CLAIMS

In the claims:

1. A genetically modified mammalian cell that has reduced immunogenicity and/or improved immunosuppression as compared to the mammalian cell without said genetic modification, wherein:

(i) the genetically modified mammalian cell comprises an exogenous nucleic acid comprising: (a) a nucleic acid sequence encoding an HLA-G protein having an amino acid sequence at least 95% identical to consensus wild-type human HLA-G, and comprising one or more amino acid mutations that reduce retention of HLA-G in the endoplasmic reticulum-golgi recycling pathway; and (b) a 3' untranslated region (UTR) that is at least 85% identical to the 3' untranslated region sequence of the consensus wild-type human HLA-G gene and does not comprise SEQ ID NO:4; and

(ii) the encoded HLA-G protein is expressed by the genetically modified mammalian cell for at least seven weeks.

2. The genetically modified mammalian cell of claim 1, wherein the HLA-G protein is expressed for at least 20 weeks.

3. The genetically modified mammalian cell of claim 2, wherein the HLA-G protein is expressed for at least 50 weeks.

4. The genetically modified cell of claim 1, wherein the one or more amino acid mutations that reduce retention of HLA-G in the endoplasmic reticulum-golgi recycling pathway comprise a K334A mutation, a K335A mutation, or both mutations.

5. The genetically modified mammalian cell of claim 1, wherein the nucleic acid sequence encodes an HLA-G protein with an amino acid sequence of SEQ ID NO:2.

6. The genetically modified mammalian cell of claim 1, further comprising an Elongation Factor-1 alpha (EF-1α) promoter, wherein the nucleic acid sequence encoding the HLA-G protein is operably linked to the EF-1α promoter.

7. The genetically modified mammalian cell of claim 6, wherein the EF-1α promoter comprises the sequence of SEQ ID NO:7.

8. The genetically modified mammalian cell of claim 1, wherein the 3' UTR comprises SEQ ID NO:3.

9. The genetically modified mammalian cell of claim 1, wherein the nucleic acid sequence encodes an HLA-G protein with an amino acid sequence of SEQ ID NO:2, wherein the 3' UTR comprises SEQ ID NO:3, and further comprises an EF-1α promoter comprising SEQ ID NO:7 that is operably linked to the nucleic acid encoding the HLA-G protein.

10. The genetically modified cell of claim 1, wherein the expressed HLA-G is present on the cell surface of the genetically modified mammalian cell.

11. The genetically modified mammalian cell of claim 1, wherein the modified mammalian cell is a human cell.

12. The genetically modified mammalian cell of claim 1, wherein the genetically modified cell is a stem cell, a progenitor cell, a cell obtained by in vitro differentiation of the stem cell or the progenitor cell, a fully differentiated cell, an epidermal progenitor cell, a pancreatic progenitor cell, a hematopoietic stem cell, a keratinocyte, a fibroblast, a hepatocyte, a mesenchymal stem cell, a cardiomyocyte, a neural stem cell, a neuron, or an astrocyte.

13. The genetically modified mammalian cell of claim 1, wherein the genetically modified cell is a human embryonic stem cell, a human mesenchymal stem cell, or a human embryonic epidermal progenitor cell.

14. The genetically modified mammalian cell of claim 1, wherein the genetically modified cell is a human dermal fibroblast.

15. The genetically modified cell of claim 1, wherein the reduced immunogenicity and/or improved immunosuppression of the genetically modified cell as compared to the mammalian cell without said genetic modification is determined by either: (1) a reduction of NK-92 cytotoxicity of the genetically modified cell as compared to the

mammalian cell without said genetic modification, (2) a reduction of in vitro peripheral blood mononuclear cell proliferation of the genetically modified cell as compared to the mammalian cell without said genetic modification, and (3) an increase in the size and weight of tumor formation by the genetically modified cell as compared to the mammalian cell without said genetic modification in humanized NSG mice.

16. An artificial tissue comprising the genetically modified mammalian cell of claim 1.

17. A skin graft, repair, or regeneration composition comprising the genetically modified mammalian cell of claim 13 or claim 14.

18. The genetically modified mammalian cell of claim 1, wherein the exogenous nucleic acid is an expression vector.

19. The genetically modified mammalian cell of claim18, wherein the mammalian expression vector is a transposon vector.

20. The genetically modified mammalian cell of claim 18, wherein the vector further comprises a nucleic acid sequence encoding a reporter protein.

21. An isolated nucleic acid comprising :

(i) a first nucleic acid sequence that encodes an amino acid sequence at least 95% identical to human HLA-G, wherein the amino acid sequence comprises a mutation that reduces retention of HLA-G in the endoplasmic reticulum-golgi recycling pathway; and

(ii) a second nucleic acid sequence that is at least 95% identical the 3' untranslated region sequence of the human HLA-G gene and operably linked to the first nucleic acid sequence, wherein the second nucleic acid sequence comprises at least one mutation that inhibits binding of a cognate microRNA to an mRNA comprising the mutated binding site within its 3' untranslated region.

22. The isolated nucleic acid of claim 21, wherein the first nucleic acid sequence encodes an amino acid sequence of SEQ ID NO:2.

23. The isolated nucleic acid of claim 21, wherein the second nucleic acid sequence does not comprise SEQ ID NO:4.

24. The isolated nucleic acid of claim 21, wherein the second nucleic acid sequence comprises SEQ ID NO:3.

25. A mammalian expression vector comprising the isolated nucleic acid of claim 21 and a promoter operably linked to the first nucleic acid sequence, wherein the promoter is not silenced in a stem cell or a in a cell generated by differentiation of the stem cell.

26. The mammalian expression vector of claim 25, wherein the promoter comprises the nucleic acid sequence of the Chinese hamster EF-1α promoter.

27. The mammalian expression vector of claim 25, further comprising a third nucleic acid sequence encoding a reporter protein.

28. The mammalian expression vector of claim 25, wherein the mammalian expression vector is a transposon vector.

29. A mammalian expression vector comprising: (a) a Chinese hamster EF-1 α promoter, (b) a nucleic acid sequence that is operably linked to the promoter and that encodes human HLA-G with an amino acid sequence of SEQ ID NO:2, and (c) a 3'UTR sequence comprising SEQ ID NO:3.

30. A genetically modified mammalian cell comprising the mammalian expression vector of claim 29.

31. A universal method of cellular or tissue repair or regeneration to a subject in need thereof, the method comprising injecting, implanting, or grafting to the subject a cellular or tissue composition comprising a population of genetically modified cells of claim 1 , wherein the subject has at least one mismatched classical HLA class I or HLA class II molecule as compared to the population of genetically modified cells, and wherein the population of genetically modified cells exhibits reduced immunogenicity and/or improved immunosuppression as compared to cells of the same-type without the genetic modification.

32. The method of claim 31, wherein the at least one mismatched classical HLA class I or HLA class II molecule is selected from the group consisting of HLA-A, HLA-B, HLA-C, HLA-DP, HLA-DQ, and HLA-DR.

33. The method of claim 31, wherein the subject has no matches with the genetically modified cells with respect to HLA-A, HLA-B, HLA-C, HLA-DP, HLA-DQ, and HLA-DR.

34. The method of claim 31, wherein the reduced immunogenicity and/or improved immunosuppression is determined by an NK-92 cytotoxicity assay, a humanized NSG tumor growth assay, and/or a peripheral blood mononuclear cell proliferation assay.

35. The method of claim 31, wherein the population of genetically modified cells comprises a population of human dermal fibroblasts.

36. The method of claim 31, wherein the population of genetically modified cells comprises a population of human epidermal progenitors.

37. The method of claim 31, wherein the population of genetically modified cells comprises a population of human embryonic stem cells.

38. The method of claim 31, wherein the population of genetically modified cells comprises a population of human mesenchymal stem cells.

39. The method of claim 31, wherein the population of genetically modified cells comprises genetically modified human embryonic stem cells that were differentiated in vitro.

40. The method of claim 31, wherein the population of genetically modified cells are not rejected by the subject's immune system for at least 2, 4, 6, 8, 10, 12, 14, 16, 18, 20, 24, 36, 48, or 52 weeks.

CLAIMS

1. A genetically modified mammalian cell that has reduced immunogenicity and/or improved immunosuppression as compared to the mammalian cell without said genetic modification, wherein:

   (i) the genetically modified mammalian cell comprises an exogenous nucleic acid comprising: (a) a nucleic acid sequence encoding an HLA-G protein having an amino acid sequence at least 95% identical to consensus wild-type human HLA-G, and comprising one or more amino acid mutations that reduce retention of HLA-G in the endoplasmic reticulum-golgi recycling pathway; and (b) a 3' untranslated region (UTR) that is at least 85% identical to the 3' untranslated region sequence of the consensus wild-type human HLA-G gene and does not comprise SEQ ID NO:4; and

   (ii) the encoded HLA-G protein is expressed by the genetically modified mammalian cell for at least six passages in *in vitro* culture conditions.

2. The genetically modified mammalian cell of claim 1, wherein the HLA-G protein is expressed for at least sixteen passages in *in vitro* culture conditions.

3. The genetically modified mammalian cell of claim 2, wherein the HLA-G protein is expressed for at least twenty passages *in vitro* culture conditions.

4. The genetically modified cell of claim 1, wherein the one or more amino acid mutations that reduce retention of HLA-G in the endoplasmic reticulum-golgi recycling pathway comprise a K334A mutation, a K335A mutation, or both mutations.

5. The genetically modified mammalian cell of claim 1, wherein the nucleic acid sequence encodes an HLA-G protein with an amino acid sequence of SEQ ID NO:2.

6. The genetically modified mammalian cell of claim 1, further comprising an Elongation Factor-1 alpha (EF-1α) promoter, wherein the nucleic acid sequence encoding the HLA-G protein is operably linked to the EF-1α promoter.

7. The genetically modified mammalian cell of claim 6, wherein the EF-1α promoter comprises the sequence of SEQ ID NO:7.

8. The genetically modified mammalian cell of claim 1, wherein the 3' UTR comprises SEQ ID NO:3.

9. The genetically modified mammalian cell of claim 1, wherein the nucleic acid sequence encodes an HLA-G protein with an amino acid sequence of SEQ ID NO:2, wherein the 3' UTR comprises SEQ ID NO:3, and further comprises an EF-1α promoter comprising SEQ ID NO:7 that is operably linked to the nucleic acid encoding the HLA-G protein.

10. The genetically modified cell of claim 1, wherein the expressed HLA-G is present on the cell surface of the genetically modified mammalian cell.

11. The genetically modified mammalian cell of claim 1, wherein the modified mammalian cell is a human cell.

12. The genetically modified mammalian cell of claim 1, wherein the genetically modified cell is a stem cell, a progenitor cell, a cell obtained by *in vitro* differentiation of the stem cell or the progenitor cell, a fully differentiated cell, an epidermal progenitor cell, a pancreatic progenitor cell, a hematopoietic stem cell, a keratinocyte, a fibroblast, a hepatocyte, a mesenchymal stem cell, a cardiomyocyte, a neural stem cell, a neuron, or an astrocyte.

13. The genetically modified mammalian cell of claim 1, wherein the genetically modified cell is a human embryonic stem cell, a human mesenchymal stem cell, or a human embryonic epidermal progenitor cell.

14. The genetically modified mammalian cell of claim 1, wherein the genetically modified cell is a human dermal fibroblast.

15. The genetically modified cell of claim 1, wherein the reduced immunogenicity and/or improved immunosuppression of the genetically modified cell as compared to the mammalian cell without said genetic modification is determined by either: (1) a

reduction of NK-92 cytotoxicity of the genetically modified cell as compared to the mammalian cell without said genetic modification, (2) a reduction of *in vitro* peripheral blood mononuclear cell proliferation of the genetically modified cell as compared to the mammalian cell without said genetic modification, and (3) an increase in the size and weight of tumor formation by the genetically modified cell as compared to the mammalian cell without said genetic modification in humanized NSG mice.

16. An artificial tissue comprising the genetically modified mammalian cell of claim 1.

17. A skin graft, repair, or regeneration composition comprising the genetically modified mammalian cell of claim 13.

18. A skin graft, repair, or regeneration composition comprising the genetically modified mammalian cell of claim 14.

19. The genetically modified mammalian cell of claim 1, wherein the exogenous nucleic acid is an expression vector.

20. The genetically modified mammalian cell of claim 19, wherein the mammalian expression vector is a transposon vector.

21. The genetically modified mammalian cell of claim 19, wherein the vector further comprises a nucleic acid sequence encoding a reporter protein.

22. An isolated nucleic acid comprising :

(i) a first nucleic acid sequence that encodes an amino acid sequence at least 95% identical to human HLA-G, wherein the amino acid sequence comprises a mutation that reduces retention of HLA-G in the endoplasmic reticulum-golgi recycling pathway; and

(ii) a second nucleic acid sequence that is at least 95% identical the 3' untranslated region sequence of the human HLA-G gene and operably linked to the first nucleic acid sequence, wherein the second nucleic acid sequence comprises at least one mutation that inhibits binding of a cognate microRNA to an mRNA comprising the mutated binding site within its 3' untranslated region.

23. A mammalian expression vector comprising the isolated nucleic acid of claim 22 and a promoter operably linked to the first nucleic acid sequence, wherein the promoter is not silenced in a stem cell or in a cell generated by differentiation of the stem cell.

24. A universal method of cellular or tissue repair or regeneration in a subject in need thereof, the method comprising injecting, implanting, or grafting to the subject a cellular or tissue composition comprising a population of genetically modified cells of claim 1 , wherein the subject has at least one mismatched classical HLA class I or HLA class II molecule as compared to the population of genetically modified cells, and wherein the population of genetically modified cells exhibits reduced immunogenicity and/or improved immunosuppression as compared to cells of the same-type without the genetic modification.

25. The method of claim 24, wherein the at least one mismatched classical HLA class I or HLA class II molecule is selected from the group consisting of HLA-A, HLA-B, HLA-C, HLA-DP, HLA-DQ, and HLA-DR.