WHAT IS CLAIMED IS:

1. A genetically-modified non-human animal expressing a fusion protein comprising β2-microglobulin (B2M) and a human or humanized major histocompatibility complex (MHC) α chain.

2. The animal of claim 1, wherein the genome of the animal comprises at least one chromosome comprising a sequence encoding the fusion protein.

3. The animal of claim 1 or 2, wherein the fusion protein comprises a human or humanized B2M protein.

4. The animal of any one of claims 1-3, wherein the MHC α chain is a MHC class I α chain.

5. The animal of any one of claims 1-4, wherein the MHC α chain is a human HLA-A protein.

6. The animal of any one of claims 1-4, wherein the MHC α chain is a chimeric MHC α chain.

7. The animal of any one of claims 1-4, wherein the MHC α chain is a human HLA-A/mouse H2-D1 chimeric molecule.

8. The animal of claim 1, wherein the fusion protein comprises a human B2M protein and a chimeric MHC α chain comprising human HLA-A α1 and α2 domains.

9. The animal of claim 8, wherein the chimeric MHC α chain further comprises a mouse H2-D1 α3 domain.

10. The animal of claim 1, wherein the fusion protein comprises a human B2M protein and a human HLA-A protein.

11. The animal of any one of claims 2-10, wherein the sequence encoding the fusion protein is operably linked to an endogenous regulatory element (e.g., a promoter) at the endogenous β2 microglobulin (B2M) gene locus in the at least one chromosome.

12. The animal of any one of claims 2-10, wherein the sequence encoding the fusion protein is operably linked to an endogenous regulatory element (e.g., a promoter) at the endogenous MHC gene locus in the at least one chromosome.

13. The animal of any one of claims 2-10, wherein the animal is a mouse, and the sequence encoding the fusion protein is operably linked to an endogenous regulatory element at the mouse H2-D1 gene locus in the at least one chromosome.

14. The animal of any one of claims 5-13, wherein the human HLA-A is human HLA-A2.1.

15. The animal of any one of claims 5-13, wherein the human HLA-A is human HLA-A1*0101.

16. The animal of any one of claims 1-4, wherein the fusion protein comprises
(a) a human B2M; and
(b) a human HLA-A.

17. The animal of claim 16, wherein the human B2M and the human HLA-A are linked via a linker peptide sequence.

18. The animal of claim 16 or 17, wherein the human B2M comprises or consists of an amino acid sequence that is at least 70%, 75%, 80%, 85%, 90%, 95%, 99%, or 100% identical to SEQ ID NO: 4 or amino acids 21-119 of SEQ ID NO: 4.

19. The animal of any one of claims 16-18, wherein the human HLA-A is HLA-A2.1.

20. The animal of any one of claims 16-19, wherein the human HLA-A comprises or consists of an amino acid sequence that is at least 70%, 75%, 80%, 85%, 90%, 95%, 99%, or 100% identical to SEQ ID NO: 8, amino acids 25-365 of SEQ ID NO: 8, SEQ ID NO: 59, or amino acids 22-362 of SEQ ID NO: 59.

21. The animal of any one of claims 16-20, wherein the fusion protein comprises or consists of an amino acid sequence that is at least 70%, 75%, 80%, 85%, 90%, 95%, 99%, or 100% identical to SEQ ID NO: 62.

22. The animal of any one of claims 1-4, wherein the fusion protein comprises

(a) a human B2M; and

(b) a chimeric MHC α chain.

23. The animal of claim 22, wherein the human B2M and the chimeric MHC α chain are linked via a linker peptide sequence.

24. The animal of claim 22 or 23, wherein the human B2M comprises or consists of an amino acid sequence that is at least 70%, 75%, 80%, 85%, 90%, 95%, 99%, or 100% identical to SEQ ID NO: 4 or amino acids 21-119 of SEQ ID NO: 4.

25. The animal of any one of claims 22-24, wherein the chimeric MHC α chain comprises human HLA-A α1 and α2 domains.

26. The animal of claim 25, wherein the chimeric MHC α chain further comprises a human HLA-A α3 domain.

27. The animal of claim 25, wherein the chimeric MHC α chain further comprises an endogenous MHC α3 domain and/or an endogenous MHC cytoplasmic region.

28. The animal of any one of claims 22-27, wherein the chimeric MHC α chain comprises an amino acid sequence that is at least 70%, 75%, 80%, 85%, 90%, 95%, 99%, or 100% identical to SEQ ID NO: 8, amino acids 25-206 of SEQ ID NO: 8, SEQ ID NO: 59, or amino acids 22-203 of SEQ ID NO: 59.

29. The animal of any one of claims 22-28, wherein the chimeric MHC α chain comprises a α3 domain, a connecting peptide, a transmembrane region, and a cytoplasmic region of an endogenous MHC.

30. The animal of any one of claims 22-28, wherein the animal is a mouse, and the chimeric MHC α chain comprises a α3 domain, a connecting peptide, a transmembrane region, and a cytoplasmic region of mouse H2-D1.

31. The animal of any one of claims 22-30, wherein the chimeric MHC α chain comprises an amino acid sequence that is at least 70%, 75%, 80%, 85%, 90%, 95%, 99%, or 100% identical to amino acids 207-362 of SEQ ID NO: 6.

32. The animal of any one of claims 22-31, wherein the chimeric MHC α chain comprises an amino acid sequence that is at least 70%, 75%, 80%, 85%, 90%, 95%, 99%, or 100% identical to SEQ ID NO: 61 or SEQ ID NO: 63.

33. The animal of any one of claims 1-32, wherein the fusion protein further comprises a signal peptide of human HLA-A2.1 (e.g., at the N-terminus of the fusion protein).

34. The animal of claim 33, wherein the signal peptide comprises an amino acid sequence that is at least 70%, 75%, 80%, 85%, 90%, 95%, 99%, or 100% identical to amino acids 1-21 of SEQ ID NO: 59.

35. The animal of any one of claims 1-34, wherein the animal is heterozygous with respect to the sequence encoding the fusion protein.

36. The animal of any one of claims 1-34, wherein the animal is homozygous with respect to the sequence encoding the fusion protein.

37. A genetically-modified, non-human animal whose genome comprises at least one chromosome comprising a sequence encoding a chimeric MHC α chain comprising a human HLA-A α1 domain, a human HLA-A α2 domain and an endogenous MHC α3 domain.

38. The animal of claim 37, wherein the sequence encoding the chimeric MHC α chain is operably linked to an endogenous regulatory element at the endogenous MHC α chain gene locus in the at least one chromosome.

39. The animal of claim 37 or 38, wherein the genome of the animal further comprises a sequence encoding a human B2M, wherein the human B2M and the chimeric MHC α chain can associate with each other, forming a functional MHC protein complex in the animal.

40. The animal of claim 39, wherein the sequence encoding the human B2M is operably linked to an endogenous regulatory element (e.g., a promoter) at the endogenous B2M gene locus.

41. The animal of any one of claims 37-40, wherein the animal is a mouse, and the sequence encoding the chimeric MHC α chain is operably linked to an endogenous regulatory element (e.g., a promoter) at the mouse H2-D1 gene locus.

42. The animal of any one of claims 37-41, wherein the human HLA-A is human HLA-A2.1.

43. A genetically-modified, non-human animal whose genome comprises at least one chromosome comprising a sequence encoding a human HLA-A.

44. The animal of claim 43, wherein the sequence encoding the human HLA-A is operably linked to an endogenous regulatory element at the endogenous MHC α chain gene locus in the at least one chromosome.

45. The animal of claim 43 or 44, wherein the genome of the animal further comprises a sequence encoding a human B2M, wherein the human B2M and the human HLA-A can associate with each other, forming a functional MHC protein complex in the animal.

46. The animal of claim 45, wherein the sequence encoding the human B2M is operably linked to an endogenous regulatory element (e.g., a promoter) at the endogenous B2M gene locus.

47. The animal of any one of claims 43-46, wherein the animal is a mouse, and the sequence encoding the human HLA-A is operably linked to an endogenous regulatory element (e.g., a promoter) at the mouse H2-D1 gene locus.

48. The animal of any one of claims 43-47, wherein the human HLA-A is human HLA-A2.1.

49. The animal of any one of claims 1-48, wherein the animal does not express endogenous B2M.

50. The animal of any one of claims 1-49, wherein the animal does not express endogenous MHC α chain.

51. The animal of any one of claims 1-50, wherein B2M and the MHC α chain can associate with each other, forming a functional MHC protein complex, wherein the protein complex can present a non-self antigen to the surface of one or more cells.

52. The animal of claim 51, wherein a human T cell (e.g., a cytotoxic T cell) can recognize the presented non-self antigen and initiate immune response.

53. The animal of claim 51, wherein an endogenous T cells (e.g., a cytotoxic T cell) can recognize the presented non-self antigen and initiate immune response.

54. The animal of any one claims 1-53, wherein the animal is a mammal, e.g., a monkey, a rodent or a mouse.

55. The animal of claim 54, wherein the animal is a mouse (e.g., with a C57BL/6 background).

56. The animal of any one of claims 1-55, wherein the animal is an immunodeficient mouse.

57. The animal of any one of claims 1-56, wherein the genome of the animal comprises a disruption in the animal's endogenous CD132 gene.

58. The animal of any one of claims 1-57, wherein the animal is a NOD/scid mouse, a NOD/scid nude mouse, or a B-NDG mouse.

59. The animal of any one of claims 1-58, wherein the animal further comprises a sequence encoding an additional human or chimeric protein.

60. The animal of claim 59, wherein the additional human or chimeric protein is programmed cell death protein 1 (PD-1), cytotoxic T-lymphocyte-associated protein 4 (CTLA-4), Lymphocyte Activating 3 (LAG-3), B And T Lymphocyte Associated (BTLA), Programmed Cell Death 1 Ligand 1 (PD-L1), CD27, CD28, SIRPα, CD47, THPO, CD137, CD154, T-Cell Immunoreceptor With Ig And ITIM Domains (TIGIT), T-cell Immunoglobulin and Mucin-Domain Containing-3 (TIM-3),

Glucocorticoid-Induced TNFR-Related Protein (GITR), Signal regulatory protein α(SIRPα) or TNF Receptor Superfamily Member 4 (OX40).

61. A method for making a genetically-modified, non-human animal, comprising:

replacing in at least one cell of the animal, at an endogenous B2M gene locus, a sequence encoding a region of endogenous B2M with a sequence encoding a human B2M or a sequence encoding a fusion protein comprising a human B2M and a human or humanized MHC α chain.

62. The method of claim 61, wherein the sequence encoding the region of endogenous B2M comprises all or a part of exon 1, exon 2, and exon 3 of endogenous B2M gene.

63. A method for making a genetically-modified, non-human animal, comprising:

replacing in at least one cell of the animal, at an endogenous MHC gene locus, a sequence encoding a region of endogenous MHC α chain with a sequence encoding a human MHC α chain or a sequence encoding a fusion protein comprising a human B2M and a human or humanized MHC α chain.

64. The method of claim 63, wherein the sequence encoding the region of endogenous MHC molecule comprises all or a part of exon 1, exon 2, exon 3, exon 4, exon 5, exon 6, exon 7, and exon 8 of endogenous MHC gene.

65. The method of claim 63, wherein the animal is mouse, and the sequence encoding the region of endogenous MHC comprises all or a part of exon 1, exon 2, exon 3 of mouse H2-D1 gene.

66. The method of any one of claims 61-65, wherein the sequence encoding the fusion protein comprises the following elements:

(a) exon 1, exon 2, and/or exon 3 of human B2M;

(b) an optional sequence encoding a linker peptide sequence; and

(c) exon 2 and/or exon 3 of human HLA-A2.1.

67. The method of claim 66, wherein the sequence encoding the fusion protein further comprises exon 4, exon 5, exon 6, exon 7, and/or exon 8 of the endogenous MHC molecule gene that is downstream of element (c).

68. The method of claim 66 or 67, wherein the animal is mouse, and the sequence encoding the fusion protein further comprises the 3' UTR of mouse H2-D1 gene.

69. The method of any one of claims 61-68, wherein the fusion protein comprises an amino acid sequence that is at least 70%, 75%, 80%, 85%, 90%, 95%, 99%, or 100% identical to SEQ ID NO: 61, SEQ ID NO: 62, SEQ ID NO: 63, or SEQ ID NO: 64.

70. A method of determining effectiveness of an agent or a combination of agents for the treatment of cancer, comprising:

engrafting tumor cells to the animal of any one of claims 1-60, thereby forming one or more tumors in the animal;

administering the agent or the combination of agents to the animal; and

determining the inhibitory effects on the tumors.

71. The method of claim 70, wherein before engrafting the tumor cells to the animal, human peripheral blood cells (hPBMC) or human hematopoietic stem cells are injected to the animal.

72. The method of claim 70, wherein the tumor cells are from cancer cell lines.

73. The method of claim 70, wherein the tumor cells are from a tumor sample obtained from a human patient.

74. The method of claim 70, wherein the inhibitory effects are determined by measuring the tumor volume in the animal.

75. The method of claim 70, wherein the tumor cells are melanoma cells, lung cancer cells, primary lung carcinoma cells, non-small cell lung carcinoma (NSCLC) cells, small cell lung cancer (SCLC) cells, primary gastric carcinoma cells, bladder cancer cells, breast cancer cells, and/or prostate cancer cells.

76. A method of producing an animal comprising a human hemato-lymphoid system, the method comprising:

engrafting a population of cells comprising human hematopoietic cells or human peripheral blood cells into the animal of any one of claims 1-60.

77. The method of claim 76, wherein the human hemato-lymphoid system comprises human cells selected from the group consisting of hematopoietic stem cells, myeloid precursor cells, myeloid cells, dendritic cells, monocytes, granulocytes, neutrophils, mast cells, lymphocytes, and platelets.

78. The method of claim 76 or 77, further comprising: irradiating the animal prior to the engrafting.

79. A fusion protein comprising β2 microglobulin (B2M) and a human or humanized MHC α chain.

80. A nucleic acid encoding the fusion protein of claim 79.

81. A protein comprising an amino acid sequence, wherein the amino acid sequence is one of the following:

(a) an amino acid sequence set forth in SEQ ID NO: 4, 8, 59, 61, 62, 63, or 64;

(b) an amino acid sequence that is at least 90% identical to SEQ ID NO: 4, 8, 59, 61, 62, 63, or 64;

(c) an amino acid sequence that is at least 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, or 99% identical to SEQ ID NO: 4, 8, 59, 61, 62, 63, or 64;

(d) an amino acid sequence that is different from the amino acid sequence set forth in SEQ ID NO: 4, 8, 59, 61, 62, 63, or 64 by no more than 10, 9, 8, 7, 6, 5, 4, 3, 2 or 1 amino acid; and

(e) an amino acid sequence that comprises a substitution, a deletion and /or insertion of one, two, three, four, five or more amino acids to the amino acid sequence set forth in SEQ ID NO: 4, 8, 59, 61, 62, 63, or 64.

82. A nucleic acid comprising a nucleotide sequence, wherein the nucleotide sequence is one of the following:

(a) a sequence that encodes the protein of claim 81;

(b) SEQ ID NO: 9, 10, 13, 14, 15, 16, 52, 54, or 65;

(c) a sequence that is at least 90% identical to SEQ ID NO: 9, 10, 13, 14, 15, 16, 52, 54, or 65; and

(d) a sequence that is at least 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, or 99% identical to SEQ ID NO: 9, 10, 13, 14, 15, 16, 52, 54, or 65.

83. A cell comprising the protein of claim 81 and/or the nucleic acid of claim 82.

84. An animal comprising the protein of claim 81 and/or the nucleic acid of claim 82.

WHAT IS CLAIMED IS:

1. A genetically-modified non-human animal expressing a fusion protein comprising β2 microglobulin (B2M) and a human or humanized major histocompatibility complex (MHC) α chain;

wherein:

the genome of the animal comprises at least one chromosome comprising a sequence encoding the fusion protein;

the fusion protein comprises a human or humanized B2M protein; and

the MHC α chain is an MHC class I α chain;

wherein:

the sequence encoding the fusion protein is operably linked to an endogenous regulatory element (e.g., a promoter) at the endogenous β2 microglobulin (B2M) gene locus in the at least one chromosome; or

the sequence encoding the fusion protein is operably linked to an endogenous regulatory element (e.g., a promoter) at the endogenous MHC gene locus in the at least one chromosome.

2. The animal of claim 1, wherein the MHC α chain is a human HLA-A protein.

3. The animal of any one of claim 1, wherein the fusion protein comprises

(a) a human B2M; and

(b) a human HLA-A.

4. The animal of claim 3, wherein the human B2M and the human HLA-A are linked via a linker peptide sequence.

5. The animal of claim 3 or 4, wherein the human B2M comprises or consists of an amino acid sequence that is at least 70%, 75%, 80%, 85%, 90%, 95%, 99%, or 100% identical to SEQ ID NO: 4 or amino acids 21-119 of SEQ ID NO: 4.

6. The animal of any one of claims 3-5, wherein the human HLA-A is HLA-A2.1.

7. The animal of any one of claims 3-6, wherein the human HLA-A comprises or consists of an amino acid sequence that is at least 70%, 75%, 80%, 85%, 90%, 95%, 99%, or 100% identical to SEQ ID NO: 8, amino acids 25-365 of SEQ ID NO: 8, SEQ ID NO: 59, or amino acids 22-362 of SEQ ID NO: 59.

8. The animal of any one of claims 3-7, wherein the fusion protein comprises or consists of an amino acid sequence that is at least 70%, 75%, 80%, 85%, 90%, 95%, 99%, or 100% identical to SEQ ID NO: 62.

9. The animal of claim 1, wherein the fusion protein comprises

(a) a human B2M; and

(b) a chimeric MHC α chain;

wherein the chimeric MHC α chain comprises human HLA-A α1 and α2 domains; or

wherein the chimeric MHC α chain further comprises an endogenous MHC α3 domain and/or an endogenous MHC cytoplasmic region.

10. The animal of claim 9, wherein the human B2M and the chimeric MHC α chain are linked via a linker peptide sequence.

11. The animal of claim 9 or 10, wherein the human B2M comprises or consists of an amino acid sequence that is at least 70%, 75%, 80%, 85%, 90%, 95%, 99%, or 100% identical to SEQ ID NO: 4 or amino acids 21-119 of SEQ ID NO: 4.

12. The animal of any one of claims 9-11, wherein the chimeric MHC α chain comprises an amino acid sequence that is at least 70%, 75%, 80%, 85%, 90%, 95%, 99%, or 100% identical to SEQ ID NO: 8, amino acids 25-206 of SEQ ID NO: 8, SEQ ID NO: 59, or amino acids 22-203 of SEQ ID NO: 59.

13. The animal of any one of claims 9-12, wherein the chimeric MHC α chain comprises a α3 domain, a connecting peptide, a transmembrane region, and a cytoplasmic region of an endogenous MHC; and

the animal is a mouse, and the chimeric MHC α chain comprises a α3 domain, a connecting peptide, a transmembrane region, and a cytoplasmic region of mouse H2-D1.

14. The animal of any one of claims 9-13, wherein the chimeric MHC α chain comprises an amino acid sequence that is at least 70%, 75%, 80%, 85%, 90%, 95%, 99%, or 100% identical to amino acids 207-362 of SEQ ID NO: 6.

15. The animal of any one of claims 9-14, wherein the chimeric MHC α chain comprises an amino acid sequence that is at least 70%, 75%, 80%, 85%, 90%, 95%, 99%, or 100% identical to SEQ ID NO: 61 or SEQ ID NO: 63.

16. The animal of any one of claims 1-15, wherein B2M and the MHC α chain can associate with each other, forming a functional MHC protein complex, wherein the protein complex can present a non-self antigen to the surface of one or more cells.

17. The animal of any one of claims 1-16, wherein the animal is a mouse (e.g., with a C57BL/6 background).

18. The animal of any one of claims 1-17, wherein the animal is an immunodeficient mouse.

19. A method for making a genetically-modified, non-human animal, comprising:

replacing in at least one cell of the animal, at an endogenous B2M gene locus, a sequence encoding a region of endogenous B2M with a sequence encoding a human B2M or a sequence encoding a fusion protein comprising a human B2M and a human or humanized MHC α chain.

20. A method of determining effectiveness of an agent or a combination of agents for the treatment of cancer, comprising:

engrafting tumor cells to the animal of any one of claims 1-18, thereby forming one or more tumors in the animal;

administering the agent or the combination of agents to the animal; and

determining the inhibitory effects on the tumors;

wherein the tumor cells are from cancer cell lines, or from a tumor sample obtained from a human patient.

21. A method of producing an animal comprising a human hemato-lymphoid system, the method comprising:

engrafting a population of cells comprising human hematopoietic cells or human peripheral blood cells into the animal of any one of claims 1-18.