CH1 domain, Sα switch region, and IGHA gene;

(v) whose genome comprises the following elements, at an endogenous immunoglobulin heavy chain gene locus in a 5' to 3' order: Sμ switch region, IGHM gene lacking a sequence encoding a CH1 domain, IGHδ gene, Sγ1 switch region, IGHG1 gene lacking a sequence encoding a CH1 domain, Sα switch region, and IGHA gene; wherein the elements are operably linked; preferably, the endogenous immunoglobulin heavy chain constant region gene locus consists of the following functional genes and switch regions: Sμ switch region, IGHM gene lacking a sequence encoding a CH1 domain, IGHδ gene, Sγ1 switch region, IGHG1 gene lacking a sequence encoding a CH1 domain, Sα switch region, and IGHA gene;

(vi) whose genome comprises the following elements, at an endogenous immunoglobulin heavy chain gene locus in a 5' to 3' order: Sμ switch region, IGHM gene lacking a sequence encoding a CH1 domain, Sγ1 switch region, IGHG1 gene lacking a sequence encoding a CH1 domain, Sα switch region, and IGHA gene; wherein the elements are operably linked; preferably, the endogenous immunoglobulin heavy chain constant region gene locus consists of the following functional genes and switch regions: Sμ switch region, IGHM gene lacking a sequence encoding a CH1 domain, Sγ1 switch region, IGHG1 gene lacking a sequence encoding a CH1 domain, Sα switch region, and IGHA gene; or,

(vii) whose genome comprises the following elements, at an endogenous immunoglobulin heavy chain gene locus in a 5' to 3' order: Sμ switch region, IGHM gene lacking a sequence encoding a CH1 domain, IGHδ gene lacking a sequence encoding a CH1 domain, Sγ1 switch region, IGHG1 gene lacking a sequence encoding a CH1 domain, Sα switch region, and IGHA gene; wherein the elements are operably linked; preferably, the endogenous immunoglobulin heavy chain constant region gene locus consists of the following functional genes and switch regions: Sμ switch region, IGHM gene lacking a sequence encoding a CH1 domain, IGHδ gene lacking a sequence encoding a CH1 domain, Sγ1 switch region, IGHG1 gene lacking a sequence encoding a CH1 domain, Sα switch region, and IGHA gene.

12. The genetically modified non-human animal of any one of claims 1-11, wherein:

(i) the animal expresses a heavy-chain antibody comprising an IgG heavy chain constant region lacking the CH1 domain;

(ii) the genetically modified non-human animal does not express IgG antibodies comprising light chains; or,

(iii) the animal expresses IgM, IgD, and/or IgA (e.g., functional IgM, IgD, and/or IgA).

13. The genetically modified non-human animal of any one of claims 1-12, wherein the animal comprises at an endogenous immunoglobulin heavy chain gene locus, one or more human IGHV genes, one or more human IGHD genes, and one or more human IGHJ genes, wherein the human IGHV genes, the human IGHD genes, and the human IGHJ genes are operably linked and can undergo VDJ rearrangement.

14. The genetically modified non-human animal of any one of claims 1-13, wherein the animal is homozygous or heterozygous with respect to the immunoglobulin heavy chain gene locus.

15. The genetically modified non-human animal of any one of claims 1-14, wherein the animal comprises an endogenous light chain immunoglobulin gene locus or comprises a disruption in the endogenous immunoglobulin light chain gene locus.

16. The genetically modified non-human animal of any one of claims 1-15, wherein the animal lacks an endogenous immunoglobulin heavy chain variable region locus that is capable of rearranging and forming a nucleic acid sequence that encodes an endogenous heavy chain variable domain.

17. The genetically modified non-human animal of any one of claims 1-16, wherein the animal can produce a humanized antibody.

18. The genetically modified non-human animal of any one of claims 1-17, wherein the animal is a mammal, e.g., a rodent, such as a mouse.

19. A cell obtained from the genetically modified non-human animal of any one of claims 1-18.

20. A method of making an antibody that specifically binds to an antigen, the method comprising
    a) exposing the genetically modified non-human animal of any one of claims 1-18 to the antigen;
    b) sequencing nucleic acids encoding human immunoglobulin heavy chain variable regions in a cell that expresses a heavy-chain antibody that specifically binds to the antigen; and
    c) operably linking in a cell the nucleic acid encoding the human immunoglobulin heavy chain variable region with a nucleic acid encoding a human immunoglobulin heavy chain constant region.