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.

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 SEQ ID NO:2; and (b) a 3' untranslated region (UTR) that is at least 85% identical to SEQ ID NO:3; 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 *in vitro* culture conditions.

4. 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.

5. The genetically modified mammalian cell of claim 4, wherein the EF-1α promoter comprises the sequence of SEQ ID NO:7.

6. The genetically modified mammalian cell of claim 1, wherein the nucleic acid sequence further comprises an EF-1α promoter comprising SEQ ID NO:7 that is operably linked to the nucleic acid encoding the HLA-G protein.

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

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

9. 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

9. 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.

10. 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.

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

12. 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.

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

14. A skin graft, repair, or regeneration composition comprising the genetically modified mammalian cell of claim 10.

15. A skin graft, repair, or regeneration composition comprising the genetically modified mammalian cell of claim 11.

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

17. The genetically modified mammalian cell of claim 16, wherein the expression vector is a transposon vector.

18. The genetically modified mammalian cell of claim 16, wherein the vector further comprises a nucleic acid sequence encoding a reporter protein.

19. An isolated nucleic acid comprising:

(i) a first nucleic acid sequence that encodes an amino acid sequence at least 95% identical to SEQ. ID NO:2; and

(ii) a second nucleic acid sequence that is at least 95% identical to SEQ. ID NO:3 and operably linked to the first nucleic acid sequence.

20. A mammalian expression vector comprising the isolated nucleic acid of claim 19 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.

21. A cellular or tissue composition comprising a population of genetically modified mammalian cells of claim 1 for use in a universal method of cellular or tissue repair or regeneration wherein the cellular or tissue composition is suitable for injecting, implanting, or grafting to a subject in need thereof, 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 mammalian cells, and wherein the population of genetically modified mammalian cells exhibits reduced immunogenicity and/or improved immunosuppression as compared to cells of the same-type without the genetic modification.

22. The composition of claim 21, 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.