What is claimed is:

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

wherein a human portion of the chimeric polypeptide comprises an extracellular domain of a human MHC I polypeptide, and

wherein the non-human animal expresses the chimeric human/non-human MHC I polypeptide.

2. The non-human animal of claim 1, wherein the animal is a rodent, wherein the rodent comprises at an endogenous Major Histocompatibility Complex I (MHC I) locus a nucleotide sequence encoding a chimeric human/rodent MHC I polypeptide,

wherein a human portion of the chimeric polypeptide comprises an extracellular domain of a human MHC I polypeptide, and

wherein the rodent expresses the chimeric human/rodent MHC I polypeptide.

3. The rodent of claim 2, wherein the rodent does not express an extracellular domain of an endogenous rodent MHC I polypeptide from an endogenous rodent MHC I locus.

4. The rodent of claim 2, wherein the nucleotide sequence is operably linked to endogenous rodent regulatory elements.

5. The rodent of claim 2, wherein the rodent is a mouse.

6. The mouse of claim 5, wherein the endogenous locus is a mouse H-2K locus.

7. The rodent of claim 2, wherein the human portion of the chimeric polypeptide comprises a human leader sequence.

8. The rodent of claim 2, wherein the human portion of the chimeric polypeptide comprises α1, α2, and α3 domains of the human MHC I polypeptide.

9. The rodent of claim 2, wherein a rodent portion of the chimeric polypeptide comprises transmembrane and cytoplasmic domains of an endogenous rodent MHC I polypeptide.

10. The rodent of claim 9, wherein the rodent is a mouse, the endogenous rodent MHC I locus is an H-2K locus, and the endogenous rodent MHC I polypeptide is H-2K.

11. The rodent of claim 2, wherein the human MHC I polypeptide is selected from the group consisting of HLA-A, HLA-B, and HLA-C.

12. The rodent of claim 11, wherein the human MHC I polypeptide is an HLA-A polypeptide.

13. A mouse comprising at an endogenous H-2K locus a nucleotide sequence encoding a chimeric human/mouse MHC I polypeptide,

wherein a human portion of the chimeric polypeptide comprises an extracellular domain of a human HLA-A2 polypeptide and a mouse portion comprises transmembrane and cytoplasmic domains of a mouse H-2K polypeptide, and

wherein the mouse expresses the chimeric HLA-A2/H-2K polypeptide.

14. The mouse of claim 13, wherein the mouse does not express an extracellular domain of the mouse H-2K polypeptide from an endogenous H-2K locus.

15. The mouse of claim 13, wherein the human portion of the chimeric polypeptide comprises a human leader sequence.

16. The mouse of claim 13, wherein the nucleotide sequence is operably liked to endogenous mouse regulatory elements.

17. The mouse of claim 13, wherein the human portion of the chimeric polypeptide comprises α1, α2, and α3 domains of the human HLA-A2 polypeptide.

18. The mouse of claim 13, wherein the human HLA-A2 polypeptide is an HLA-A2.1 polypeptide.

19. The mouse of claim 13, wherein the mouse H-2K locus is an H-2Kb locus.

20. A method of modifying an MHC I locus of a mouse to express a chimeric human/mouse MHC I polypeptide, wherein the method comprises replacing at the endogenous MHC I locus a nucleotide sequence encoding an extracellular domain of a mouse MHC I polypeptide with a nucleotide sequence encoding an extracellular domain of a human MHC I polypeptide.

21. The method of claim 20, wherein the mouse does not express the extracellular domain of the mouse MHC I polypeptide from an endogenous mouse MHC I locus.

22. The method of claim 20, wherein the mouse MHC I locus is an H-2K locus, and the mouse MHC I polypeptide is an H-2K polypeptide.

23. The method of claim 20, wherein the human MHC I polypeptide is an HLA-A polypeptide.

24. The method of claim 20, wherein the mouse expresses α1, α2, and α3 domains of the human MHC I polypeptide.

25. The method of claim 20, wherein the mouse expresses transmembrane and cytoplasmic domains of the mouse MHC I polypeptide.

26. The method of claim 20, 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.

27. A non-human animal comprising at an endogenous non-human β2 microglobulin locus a nucleotide sequence encoding a polypeptide comprising a human β2 microglobulin amino acid sequence, wherein the non-human animal expresses a human or humanized β2 microglobulin polypeptide.

28. The non-human animal of claim 27, wherein the animal is a rodent, wherein the rodent comprises at an endogenous rodent β2 microglobulin locus a nucleotide sequence encoding a polypeptide comprising a human β2 microglobulin amino acid sequence, and wherein the rodent expresses a human or humanized β2 microglobulin polypeptide.

29. The rodent of claim 28, wherein the rodent does not express a functional endogenous rodent β2 microglobulin polypeptide from an endogenous rodent β2 microglobulin locus.

30. The rodent of claim 28, wherein the nucleotide sequence is operably linked to endogenous rodent β2 microglobulin regulatory elements.

31. The rodent of claim 28, wherein the nucleotide sequence comprises a nucleotide sequence set forth in exon 2 to exon 4 of a human β2 microglobulin gene.

32. The rodent of claim 28, wherein the nucleotide sequence comprises nucleotide sequences set forth in exons 2, 3, and 4 of a human β2 microglobulin gene.

33. The rodent of claim 31, wherein the nucleotide sequence further comprises a nucleotide sequence set forth in exon 1 of a rodent β2 microglobulin gene.

34. The rodent of claim 32, wherein the nucleotide sequence further comprises a nucleotide sequence set forth in exon 1 of a rodent β2 microglobulin gene.

35. The rodent of claim 28, wherein the rodent is a mouse.

36. A mouse comprising at an endogenous β2 microglobulin locus a nucleotide sequence encoding a polypeptide comprising a human β2 microglobulin amino acid sequence, wherein the mouse expresses a human or humanized β2 microglobulin polypeptide.

37. The mouse of claim 36, wherein the mouse does not express a functional endogenous mouse β2 microglobulin from an endogenous mouse β2 microglobulin locus.

38. The mouse of claim 36, wherein the nucleotide sequence is operably linked to endogenous mouse regulatory elements.

39. The mouse of claim 36, wherein the nucleotide sequence comprises a nucleotide sequence set forth in exon 2 to exon 4 of a human β2 microglobulin gene.

40. The mouse of claim 36, wherein the nucleotide sequence comprises nucleotide sequences set forth in exons 2, 3, and 4 of a human β2 microglobulin gene.

41. The mouse of claim 39, wherein the nucleotide sequence further comprises a nucleotide sequence set forth in exon 1 of a mouse β2 microglobulin gene.

42. The mouse of claim 40, wherein the nucleotide sequence further comprises a nucleotide sequence set forth in exon 1 of a mouse β2 microglobulin gene.

43. A method of modifying a β2 microglobulin locus of a mouse to express a human or humanized β2 microglobulin polypeptide, wherein the method comprises replacing at the endogenous mouse β2 microglobulin locus a nucleotide sequence encoding a mouse β2 microglobulin polypeptide with a nucleotide sequence encoding a human or humanized β2 microglobulin polypeptide.

44. The method of claim 43, wherein the mouse does not express a functional mouse β2 microglobulin polypeptide from an endogenous β2 microglobulin locus.

45. The method of claim 43, wherein the nucleotide sequence encoding the human or humanized β2 microglobulin polypeptide comprises a nucleotide sequence set forth in exon 2 to exon 4 of a human β2 microglobulin gene.

46. The method of claim 43, wherein the nucleotide sequence encoding the human or humanized β2 microglobulin polypeptide comprises nucleotide sequences set forth in exons 2, 3, and 4 of a human β2 microglobulin gene.

47. The method of claim 43, wherein the modified locus retains a nucleotide sequence of exon 1 of a mouse β2 microglobulin gene.

48. The method of claim 43, 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.

49. A non-human animal comprising in its genome:

a first nucleotide sequence encoding a chimeric human/non-human MHC I polypeptide, wherein a human portion of the chimeric polypeptide comprises an extracellular domain of a human MHC I polypeptide; and

a second nucleotide sequence encoding a human or humanized β2 microglobulin polypeptide,

wherein the first nucleotide sequence is located at an endogenous non-human MHC I locus, and the second nucleotide sequence is located at an endogenous non-human β2 microglobulin locus, and

wherein the non-human animal expresses the chimeric human/non-human MHC I polypeptide and the human or humanized β2 microglobulin polypeptide.

50. The non-human animal of claim 49, wherein the animal is a rodent, and wherein the rodent comprises in its genome:

a first nucleotide sequence encoding a chimeric human/rodent MHC I polypeptide, wherein a human portion of the chimeric polypeptide comprises an extracellular domain of a human MHC I polypeptide; and

a second nucleotide sequence encoding a human or humanized β2 microglobulin polypeptide,

wherein the first nucleotide sequence is located at an endogenous rodent MHC I locus, and the second nucleotide sequence is located at an endogenous rodent β2 microglobulin locus, and

wherein the rodent expresses the chimeric human/rodent MHC I polypeptide and the human or humanized β2 microglobulin polypeptide.

51. The rodent of claim 50, wherein the rodent does not express an extracellular domain of an endogenous rodent MHC I polypeptide and a functional endogenous rodent β2 microglobulin polypeptide from their endogenous rodent loci.

52. The rodent of claim 50, wherein the first nucleotide sequence is operably linked to endogenous rodent MHC I regulatory elements, and the second nucleotide sequence is operably linked to endogenous rodent β2 microglobulin regulatory elements.

53. The rodent of claim 50, wherein the rodent is a mouse.

54. The mouse of claim 53, wherein the endogenous MHC I locus is a mouse H-2K locus.

55. The rodent of claim 50, wherein the human portion of the chimeric polypeptide comprises α1, α2, and α3 domains of the human MHC I polypeptide.

56. The rodent of claim 50, wherein a rodent portion of the chimeric human/rodent MHC I polypeptide comprises cytoplasmic and transmembrane domains of a rodent MHC I polypeptide.

57. The rodent of claim 50, wherein the human MHC I polypeptide is selected from HLA-A, HLA-B, and HLA-C.

58. The rodent of claim 57, wherein the human MHC I polypeptide is a HLA-A polypeptide.

59. The rodent of claim 50, wherein the second nucleotide sequence comprises a nucleotide sequence set forth in exon 2 to exon 4 of a human β2 microglobulin gene.

60. The rodent of claim 50, wherein the second nucleotide sequence comprises nucleotide sequences set forth in exons 2, 3, and 4 of a human β2 microglobulin gene.

61. A mouse comprising in its genome:

a first nucleotide sequence encoding a chimeric human/mouse MHC I polypeptide, wherein a human portion of the chimeric polypeptide comprises an extracellular domain of a human HLA-A2 and a mouse portion comprises transmembrane and cytoplasmic domains of a mouse H-2K; and

a second nucleotide sequence encoding a human or humanized β2 microglobulin polypeptide,

wherein the first nucleotide sequence is located at an endogenous H-2K locus and the second nucleotide sequence is located at an endogenous mouse β2 microglobulin locus, and

wherein the mouse expresses the chimeric human/mouse MHC I polypeptide and the human or humanized β2 microglobulin polypeptide.

62. The mouse of claim 61, wherein the mouse does not express endogenous mouse H-2K and β2 microglobulin polypeptides from their endogenous loci.

63. The mouse of claim 61, wherein the first nucleotide sequence is operably linked to endogenous mouse H-2K regulatory elements, and the second nucleotide sequence is operably linked to endogenous mouse β2 microglobulin regulatory elements.

64. The mouse of claim 61, wherein the human portion of the chimeric polypeptide comprises α1, α2, and α3 domains of the human MHC I polypeptide.

65. The mouse of claim 61, wherein the second nucleotide sequence comprises a nucleotide sequence set forth in exon 2 to exon 4 of a human β2 microglobulin gene.

66. The mouse of claim 61, wherein the second nucleotide sequence comprises nucleotide sequences set forth in exons 2, 3, and 4 of a human β2 microglobulin gene.

67. The mouse of claim 61, wherein the expression of the human or humanized β2 microglobulin polypeptide increases the expression of the chimeric human/mouse MHC I polypeptide as compared to the expression of the chimeric human/mouse MHC I polypeptide in the absence of expression of human or humanized β2 microglobulin polypeptide.

68. A method of making a genetically modified mouse comprising:

modifying an MHC I locus of a first mouse to express a chimeric human/mouse MHC I polypeptide comprising replacing at the endogenous mouse MHC I locus a nucleotide sequence encoding an extracellular domain of a mouse MHC I polypeptide with a nucleotide sequence encoding an extracellular domain of a human MHC I polypeptide;

modifying a β2 microglobulin locus of a second mouse to express a human or humanized β2 microglobulin polypeptide comprising replacing at the endogenous mouse β2 microglobulin locus a nucleotide sequence encoding a mouse β2 microglobulin polypeptide with a nucleotide sequence encoding a human or humanized β2 microglobulin polypeptide; and

breeding the first and the second mouse to generate a genetically modified mouse comprising in its genome a first nucleotide sequence encoding a chimeric human/mouse MHC I polypeptide and a second nucleotide sequence encoding a human or humanized β2 microglobulin polypeptide, wherein the genetically modified mouse expresses the chimeric human/mouse MHC I polypeptide and the human or humanized β2 microglobulin polypeptide.

69. The method of claim 68, wherein the MHC I locus is an H-2K locus, the human MHC I polypeptide is HLA-A2, and the mouse expresses a chimeric HLA-A2/H-2K polypeptide.

70. The method of claim 69, wherein the chimeric HLA-A2/H-2K polypeptide comprises an extracellular domain of the HLA-A2 polypeptide and cytoplasmic and transmembrane domains of H-2K polypeptide.

71. The method of claim 68, wherein the second nucleotide sequence comprises nucleotide sequences set forth in exons 2, 3, and 4 of a human β2 microglobulin gene, and a nucleotide sequence set forth in exon 1 of a mouse β2 microglobulin gene.

CLAIMS

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

wherein a human portion of the chimeric polypeptide comprises α1, α2, and α3 domains of a human MHC I polypeptide, and

wherein the non-human animal expresses the chimeric human/non-human MHC I polypeptide.

2. The non-human animal of claim 1, wherein the animal is a rodent, wherein the rodent comprises at an endogenous Major Histocompatibility Complex I (MHC I) locus a nucleotide sequence encoding a chimeric human/rodent MHC I polypeptide,

wherein a human portion of the chimeric polypeptide comprises α1, α2, and α3 domains of a human MHC I polypeptide, and

wherein the rodent expresses the chimeric human/rodent MHC I polypeptide.

3. The rodent of claim 2, wherein the rodent does not express α1, α2, and α3 domains of an endogenous rodent MHC I polypeptide from an endogenous rodent MHC I locus.

4. The rodent of claim 2, wherein the nucleotide sequence is operably linked to endogenous rodent regulatory elements.

5. The rodent of claim 2, wherein the rodent is a mouse.

6. The mouse of claim 5, wherein the endogenous locus is a mouse H-2K locus.

7. The rodent of claim 2, wherein a rodent portion of the chimeric polypeptide comprises transmembrane and cytoplasmic domains of an endogenous rodent MHC I polypeptide.

8. The rodent of claim 7, wherein the rodent is a mouse, the endogenous rodent MHC I locus is an H-2K locus, and the endogenous rodent MHC I polypeptide is H-2K.

9. The rodent of claim 2, wherein the human MHC I polypeptide is selected from the group consisting of HLA-A, HLA-B, and HLA-C.

10. The mouse of claim 5 comprising at an endogenous H-2K locus a nucleotide sequence encoding a chimeric human/mouse MHC I polypeptide,

wherein a human portion of the chimeric polypeptide comprises α1, α2, and α3 domains of a human HLA-A2 polypeptide and a mouse portion comprises transmembrane and cytoplasmic domains of a mouse H-2K polypeptide, and

wherein the mouse expresses the chimeric HLA-A2/H-2K polypeptide.

11. The mouse of claim 10, wherein the mouse does not express α1, α2, and α3 domains of the mouse H-2K polypeptide from an endogenous H-2K locus.

12. The rodent of claim 2 or the mouse of claim 10, wherein the human portion of the chimeric polypeptide comprises a human leader sequence.

13. The mouse of claim 10, wherein the nucleotide sequence is operably liked to endogenous mouse regulatory elements.

14. The mouse of claim 10, wherein the human HLA-A2 polypeptide is an HLA-A2.1 polypeptide.

15. The mouse of claim 11, wherein the mouse H-2K locus is an H-2Kb locus.

16. A method of modifying an MHC I locus of a mouse to express a chimeric human/mouse MHC I polypeptide, wherein the method comprises replacing at the endogenous MHC I locus a nucleotide sequence encoding α1, α2, and α3 domains of a mouse MHC I polypeptide with a nucleotide sequence encoding α1, α2, and α3 domains of a human MHC I polypeptide.

17. The method of claim 16, wherein the mouse does not express the α1, α2, and α3 domains of the mouse MHC I polypeptide from an endogenous mouse MHC I locus.

18. The method of claim 17, wherein the mouse MHC I locus is an H-2K locus, and the mouse MHC I polypeptide is an H-2K polypeptide.

19. The rodent of claim 9 or the method of claim 17, wherein the human MHC I polypeptide is an HLA-A polypeptide.

20. The method of claim 17, wherein the mouse expresses transmembrane and cytoplasmic domains of the mouse MHC I polypeptide.

21. A non-human animal, rodent or mouse according to any one of claims 1-15 further comprising at an endogenous non-human β2 microglobulin locus a nucleotide sequence encoding a polypeptide comprising a human β2 microglobulin amino acid sequence, wherein the non-human animal expresses a human or humanized β2 microglobulin polypeptide.

22. The non-human animal of claim 21, wherein the animal is a rodent, wherein the rodent comprises at an endogenous rodent β2 microglobulin locus a nucleotide sequence encoding a polypeptide comprising a human β2 microglobulin amino acid sequence, and wherein the rodent expresses a human or humanized β2 microglobulin polypeptide.

23. The rodent of claim 22, wherein the rodent does not express a functional endogenous rodent β2 microglobulin polypeptide from an endogenous rodent β2 microglobulin locus.

24. The rodent of claim 22, wherein the nucleotide sequence is operably linked to endogenous rodent β2 microglobulin regulatory elements.

25. The rodent of claim 22, wherein the nucleotide sequence comprises a nucleotide sequence set forth in exon 2 to exon 4 of a human β2 microglobulin gene.

26. The rodent of claim 22, wherein the nucleotide sequence comprises nucleotide sequences set forth in exons 2, 3, and 4 of a human β2 microglobulin gene.

27. The rodent of claim 26, wherein the nucleotide sequence further comprises a nucleotide sequence set forth in exon 1 of a rodent β2 microglobulin gene.

28. The rodent of any one of claims 22-27, wherein the rodent is a mouse.

29. The method of any one of claims 16-20, further comprising modifying a β2 microglobulin locus of a mouse to express a human or humanized β2 microglobulin polypeptide, wherein the method comprises replacing at the endogenous mouse β2 microglobulin locus a nucleotide

sequence encoding a mouse β2 microglobulin polypeptide with a nucleotide sequence encoding a human or humanized β2 microglobulin polypeptide.

30. The method of claim 29, wherein the mouse does not express a functional mouse β2 microglobulin polypeptide from an endogenous β2 microglobulin locus.

31. The method of claim 29, wherein the nucleotide sequence encoding the human or humanized β2 microglobulin polypeptide comprises a nucleotide sequence set forth in exon 2 to exon 4 of a human β2 microglobulin gene.

32. The method of claim 29, wherein the nucleotide sequence encoding the human or humanized β2 microglobulin polypeptide comprises nucleotide sequences set forth in exons 2, 3, and 4 of a human β2 microglobulin gene.

33. The method of claim 29, wherein the modified locus retains a nucleotide sequence of exon 1 of a mouse β2 microglobulin gene.

34. The method of any one of claims 16 – 20 or 29, 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.

35. The mouse of claim 28, wherein the expression of the human or humanized β2 microglobulin polypeptide increases the expression of the chimeric human/mouse MHC I polypeptide as compared to the expression of the chimeric human/mouse MHC I polypeptide in the absence of expression of human or humanized β2 microglobulin polypeptide.