

What is claimed is:

1. A non-human animal comprising at an endogenous Major Histocompatibility Complex II (MHC II) α gene locus a nucleotide sequence encoding a chimeric human/non-human MHC II α polypeptide,

wherein a human portion of the chimeric human/non-human MHC II α polypeptide comprises a human MHC II α extracellular domain, and

wherein the animal expresses a functional MHC II complex on a surface of a cell of the animal.

2. The animal of claim 1, wherein the human MHC II α extracellular domain comprises human $\alpha 1$ and $\alpha 2$ domains.

3. The animal of claim 1, wherein the nucleotide sequence is expressed under regulatory control of endogenous non-human MHC II α promoter and regulatory elements.

4. The animal of claim 1, wherein a non-human portion of the chimeric human/non-human MHC II α polypeptide comprises transmembrane and cytoplasmic domains of an endogenous non-human MHC II α polypeptide.

5. The animal of claim 1, wherein the human portion of the chimeric human/non-human MHC II α polypeptide is derived from a human HLA class II protein selected from the group consisting of HLA-DR, HLA-DQ, and HLA-DP.

6. The animal of claim 5, wherein the human portion of the chimeric human/non-human MHC II α polypeptide is derived from a human HLA-DR4 protein.

7. The animal of claim 1, wherein the animal is a rodent.

8. The rodent of claim 7, wherein the rodent is a mouse.

9. The animal of claim 1, wherein the animal further comprises at an endogenous MHC II β gene locus a nucleotide sequence encoding a chimeric human/non-human MHC II β polypeptide.

10. A non-human animal comprising at an endogenous MHC II β gene locus a nucleotide sequence encoding a chimeric human/non-human MHC II β polypeptide,

wherein a human portion of the chimeric human/non-human MHC II β polypeptide comprises a human MHC II β extracellular domain, and

wherein the animal expresses a functional MHC II complex on a surface of a cell of the animal.

11. The animal of claim 10, wherein the human MHC II β extracellular domain comprises human β 1 and β 2 domains.
12. The animal of claim 10, wherein the nucleotide sequence is expressed under regulatory control of endogenous non-human MHC II β promoter and regulatory elements.
13. The animal of claim 10, wherein a non-human portion of the chimeric human/non-human MHC II β polypeptide comprises transmembrane and cytoplasmic domains of an endogenous non-human MHC II β polypeptide.
14. The animal of claim 10, wherein the human portion of the chimeric human/non-human MHC II β polypeptide is derived from a human HLA class II protein selected from the group consisting of HLA-DR, HLA-DQ, and HLA-DP.
15. The animal of claim 14, wherein the human portion of the chimeric human/non-human MHC II β polypeptide is derived from a human HLA-DR4 protein.
16. The animal of claim 10, wherein the animal is a rodent.
17. The rodent of claim 16, wherein the rodent is a mouse.
18. The animal of claim 10, wherein the animal further comprises at an endogenous MHC II α gene locus a nucleotide sequence encoding a chimeric human/non-human MHC II α polypeptide.
19. A rodent comprising at an endogenous MHC II gene locus a first nucleotide sequence encoding a chimeric human/rodent MHC II α polypeptide and a second nucleotide sequence encoding a chimeric human/rodent MHC II β polypeptide,
wherein a human portion of the chimeric human/rodent MHC II α polypeptide comprises a human MHC II α extracellular domain and a human portion of the chimeric human/rodent MHC II β polypeptide comprises a human MHC II β extracellular domain, and
wherein the chimeric human/rodent MHC II α and MHC II β polypeptides form a functional MHC II complex on a surface of a cell of the rodent.
20. The rodent of claim 19, wherein the human MHC II α extracellular domain comprises human α 1 and α 2 domains.
21. The rodent of claim 19, wherein the human MHC II β extracellular domain comprises human β 1 and β 2 domains.
22. The rodent of claim 19, wherein the first nucleotide sequence is expressed under regulatory control of endogenous rodent MHC II α promoter and regulatory elements, and

the second nucleotide sequence is expressed under regulatory control of endogenous rodent MHC II β promoter and regulatory elements.

23. The rodent of claim 19, wherein a rodent portion of the chimeric human/rodent MHC II α polypeptide comprises transmembrane and cytoplasmic domains of an endogenous rodent MHC II α polypeptide.

24. The rodent of claim 19, wherein a rodent portion of the chimeric human/rodent MHC II β polypeptide comprises transmembrane and cytoplasmic domains of an endogenous rodent MHC II β polypeptide.

25. The rodent of claim 19, wherein the human portions of the chimeric human/rodent MHC II α and β polypeptides are derived from a human HLA class II protein selected from the group consisting of HLA-DR, HLA-DQ, and HLA-DP.

26. The rodent of claim 25, wherein the human portions of the chimeric human/rodent MHC II α and β polypeptides are derived from a human HLA-DR4 protein.

27. The rodent of claim 19, wherein the rodent is a mouse.

28. The mouse of claim 27, wherein rodent portions of the chimeric MHC II α and β polypeptides are derived from a mouse H-2E protein.

29. The rodent of claim 19, wherein the rodent does not express functional endogenous MHC II polypeptides from their endogenous rodent MHC II loci.

30. A mouse comprising at an endogenous mouse MHC II locus a first nucleotide sequence encoding a chimeric human/mouse MHC II α polypeptide and a second nucleotide sequence encoding a chimeric human/mouse MHC II β polypeptide,

wherein a human portion of the chimeric MHC II α polypeptide comprises an extracellular domain derived from an α polypeptide of a human HLA-DR4 protein and the human portion of the chimeric MHC II β polypeptide comprises an extracellular domain derived from a β polypeptide of a human HLA-DR4 protein,

wherein a mouse portion of the chimeric MHC II α polypeptide comprises transmembrane and cytoplasmic domains of a mouse H-2E α chain and a mouse portion of the chimeric MHC II β polypeptide comprises transmembrane and cytoplasmic domains of a mouse H-2E β chain,

and wherein the mouse expresses a functional chimeric HLA-DR4/H-2E MHC II complex on a surface of a cell of the mouse.

31. The mouse of claim 30, wherein the extracellular domain of the α polypeptide comprises human α 1 and α 2 domains.
32. The mouse of claim 30, wherein the extracellular domain of the β polypeptide comprises human β 1 and β 2 domains.
33. The mouse of claim 30, wherein the first nucleotide sequence is expressed under regulatory control of endogenous mouse MHC II α promoter and regulatory elements, and the second nucleotide sequence is expressed under regulatory control of endogenous mouse MHC II β promoter and regulatory elements.
34. The mouse of claim 30, wherein the mouse does not express functional endogenous MHC II polypeptides from their endogenous mouse loci.
35. A method of modifying an MHC II locus of a mouse to express a chimeric human/mouse MHC II complex comprising replacing at the endogenous mouse MHC II locus a nucleotide sequence encoding a mouse MHC II complex with a nucleotide sequence encoding a chimeric human/mouse MHC II complex.
36. The method of claim 35, wherein the nucleotide sequence encoding the chimeric human/mouse MHC II complex comprises a first nucleotide sequence encoding an extracellular domain of a human MHC II α polypeptide and a transmembrane and cytoplasmic domains of a mouse MHC II α polypeptide and a second nucleotide sequence encoding an extracellular domain of a human MHC II β polypeptide and transmembrane and cytoplasmic domains of a mouse MHC II β polypeptide.
37. The method of claim 35, wherein a human portion of the chimeric MHC II complex is derived from a human HLA class II protein selected from the group consisting of HLA-DR, HLA-DQ, and HLA-DP.
38. The method of claim 35, wherein a mouse portion of the chimeric MHC II complex is derived from a mouse H-2E protein, and a human portion of the chimeric MHC II complex is derived from a human HLA-DR4 protein.
39. The method of claim 36, wherein human portions of chimeric MHC II α and β polypeptides are derived a human HLA class II protein selected from the group consisting of HLA-DR, HLA-DQ, and HLA-DP.
40. The method of claim 36, wherein mouse portions of chimeric MHC II α and β polypeptides are derived from a mouse H-2E protein, and human portions of chimeric MHC II α and β polypeptides are derived from a human HLA-DR4 protein.

41. The method of claim 35, wherein the replacement is made in a single ES cell, and the single ES cell is introduced into a mouse embryo to make a mouse.

CLAIMS

What is claimed is:

1. A mouse comprising at an endogenous Major Histocompatibility Complex (MHC) II gene locus a first nucleotide sequence encoding a chimeric human/mouse MHC II α polypeptide and a second nucleotide sequence encoding a chimeric human/mouse MHC II β polypeptide, wherein a human portion of the chimeric human/mouse MHC II α polypeptide comprises a human MHC II α 2 domain and a human portion of the chimeric human/mouse MHC II β polypeptide comprises a human MHC II β 2 domain,

wherein the first nucleotide sequence is expressed under regulatory control of an MHC II α promoter, and the second nucleotide sequence is expressed under regulatory control of an MHC II β promoter, and

wherein the mouse expresses the chimeric human/mouse MHC II α and β polypeptides on the surface of an antigen presenting cell of the mouse.

2. The mouse of claim 1, wherein the chimeric human/mouse MHC II α polypeptide further comprises a human α 1 domain.

3. The mouse of claim 1, wherein the chimeric human/mouse MHC II β polypeptide further comprises a human β 1 domain.

4. The mouse of claim 1, wherein the first nucleotide sequence is expressed under regulatory control of endogenous mouse MHC II α promoter and regulatory elements, and the second nucleotide sequence is expressed under regulatory control of endogenous mouse MHC II β promoter and regulatory elements.

5. The mouse of claim 1, wherein a mouse portion of the chimeric human/mouse MHC II α polypeptide comprises transmembrane and cytoplasmic domains of an endogenous mouse MHC II α polypeptide.

6. The mouse of claim 1, wherein a mouse portion of the chimeric human/mouse MHC II β polypeptide comprises transmembrane and cytoplasmic domains of an endogenous mouse MHC II β polypeptide.

7. The mouse of claim 1, wherein the human portion of the chimeric human/mouse MHC II α polypeptide is encoded by a Human Leukocyte Antigen (HLA) class II gene selected from the group consisting of any α chain gene of HLA-DR, HLA-DQ, and HLA-DP; and wherein the human portion of the chimeric human/mouse MHC β polypeptide is encoded by a HLA class II gene selected from the group consisting of any β chain gene of HLA-DR, HLA-DQ, and HLA-DP.

8. The mouse of claim 7, wherein the human portion of the chimeric human/mouse MHC II α polypeptide is encoded by a human HLA-DRA gene and the human portion of the chimeric human/mouse MHC II β polypeptide is encoded by a human HLA-DRB1*04 gene.

9. The mouse of claim 1, wherein the mouse portion of the chimeric human/mouse MHC II α polypeptide comprises cytoplasmic and transmembrane domains from a mouse H-2E α polypeptide, and the mouse portion of the chimeric human/mouse MHC II β polypeptide comprises cytoplasmic and transmembrane domains from a mouse H-2E β polypeptide.

10. The mouse of claim 1, wherein the mouse does not express functional endogenous MHC II polypeptides from their endogenous mouse MHC II loci.

11. A mouse comprising at an endogenous mouse Major Histocompatibility Complex (MHC) II locus a first nucleotide sequence encoding a chimeric human/mouse MHC II α polypeptide and a second nucleotide sequence encoding a chimeric human/mouse MHC II β polypeptide, wherein a human portion of the chimeric MHC II α polypeptide comprises a human $\alpha 2$ domain encoded by a human HLA-DRA gene and the human portion of the chimeric MHC II β polypeptide comprises a human $\beta 2$ domain encoded by a human HLA-DRB gene,

wherein a mouse portion of the chimeric MHC II α polypeptide comprises transmembrane and cytoplasmic domains of a mouse H-2E α chain and a mouse portion of the chimeric MHC II β polypeptide comprises transmembrane and cytoplasmic domains of a mouse H-2E β chain,

wherein the first nucleotide sequence is expressed under regulatory control of an MHC II α promoter and the second nucleotide sequence is expressed under regulatory control of an MHC II β promoter,

and wherein the mouse expresses a chimeric HLA-DR/H-2E MHC II polypeptide on the surface of an antigen presenting cell of the mouse.

12. The mouse of claim 11, wherein the extracellular domain of the α polypeptide further comprises a human $\alpha 1$ domain encoded by a human HLA-DRA gene.

13. The mouse of claim 11, wherein the extracellular domain of the β polypeptide further comprises a human $\beta 1$ domain encoded by a human HLA-DRB gene.

14. The mouse of claim 11, wherein the first nucleotide sequence is expressed under regulatory control of endogenous mouse MHC II α promoter and regulatory elements, and the second nucleotide sequence is expressed under regulatory control of endogenous mouse MHC II β promoter and regulatory elements.

15. The mouse of claim 11, wherein the mouse does not express functional endogenous MHC II polypeptides from their endogenous mouse loci.

16. The mouse of claim 11, wherein the mouse expresses a chimeric HLA-DR4/H-2E MHC II polypeptide.