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**GATTONI-CELLI S ET AL: "BETA-2 MICROGLOBULIN GENE IS MUTATED IN A HUMAN COLON CANCER CELL
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DESCRIPTION

BACKGROUND OF THE INVENTION

[0001] Human pluripotent stem cells have the potential to treat diseases affecting almost every organ system. However, the clinical use of human pluripotent stem cells and their derivatives has a major limitation - rejection of transplanted cells by the recipient due to differences in the major histocompatibility complex.

[0002] The major histocompatibility complex (MHC) is a cell surface multi-component molecule found in all vertebrates that mediates interactions of leukocytes with other leukocytes or other cells. The MHC gene family is divided into three groups: class I, class II and class III. In humans, MHC is referred to as human leukocyte antigen (HLA). The HLA class I (HLA-I) protein is expressed on all nucleated cells and consists of an HLA class I heavy chain (or α chain) and β -2 microglobulin (B2M). HLA class I protein presents peptides on the cell surface to CD8+ cytotoxic T cells. Six HLA class I α chains have been identified to date, including three classical (HLA-A, HLA-B and HLA-C) and three non-classical (HLA-E, HLA-F and HLA-G) α chains. The specificity for peptide binding on the HLA class I molecule peptide binding cleft is determined by the α chain. Recognition by CD8+ T cells of the peptides presented by the HLA class I molecule mediates cellular immunity.

[0003] The HLA class I protein itself from an allogeneic source constitutes a foreign antigen in the context of transplantation. The recognition of non-self HLA class I protein is a major hurdle in using pluripotent cells for transplantation or replacement therapies. The first two clinical trials of human embryonic stem cells (ESCs) have been conducted that delivered ESCs to immune-privileged sites (such as spinal cord and eye) where allogeneic cells might survive. However, even these immune-privileged sites can eventually reject allogeneic cells, and most potential clinical applications do not involve immune-privileged sites. Alternatively, HLA-matched or partially matched cells from HLA-typed stem cell banks or pluripotent stem cell (iPSC) lines derived from each patient can be developed for transplantation. However, the development of individually matched cell line requires significant costs, months of cell culture, highly trained personnel, and extensive validation of the final product, all of which must be done with the approval of regulatory agencies. Furthermore, each cell line will likely behave somewhat differently in gene expression patterns, culture characteristics, differentiation potentials, and genetic variations.

[0004] Thus, although individualized stem cell preparations or HLA-diverse stem cell banks may address the current problem of transplantation, they require that multiple cell lines be characterized, differentiated into therapeutic cell products, and approved for human administration. This time-consuming, technically difficult, and expensive process is a major factor preventing stem cell-based therapies from entering clinical trials. Thus, there exists a need for a more effective and less expensive cell-based therapies that are not impeded by

rejection.

[0005] US 6,514,752 B1 describes the inactivation of genes associated with MHC antigens resulting in reducing or eliminating the expression of functional MHC class I antigens. WO 92/09688 A1 describes mutant heterologous non-human mammals (mice) having a disruption β 2-m gene and also relates to MHC class I deficient cells.

SUMMARY OF THE INVENTION

[0006] The invention is defined in the accompanying claims. In accordance with the present invention, in one aspect the invention provides an isolated cell comprising a genetically engineered disruption in a beta-2 microglobulin (*B2M*) gene, wherein the cell is a primate cell, and is a non-transformed cell, wherein the cell further comprises one or more recombinant immunomodulatory genes, each capable of expressing an immunomodulatory polypeptide in the cell, wherein the one or more immunomodulatory genes comprise a polynucleotide capable of encoding a single chain fusion human leukocyte antigen (HLA) class I protein comprising at least a portion of the B2M protein covalently linked, either directly or via a linker sequence, to at least a portion of an HLA-I α chain, wherein the single chain fusion human HLA class I protein is capable of normal HLA class I function with respect to forming proper secondary structure of single chain fusion heterodimers on the cell surface, presenting peptides in the HLA I peptide binding cleft, and engaging the inhibitory receptors on the surface of NK cells. In certain particular embodiments, the cell comprises genetically engineered disruptions of all copies of the *B2M* gene. In a particular embodiment, the invention provides an isolated cell comprising a genetically engineered disruption in a beta-2 microglobulin (*B2M*) gene, wherein the cell is a primate cell, and is a non-transformed cell, wherein the cell further comprises one or more recombinant immunomodulatory genes, each capable of expressing an immunomodulatory polypeptide in the cell, wherein the one or more immunomodulatory genes comprise a polynucleotide capable of encoding a single chain fusion human leukocyte antigen (HLA) class I protein comprising at least a portion of the B2M protein covalently linked, either directly or via a linker sequence, to at least a portion of an HLA-I α chain, wherein the single chain fusion human HLA class I protein is capable of normal HLA class I function with respect to forming proper secondary structure of single chain fusion heterodimers on the cell surface, presenting peptides in the HLA I peptide binding cleft, and engaging the inhibitory receptors on the surface of NK cells.

[0007] In certain other embodiments, the cell further comprises one or more recombinant immunomodulatory genes. Suitable immunomodulatory genes include without limitation a gene encoding a viral protein that inhibits antigen presentation, a microRNA gene, and a gene that encodes a single chain (SC) fusion human leukocyte antigen (HLA) class I protein as described below. In certain preferred embodiments, the primate cell is a human cell.

[0008] In certain preferred embodiments, the one or more immunomodulatory genes comprise a polynucleotide capable of encoding a single chain fusion HLA class I protein. In certain

particular embodiments, the single chain fusion HLA class I protein comprises at least a portion of B2M covalently linked to at least a portion of an HLA class I α chain selected from the group consisting of HLA-A, HLA-B, HLA-C, HLA-E, HLA-F and HLA-G. In certain preferred embodiments, the single chain fusion HLA class I protein comprises at least a portion of B2M and at least a portion of an HLA class I α chain selected from the group consisting of HLA-C, HLA-E and HLA-G. In certain other preferred embodiments, the single chain fusion HLA class I protein comprises at least a portion of B2M and at least a portion of an HLA class I α chain selected from the group consisting of HLA-A, HLA-E and HLA-G. In certain particular embodiments, the single chain fusion HLA class I protein comprises at least a portion of B2M and at least a portion of HLA-A0201 (e.g., SEQ ID NO:16). In certain other particular embodiments, the single chain fusion HLA class I protein comprises at least a portion of B2M and at least a portion of HLA-E (e.g., SEQ ID NOs:18 and 20).

[0009] In yet other particular embodiments, the cell has a normal karyotype. The cell is a non-transformed cell. In particular, the cell can be a stem cell selected from the group consisting of a hematopoietic stem cell, an induced pluripotent stem cell, a liver stem cell, a neural stem cell, a pancreatic stem cell and a mesenchymal stem cell. Furthermore, an embryonic stem cell is disclosed without being claimed. In certain further embodiments, the cell further comprises one or more recombinant genes capable of encoding a suicide gene product. In certain particular embodiments, the suicide gene product comprises a protein selected from the group consisting of thymidine kinase and an apoptotic signaling protein.

[0010] In certain preferred embodiments, the stem cell is a pluripotent stem cell that expresses a single chain fusion HLA class I protein comprising at least a portion of B2M and at least a portion of an HLA class I α chain selected from the group consisting of HLA-A, HLA-B, HLA-C, HLA-E, HLA-F and HLA-G. In certain particular embodiments, the single chain fusion HLA class I protein comprises at least a portion of B2M and at least a portion of HLA-A0201.

[0011] In certain other particular embodiments, the stem cell is a differentiated cell. In certain embodiments, the differentiated cell is selected from the group consisting of a dendritic cell, a pancreatic islet cell, a liver cell, a muscle cell, a keratinocyte, a neuronal cell, a hematopoietic cell, a lymphocyte, a red blood cell, a platelet, a skeletal muscle cell, an ocular cell, a mesenchymal cell, a fibroblast, a lung cell, a GI tract cell, a vascular cell, an endocrine cell, an adipocyte and a cardiomyocyte. In certain preferred embodiments, the differentiated cell is a human cell expressing a single chain fusion HLA class I protein comprising at least a portion of B2M and at least a portion of an HLA class I α chain selected from the group consisting of HLA-A, HLA-B, HLA-C, HLA-E, HLA-F and HLA-G. In certain particular embodiments, the single chain fusion HLA class I protein comprises at least a portion of B2M and at least a portion of HLA-A0201.

[0012] In certain other embodiments, the cell further expresses a target peptide antigen that is presented by the single chain fusion HLA class I protein on the cell surface. In certain particular embodiments, the target peptide antigen is covalently linked to the single chain fusion HLA class I protein. In certain preferred embodiments, the target peptide antigen is derived from a

protein of a pathogen or a cancer cell. Thus, in a related aspect, the invention provides a vaccine comprising the *B2M*^{-/-}-cells of the invention, wherein the vaccine is capable of eliciting in a primate an immune response specific for the target peptide antigen. In certain particular embodiments, the vaccine comprises a cell of the invention that is a differentiated dendritic cell. In certain other embodiments, the cell is a human cell of the invention, wherein the cell expresses a cytokine that further enhances the immune response. In certain preferred embodiments, the cytokine is IL2. In certain other preferred embodiments, the cytokine is IFN- γ . In certain embodiments, the immune response comprises a humoral immune response; while in other embodiments, the immune response comprises a cellular immune response. In a further related aspect, the invention provides a kit comprising a vaccine that comprises the isolated cells of the invention and an immune adjuvant. In certain embodiments, the cell is a human cell.

[0013] Furthermore, a method of transplantation in a patient in need thereof is disclosed comprising the step of administering to the patient an effective amount of the disclosed isolated cell of the invention. In yet another aspect, the invention provides an inventive cell for use in transplantation in a patient in need thereof, whereby the cell is administered to the patient in an effective amount, wherein

1. a. the cell is a differentiated cell;
2. b. the patient is human and the cell is a human cell; and/or
3. c. the cell further expresses a single chain fusion HLA class I protein.

In certain disclosed embodiments, the patient is immune competent. In certain particular embodiments, the patient is a primate and preferably a human. In certain preferred embodiments, the patient is a human and the cell is a human cell. In further embodiments the cell is a stem cell, optionally expressing a single chain fusion HLA class I protein.

[0014] Furthermore a method of treating a disease condition in a patient in need thereof is disclosed comprising the step of administering to the patient an effective amount of the disclosed *B2M*^{-/-}-cells of the invention, wherein the disease condition includes without limitation an endocrine disorder, diabetes, an autoimmune disease, cancer, infection, anemia, a platelet disorder, immunodeficiency, cytopenia, myocardial infarction, heart failure, liver failure, skeletal or joint condition, a neurological condition, stroke, paralysis, blindness or another visual disorder, muscular dystrophy, osteogenesis imperfecta, pulmonary disease, skin condition, or burns. In yet another aspect, the invention provides an inventive cell for use in treating a disease condition in a patient in need thereof, whereby the cell is administered to the patient in an effective amount, and wherein the disease condition is diabetes, an autoimmune disease, cancer, infection, anemia, cytopenia, myocardial infarction, heart failure, skeletal or joint condition, osteogenesis imperfecta or burns. Preferably,

1. a. the cell is a differentiated cell;
2. b. the patient is a human and the cell is a human cell;
3. c. the disease condition is diabetes and the cell is a pancreatic islet cell; and/or
4. d. the cell further expresses a single chain fusion HLA class I protein.

In certain embodiments, the patient is immune competent. In certain particular embodiments, the patient is a primate and preferably a human. In certain preferred embodiments, the patient is a human and the cell is a human cell. In further embodiments the cell is a stem cell or a differentiated cell, optionally expressing a single chain fusion HLA class I protein. In certain particular embodiments, the disease condition is diabetes and the cell is a differentiated pancreatic islet cell. In further embodiments the differentiated pancreatic islet cell expresses a single chain fusion HLA class I protein.

[0015] In another aspect, the invention provides a kit comprising the isolated primate cells, preferably human cells, of the invention. In certain embodiments, the kit is for use in transplantation or for use in treating a disease condition. In certain other embodiments, the kit comprises an implant comprising the isolated primate cells, preferably human cells, of the invention.

[0016] Specific embodiments of the present invention will become evident from the following more detailed description of certain preferred embodiments and the claims.

BRIEF DESCRIPTION OF THE DRAWINGS

[0017]

Figure 1. Creation of *B2M*^{-/-} ESCs. **Figure 1A** is an illustration of the AAV B2M targeting vectors with exons shown in large boxes. **Figure 1B** presents Southern blots showing the results of gene targeting and Cre-mediated transgene excision (Cre-out). **Figure 1C** presents results of flow cytometry showing a lack of HLA class I expression after gene targeting (with isotype controls).

Figure 2. Tissue sections of teratoma developed from *B2M*^{-/-}Cre-out human ESCs transplanted in immune-deficient mice. The sections were stained with DAPI, hematoxylin and eosin, or lineage-specific markers MAP-2 (microtubule associated protein-2) for ectoderm, α -SAM (α -smooth muscle actin) for mesoderm or FoxA2 (forkhead box protein A2) for endoderm. Scale bar = 100 microns.

Figure 3. Single chain fusion HLA class I constructs. **Figure 3A** shows the foamy viral vector design for expressing single chain fusion HLA class I proteins. **Figure 3B** illustrates the linear protein structure of single chain fusion HLA class I proteins. Sequences for exemplary single chain fusion HLA class I proteins are provided for HLA-bGBE (SEQ ID NOs:19 and 20, DNA and protein sequences, respectively), HLA-gBE (SEQ ID NOs:17 and 18) and HLA-bBA0201 (SEQ ID NOs:15 and 16). **Figure 3C** presents results of flow cytometry showing single chain fusion HLA-E expression in *B2M*^{-/-}ESCs (isotype controls). **Figure 3D** presents results of flow cytometry showing single chain fusion HLA-A0201 expression in *B2M*^{-/-}ESCs (isotype controls).

Figure 4 outlines the experimental design for each differentiated cell type.

Figure 5 shows differentiation of keratinocytes from *B2M*^{-/-} ESCs.

DETAILED DESCRIPTION OF THE INVENTION

[0018] Within this application, unless otherwise stated, the techniques utilized may be found in any of several well-known references such as: Molecular Cloning: A Laboratory Manual (Sambrook, et al., 1989, Cold Spring Harbor Laboratory Press) and PCR Protocols: A Guide to Methods and Applications (Innis, et al. 1990. Academic Press, San Diego, CA).

[0019] As used herein, the singular forms "a", "an" and "the" include plural referents unless the context clearly dictates otherwise. For example, reference to "an isolated cell" means one or more isolated cells.

[0020] All embodiments disclosed herein can be combined unless the context clearly dictates otherwise.

[0021] In one aspect, the invention provides *B2M* deficient cells as defined in the claims. In particular, the invention provides isolated non-transformed primate cells, preferably human cells, comprising a genetically engineered disruption in a *B2M* gene. In certain preferred embodiments, the cell is a human cell comprising a genetically engineered disruption in the *B2M* gene. In a related aspect, the cell comprises genetically engineered disruptions of all copies of the *B2M* gene. In certain embodiments, the genetic disruptions in the *B2M* gene result in defective or no expression of the B2M protein. Since B2M is a common component of all HLA class I proteins, the disruptions preclude the expression of all natural HLA class I proteins on the cell surface. The *B2M* coding sequence is shown in SEQ ID NO:1 (GenBank Accession Number NM_004048) and the *B2M* protein sequence is shown in SEQ ID NO:2. There may be many single nucleotide polymorphisms (SNPs) in the gene; as will be understood by those of skill in the art, the human cells and methods of the invention are applicable to any such *B2M* gene and SNPs.

[0022] The cells of these embodiments of the invention can be used, for example, as donor cells for transplantation in a recipient in need thereof. *B2M* deficient cells encompass cells that comprise a *B2M*^{-/-} genetic background (referred to as *B2M*^{-/-} cells). The term "*B2M*^{-/-} cells" refers to primate cells, preferably human cells, that comprise genetically engineered disruptions in all copies of the *B2M* gene. The *B2M*^{-/-} cells can serve as "universal donor cells" in that they are immunologically compatible to all or a significant percentage of recipients in a population. As used herein, a recipient or patient refers to a primate, and preferably a human. In certain particular embodiments, the cell is a human cell and the patient is a human.

[0023] The cells of the invention can be engineered to disrupt the *B2M* gene such that no

functional endogenous B2M protein is produced from the disrupted genetic loci. In certain embodiments, the disruption results in expression of non-functional B2M proteins, including but not limited to truncations, deletions, point mutations and insertions. In other embodiments, the disruption results in no protein expression from the *B2M* gene.

[0024] Cells deficient in B2M expression are unable to express HLA class I proteins on the cell surface. HLA class I-deficiency provides further benefits; for example, cells without HLA class I expression cannot present auto-antigens that would otherwise prevent successful cell therapies for autoimmune diseases such as diabetes and rheumatoid arthritis. Similarly, therapeutic gene products introduced by the inventive cell therapies (e.g., dystrophin) that are missing in patients with certain genetic diseases (e.g., muscular dystrophy) will not be presented and recognized by the immune system as neo-antigens in replacement therapies.

[0025] Any suitable technique for disrupting one, two or all copies of the *B2M* gene can be used; exemplary techniques are disclosed throughout the application and are within the level of skill in the art based on the teachings herein and the teachings known in the art. Exemplary other techniques can be found, for example, in U.S. Patent Application Publication Number US2008/0219956, published September 11, 2008. These techniques may optionally include steps to remove non-human DNA sequences from the cells after *B2M* gene disruption.

[0026] An exemplary embodiment of this method is as disclosed throughout the application, using an adeno-associated virus gene targeting vector, optionally including removing the transgene used for targeting via techniques such as those described below, or by removing the transgene used for targeting by Cre-mediated loxP recombination, or other suitable recombination techniques. See Khan et al. 2011, Protocol, 6:482-501. Exemplary targeting vectors and exemplary vector diagrams are also disclosed herein. It is within the level of those of skill in the art, based on the teachings herein and known in the art, to utilize a variety of techniques for making the *B2M*^{-/-} cells, preferably human cells, of the invention.

[0027] In certain embodiments, the cell genome of the *B2M*^{-/-}-cells may comprise no more than 100, no more than 50 or no more than 30 nucleotides of non-human DNA sequences. In certain other embodiments, the cell genome may comprise 6, 5, 4, 3, 2, 1, or 0 nucleotides of non-human DNA sequences. An exemplary technique for removing any non-human DNA introduced in disrupting the *B2M* gene is provided in Figure 1A. The non-human DNA sequences can be removed by a second round of targeting to delete the HyTK or TKNeo transgenes in the first vectors or by the Cre-mediated loxP recombination.

[0028] In other embodiments, the cells instead can be engineered to recombinantly express a single chain fusion HLA class I protein in a *B2M*^{-/-}-genetic background. Thus, the *B2M*^{-/-}-cells as used herein also encompass primate, preferably human, cells that express one or more single chain fusion HLA class I proteins in a *B2M*^{-/-}-genetic background. The *B2M*^{-/-}-cells recombinantly expressing a single chain fusion HLA class I protein are nevertheless deficient in normal B2M function in that the cells do not express wild type B2M protein that form a non-covalently associated heterodimer with any HLA class I α chain on the cell surface.

[0029] The term "single chain fusion HLA class I protein," "single chain fusion HLA class I molecule" or "single chain fusion HLA class I antigen" refers to a fusion protein comprising at least a portion of the B2M protein covalently linked, either directly or via a linker sequence, to at least a portion of an HLA-I α chain. On the other hand, the term "HLA class I protein," "HLA class I molecule" or "HLA class I antigen" refers to a non-covalently associated heterodimer of B2M and an HLA α chain expressed on the surface of a wild type cell.

[0030] As used herein, the term "HLA class I α chain" or "HLA-I heavy chain" refers to the α chain of the HLA class I heterodimer. HLA class I heavy chain includes without limitation HLA class I α chains HLA-A, HLA-B, HLA-C, HLA-E, HLA-F, and HLA-G. Representative DNA and protein sequences are provided for HLA-A (GenBank No. K02883.1, SEQ ID NO:3; UniProt No. P01892, SEQ ID NO:4), HLA-B (NM_005514, SEQ ID NO:5; NP_005505; SEQ ID NO:6), HLA-C (NM_002117, SEQ ID NO:7; NP_002108, SEQ ID NO:8), HLA-E (NM_005516, SEQ ID NO:9; NP_005507, SEQ ID NO:10), HLA-F (NM_018950, SEQ ID NO:11; NP_061823, SEQ ID NO:12), and HLA-G (NM_002127, SEQ ID NO:13; NP_002118, SEQ ID NO: 14).

[0031] In addition, although the term "HLA class I protein/molecule" is known to refer to the MHC class I protein/molecule in human, the terms HLA and MHC are sometimes used interchangeably throughout this application: for example, the term HLA class I protein can also be used to refer to the primate equivalent to the HLA class I protein in a primate. One of skill in the art will be able to discern the meaning of the term based on the content.

[0032] The term *B2M*^{-/-}-cells as used herein also encompasses cells having genetically engineered disruptions in all copies of the *B2M* gene, wherein one *B2M* allele is genetically engineered to express, instead of the wild type B2M protein, a single chain fusion HLA class I protein (*i.e.*, genetically targeted knockin in one *B2M* allele). *B2M*^{-/-}-cells with such genetic background express B2M only in the context of the single chain fusion HLA class I protein from a *B2M* genetic locus. In certain advantageous embodiments, the expression of the single chain fusion HLA class I protein is regulated by the endogenous B2M regulatory sequence located at the *B2M* locus.

[0033] In related embodiments, *B2M*^{-/-}-cells further encompass cells having genetically engineered disruptions in all copies of the *B2M* gene, wherein all *B2M* alleles are genetically engineered to express, instead of the wild type B2M protein, single chain fusion HLA class I proteins (*i.e.*, genetically targeted knockin in all *B2M* alleles). *B2M*^{-/-}-cells with such genetic disruptions express B2M only in the context of single chain fusion HLA class I proteins from the genetic loci of all the alleles of the *B2M* gene. In certain embodiments, the cells are genetically engineered to express the same type of single chain fusion HLA class I protein from the genetic loci of all alleles of the *B2M* gene; while in other embodiments, the cells are genetically engineered to express different types of single chain fusion HLA class I proteins from different genetic loci of different alleles of the *B2M* gene.

[0034] Throughout the application, the "cells of the invention," "isolated cells of the invention,"

"*B2M*^{-/-}-cells," "*B2M*^{-/-}-cells of the invention" or "stem cells or differentiated cells of the invention" sometimes can be used interchangeably to encompass all the *B2M*^{-/-}-cells described herein of the invention. In certain particular embodiments, the *B2M*^{-/-}-cells of the invention express a single chain fusion HLA class I protein as defined herein, in a *B2M*^{-/-}-background. The *B2M*^{-/-}-cells can be genetically engineered to express a single chain HLA class I protein either from the *B2M* locus or from other location of the genome. In certain particular embodiments, the cells of the invention comprise genetically engineered disruptions in all alleles of the *B2M* gene that preclude the expression of wild type B2M protein, and nevertheless express a single chain fusion HLA class I protein from a *B2M* genetic locus. In certain other particular embodiments, the cells of the invention comprise genetically engineered disruptions in all alleles of the *B2M* gene that preclude the expression of wild type B2M protein, and nevertheless express single chain fusion HLA class I proteins from all *B2M* genetic loci. The term "gene," "allele," and "genetic locus" may be used interchangeably throughout the application.

[0035] The "isolated cell" can be any suitable cell type for a given purpose. For example, the cell can be a pluripotent stem cell or a differentiated cell. "A stem cell" broadly encompasses any cells that are capable of further differentiation. "A pluripotent stem cell" refers to a stem cell that has the potential to differentiate into any of the three germ layers: endoderm, mesoderm or ectoderm. "An adult stem cell," on the other hand, is multipotent in that it can produce only a limited number of cell types.. "Induced pluripotent stem cells (iPS cells)" are pluripotent stem cell artificially derived from a non-pluripotent cell, typically an adult somatic cell, by artificially inducing expression of certain genes.

[0036] In certain embodiments, the single chain fusion HLA class I protein comprises at least a portion of B2M and at least a portion of HLA-A, HLA-B, HLA-C, HLA-E, HLA-F or HLA-G (also referred to as a dimeric construct). In certain preferred embodiments, the HLA α chain contained in the single chain fusion HLA class I protein does not contain the leader sequence (or signal sequence) of the HLA class I α chain (leaderless HLA α chain). In certain other embodiments, the single chain fusion HLA class I protein comprises at least a portion of B2M and at least a portion of HLA-C, HLA-E or HLA-G. In certain further embodiments, the single chain fusion HLA class I protein comprises at least a portion of B2M and at least a portion of HLA-A, HLA-E or HLA-G. In certain preferred embodiments, the single chain fusion HLA class I protein comprises a leader sequence (or signal peptide) covalently linked to the at least a portion of B2M and at least a portion of an HLA α chain to ensure proper folding of the single chain fusion on the cell surface. The leader sequence can be the leader sequence of the B2M protein, the leader sequence of an HLA α chain protein or the leader sequence of other secretory proteins. In certain particular embodiments, the single chain fusion HLA class I protein comprises a B2M protein with its leader sequence removed. In certain other particular embodiments, the single chain fusion HLA class I protein comprises an HLA α chain protein with its leader sequence removed. Certain HLA class I α chains are highly polymorphic. As will be understood by those of skill in the art, the human cells and methods of the invention are applicable to any such HLA α chains and polymorphism thereof.

[0037] Single chain fusion HLA class I proteins comprising sequence variants and fragments of B2M and/or HLA α chains are contemplated by the instant invention, wherein such single chain fusion constructs nevertheless possess normal HLA class I functions, e.g., forming proper secondary structure of the heterodimer on the cell surface, presenting peptides in the peptide binding cleft and engaging the inhibitory receptors on the surface of NK cells. In certain embodiments, the variants share at least 75%, 80%, 81%, 85%, 88%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or complete sequence homology with the naturally occurring HLA heavy chains and B2M sequences, wherein the variants possess normal HLA class I functions. In certain other embodiments, the variants share at least 75%, 80%, 81%, 85%, 88%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or complete sequence homology with the sequences of B2M or HLA heavy chains as shown in SEQ ID NOs:2, 4, 6, 8, 10, 12 or 14.

[0038] In certain particular embodiments, the HLA-A variants share at least 85%, 88%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or complete sequence homology with SEQ ID NO:4. In certain other particular embodiments, the HLA-B variants share at least 81 %, 83%, 85%, 88,%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or complete sequence homology with SEQ ID NO:6. In certain further embodiments, the HLA-C variants share at least 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or complete sequence homology with SEQ ID NO:8. In yet other embodiments, the HLA-E variants share at least 97%, 98%, 99%, or complete sequence homology with SEQ ID NO:10. In certain particular embodiments, the HLA-F variants share at least 99%, or complete sequence homology with SEQ ID NO:12. In certain other embodiments, the HLA-G variants share at least 98%, 99%, or complete sequence homology with SEQ ID NO:14.

[0039] In certain other embodiments, the single chain fusion HLA class I protein comprises a full length B2M (including its leader sequence) and an HLA α chain without the leader sequence (leaderless HLA α chain); while in certain other embodiments, the single chain fusion HLA class I protein comprises a B2M protein without the leader sequence. It is understood that *B2M*^{-/-} cells expressing two, three or more different types of single chain fusion HLA class I protein in any combination, for example, expressing SC fusion comprising HLA-A (or a leaderless HLA-A) and SC fusion comprising HLA-C (or a leaderless HLA-C), expressing SC fusion comprising HLA-A (or a leaderless HLA-A) and SC fusion comprising HLA-E (or a leaderless HLA-E), or expressing SC fusion comprising HLA-B (or a leaderless HLA-B), SC fusion comprising HLA-E (or a leaderless HLA-E) and SC fusion comprising HLA-G (or a leaderless HLA-G), etc., are all contemplated by the invention.

[0040] Natural killer (NK) cells are part of the innate immune response. Several pathogens can down regulate HLA class I protein expression in infected cells. The NK cells monitor infection by recognizing and inducing apoptosis in cells that do not express HLA class I proteins. The inhibitory receptors on the NK cell surface recognize HLA class I α chain alleles thereby preventing NK-mediated apoptosis in uninfected normal cells. Thus, in certain particular embodiments, the single chain fusion HLA-I protein inhibits NK cell-mediated killing of cells that do not express endogenous HLA class I proteins by binding to the inhibitory receptors on the

NK cells. For example, HLA-E is a ligand for the CD94/NKG2 receptor of NK cells that inhibits NK cell-mediated apoptosis. Thus, in certain particular embodiments, the *B2M*^{-/-}-cell expresses the single chain fusion HLA class I protein comprising at least a portion of B2M and at least a portion of HLA-E. In addition, HLA-G is normally expressed on the surface of placental cytotrophoblasts that do not express HLA-A, B or C, and it protects these cells from NK cell-mediated lysis by interacting with the inhibitory ILT2(LIR1) receptor on NK cells (Pazmany et al., 1996, Science 274, 792-795). Thus, in certain other preferred embodiments, the *B2M*^{-/-}-cell expresses the single chain fusion HLA class I protein comprising at least a portion of B2M and at least a portion of HLA-G.

[0041] In certain particular embodiments, the single chain fusion HLA class I protein comprises at least a portion of B2M and at least a portion of HLA-A0201, an allele of HLA-A. HLA-A0201 (SEQ ID NO:4) is a common HLA class I allele found in a large percentage of the population in the United States. Thus, in certain advantageous embodiments, the isolated cell expresses the single chain fusion HLA class I protein comprising at least a portion of B2M and at least a portion of HLA-A0201 in a *B2M*^{-/-}-genetic background, wherein the isolated cell is immune compatible with a large percentage of the human population in the United States. Other suitable common alleles that can be used include without limitation HLA-A0101, HLA-A0301, HLA-B0702, HLA-B0801, HLA-C0401, HLA-C0701, and HLA-C0702. In certain preferred embodiments, the HLA allele comprises at least a portion of HLA-A0201 (SEQ ID NO:4), HLA-B0702 (SEQ ID NO:6) or HLA-C0401 (SEQ ID NO:8).

[0042] In certain further embodiments, the single chain fusion HLA class I protein also comprises a specific peptide antigen that occupies the peptide binding cleft of the single chain fusion HLA class I protein, wherein the peptide antigen is covalently linked to the single chain fusion HLA class I protein (also referred to as a trimeric construct). An example of the trimeric construct is shown in Figure 3B. The HLA-bGBE construct of Figure 3B comprises B2M and HLA-E covalently linked to a peptide antigen (such as, but not limited to, the HLA-G peptide antigen as illustrated in the figure) (SEQ ID NO:23) designed to occupy the peptide binding cleft of the single chain fusion HLA class I protein. In certain other embodiments, the covalently linked peptide antigen is cleaved via a built in protease cleavage site, and the cleaved peptide antigen can bind to the peptide binding cleft of the single chain fusion HLA-I protein for presentation. In certain alternative embodiments, the peptide antigen occupying the peptide binding cleft of the single chain fusion HLA class I protein is produced by the intracellular antigen processing pathway, in which the peptide antigen is produced by proteasome, transported to and loaded onto the single chain fusion HLA class I protein in the endoplasmic reticulum. In certain particular embodiments, the peptide antigen comprises a peptide of a tumor antigen. In certain other embodiments, the peptide antigen comprises a peptide of a protein from a pathogen including without limitation a bacterium, a virus, a fungus and a parasite. In further embodiments, the peptide antigen comprises a peptide of a tumor antigen. In certain particular embodiments, the *B2M*^{-/-}-cell of the invention expresses a single chain fusion HLA class I protein that is covalently linked to a peptide that does not comprise an auto-antigen or neo-antigen to the patient. It is within the ability of a skilled person to design the single chain fusion HLA class I protein and the peptide antigen presented thereon to modulate

the immune response that may be elicited in a recipient.

[0043] The isolated *B2M*^{-/-}-cell of the invention expressing a single chain fusion HLA class I protein comprising a specific peptide antigen either covalently or non-covalently bound to the single chain fusion HLA class I protein can be used, for example, for administration to a recipient to elicit an immune response. Accordingly, in a related aspect, the invention provides a vaccine comprising the isolated cell of the invention, wherein the vaccine is capable of eliciting in a recipient an immune response specific for the target peptide antigen. The immune response includes without limitation a cellular immune response and/or a humoral immune response. The vaccine may comprise a stem cell or a differentiated cell; in certain particular embodiments, the cell is a differentiated dendritic cell. In certain other embodiments, the cell further expresses a cytokine. Any suitable cytokine can be used; in certain particular embodiments, the cytokine is IL2 or IFN- γ . In certain preferred embodiments, the cell is a human cell and the recipient is a human.

[0044] The single chain fusion HLA class I protein can be expressed from an expression vector that allows either transient or more preferably, stable expression of the protein in a *B2M*^{-/-}-cell. Exemplary suitable expression vectors are known in the art. One such example is a retroviral vector, which is capable of integrating into the cellular genome to provide long-term, stable expression of an exogenous gene. In certain particular embodiments, the viral vector is derived from human foamy virus, a type of retrovirus. Other suitable viral vectors include without limitation vectors derived from retrovirus, adenoviral virus, adeno-associated virus, lentivirus, herpes simplex virus, vaccinia virus, and pox virus.

[0045] In certain preferred embodiments, the polynucleotide capable of encoding a single chain fusion HLA class I protein is integrated into the chromosome of the cells, preferably into the *B2M* or the *HLA* loci, for stable expression. Thus, in certain preferred embodiments, the *B2M* loci are disrupted by inserting in the *B2M* loci the polynucleotide capable of encoding a single chain fusion HLA class I protein to replace the expression of the endogenous wild type *B2M* protein. The result of such gene targeting disrupts normal *B2M* expression and precludes formation of wild type HLA class I proteins but permits expression of a predetermined single chain fusion HLA class I protein of choice on the surface of the otherwise *B2M* deficient cells. Other expression vectors are also contemplated and the selection of suitable expression vector is within the ability of one ordinary skill in the art.

[0046] According to the vector design, the polynucleotide capable of expressing a single chain fusion HLA class I protein is delivered to a cell by viral infection (when a viral vector is used) or by other delivery methods including without limitation transfection, electroporation, gene targeting or liposome-mediated DNA delivery.

[0047] Any immune effects of the single chain fusion HLA class I protein expressing *B2M*^{-/-}-cells can be studied by various means. For example, *B2M*^{-/-}-cells expressing a SC fusion HLA class I protein can be differentiated into antigen-presenting dendritic cells (iDCs). Suppression of NK cell-mediated lysis can be measured by chromium release assays after incubating iDCs

with normal human NK cells and NKL cell lines. A variety of controls (untransduced *B2M*^{-/-} iDCs, *B2M*^{+/+} iDCs, the 721.221 class I-negative cell line, and anti-receptor and anti-HLA antibodies) can be used to establish the specificity of the interactions. Additional characterization can be done with Elispot assays by incubating the cells with T cells.

[0048] In a related aspect, the invention provides an HLA class I-typed *B2M*^{-/-}-cell bank of the cells of the invention, wherein the cells of the cell bank comprise a *B2M*^{-/-} genetic background and are engineered to express one or more types of single chain fusion HLA class I proteins in which the HLA α chain is selected from the group consisting of HLA-A, HLA-B, HLA-C, HLA-E, HLA-F and HLA-G. In certain embodiments, the cell bank comprises a population of cells that expresses a single chain fusion HLA class I protein in which the HLA α chain comprises HLA-A. In certain other embodiments, the cell bank comprises a population of cells that expresses a single chain fusion HLA class I protein in which the HLA α chain comprises HLA-B. In certain further embodiments, the cell bank comprises a population of cells that expresses a single chain fusion HLA class I protein in which the HLA α chain comprises HLA-C. In yet other embodiments, the cell bank comprises a population of cells that expresses a single chain fusion HLA class I protein in which the HLA α chain comprises HLA-E. In certain other embodiments, the cell bank comprises a population of cells that expresses a single chain fusion HLA class I protein in which the HLA α chain comprises HLA-F. In certain particular embodiments, the cell bank comprises a population of cells that expresses a single chain fusion HLA class I protein in which the HLA α chain comprises HLA-G. In certain particular embodiments, the cell bank comprises the above-described one or more or preferably all populations of cells.

[0049] The cells of the cell bank can be pluripotent stem cells or differentiated cells. In certain particular embodiments, the cell bank comprises different types of differentiated cells, such as skin cells, pancreatic beta islet cells, etc., that express the same single chain fusion HLA class I protein. While in other particular embodiments, the cell bank comprises different types of differentiated cells, such as skin cells, pancreatic beta islet cells, etc., that each express different single chain fusion HLA class I proteins. It can be determined by a skilled researcher or clinician to choose suitable donor cells from the cell bank for a given patient. In certain other embodiments, some of the cells of the cell bank express the HLA class I allele that matches the HLA class I allele of the patient to whom the cells are administered. In certain preferred embodiments, the cell is a human cell and the patient is a human. In certain particular embodiments, the cells express a single chain fusion HLA class I protein comprising B2M and HLA-A0201 that matches the HLA allele of a large portion of the population in the United States.

[0050] Furthermore, a method of transplantation in a patient in need thereof is disclosed comprising the step of administering to the patient an effective amount of the disclosed cells of the invention for transplantation. In yet another aspect, the invention provides an inventive cell for use in transplantation in a patient in need thereof, whereby the cell is administered to the patient in an effective amount, wherein

1. a. the cell is a differentiated cell;
2. b. the patient is human and the cell is a human cell; and/or
3. c. the cell further expresses a single chain fusion HLA class I protein.

Because the *B2M*^{-/-} cells do not express wild type HLA class I protein on the cell surface, the cells when administered to a patient elicit minimal or no immune responses in the patient. Thus, transplantation using the *B2M*^{-/-} cells limits the need for taking immune suppressant therapies. Thus, in disclosed preferred embodiments, the patient is immune competent. In certain other embodiments, the cell is an isogeneic cell; while in other embodiments, the cell is an allogeneic cell.

[0051] In certain further embodiments, the cells of the invention are pluripotent stem cells; while in other embodiments, the cells of the invention are differentiated cells. In certain preferred embodiments, the cell is a human cell and the patient is a human patient. In certain particular embodiments, the inventive cell for use in transplantation comprises administering to a human an effective amount of the pluripotent stem cells or differentiated cells. In certain preferred embodiments, the cells of the invention further express one or more engineered single chain fusion HLA class I proteins. In certain other embodiments, the cells are able to escape NK cell-mediated killing and elicit minimal or no immune response in the recipient after transplantation.

[0052] Transplantation therapy, replacement therapy or regenerative therapy refers to therapies for a disease condition by administering to a patient cells or tissues to replenish or replace defective cellular functions in a target organ. In certain particular embodiments, the need for transplantation arises as a result of physical or pathological injuries to a tissue or organ. In certain other particular embodiments, the need for transplantation arises as a result of one or more genetic defect or mutation in the patient and the inventive cell for use in transplantation replenishes or replaces defective cellular functions in the patient without the need for gene therapy to correct the underlying genetic mutation of the patient. In certain further embodiments, inventive cell for use in the transplantation includes without limitation hematopoietic stem cell for use in transplantation, or cells for use in transplantation that are incorporated into an organ such as liver, kidney, pancreas, lung, brain, muscle, heart, gastrointestinal tract, nervous system, skin, bones, bone marrow, fat, connective tissue, immune system, or blood vessels. In certain particular embodiments, the target organ is a solid organ.

[0053] In certain particular embodiments, the cells administered to the recipient may or may not be incorporated into an organ in need of such therapy. In certain embodiments, the cells of the invention for use in transplantation are differentiated into the desired cell type, either before or after their use in transplantation, and provide the necessary cellular function without itself being incorporated into the tissue at the site of transplantation. For example, in certain embodiments for treating diabetes, the cells of the invention for use in transplantation either as pluripotent stem cells or differentiated pancreatic beta islet cells are used to be transplanted to a diabetic patient. The transplanted cells need not reconstitute a functioning pancreas: they

just need to secrete insulin in response to glucose levels. In certain particular embodiments, the cells for use in transplantation are transplanted into an ectopic location and are not fully incorporated into the pancreas. Pluripotent cells of the invention for use in transplantation, differentiated cells of the invention for use in transplantation, or a tissue differentiated and developed *ex vivo* from the cells of the invention for use in transplantation are all contemplated by the invention. In certain preferred embodiments, the cell is a human cell and the patient is a human patient. In certain other preferred embodiments, the cells of the invention express one or more single chain fusion HLA class I proteins.

[0054] In a further aspect, the invention provides a cell for use in treating a disease condition in a patient in need thereof comprising the step of administering to the patient an effective amount of the cell of the invention to treat the disease condition, wherein the disease condition is diabetes, an autoimmune disease, cancer, infection, anemia, cytopenia, myocardial infarction, heart failure, skeletal or joint condition, osteogenesis imperfecta or burns. In certain particular embodiments, the disease condition results from pathological or physical injuries to a tissue or organ. In certain embodiments, the cells of the invention are stem cells; while in other embodiments, the cells of the invention are differentiated cells. In certain preferred embodiments, the cell is a human cell and the patient is a human patient. In certain particular embodiments, the human cell is a differentiated cell. A tissue developed *ex vivo* from the cells of the invention for use in transplantation is also contemplated by the invention. In certain preferred embodiments, the cells of the invention further express one or more single chain fusion HLA class I proteins. In certain embodiments, the cell is an isogeneic cell; while in other embodiments, the cell is an allogeneic cell.

[0055] In certain particular embodiments, the cell is a differentiated cell including without limitation a dendritic cell, lymphocyte, red blood cell, platelet, hematopoietic cell, pancreatic islet cell, liver cell, muscle cell, keratinocyte, cardiomyocyte, neuronal cell, skeletal muscle cell, ocular cell, mesenchymal cell, fibroblast, lung cell, GI tract cell, vascular cell, endocrine cell and adipocyte. In certain other particular embodiments, the invention provides a cell of the invention for use in treating a disease condition in a solid organ. In certain embodiments, the cells of the invention used in treating a disease condition express one or more single chain fusion HLA class I proteins.

[0056] "Treating" a patient having a disease or disorder means accomplishing one or more of the following: (a) reducing the severity of the disease; (b) arresting the development of the disease or disorder; (c) inhibiting worsening of the disease or disorder; (d) limiting or preventing recurrence of the disease or disorder in patients that have previously had the disease or disorder; (e) causing regression of the disease or disorder; (f) improving or eliminating the symptoms of the disease or disorder; and (f) improving survival. In certain preferred embodiments, the disease or disorder is a disease or disorder that can be treated by a cell of the invention for use in transplantation.

[0057] The effective amount of the isolated cells of the invention for use in transplantation or for use in treating a disease condition depends on a number of factors, such as the type of

tissue, the severity of the disease condition, the transplantation reaction, the reason for transplantation, and the age and general health of the patient. The effective amount can be determined by a skilled researcher or clinician by routine practice. Due to the reduced immunogenicity of the transplanted cells, relative large amount of cells can be tolerated by a patient to achieve the desired therapeutic effects. Alternatively, the cells can be repeatedly transplanted at intervals until a desired therapeutic effect is achieved.

[0058] The route for administration of the cells of the invention is not limited in any particular way. Exemplary delivery routes include without limitation intravenous, intramuscular, subdermal, intraperitoneal, transcutaneous, intracutaneous, and subcutaneous route. The cells of the present invention can also be administered topically by injection. For example, the cells can be injected into an injured joint, a fractured bone, an infarct site, an ischemic site or their periphery.

[0059] In certain particular embodiments, the cells are administered via a delivery device including without limitation a syringe. For example, the cells can be suspended in a solution or a pharmaceutical composition contained in such a delivery device. The "solution" or "pharmaceutical composition" comprises a physiological compatible buffer and optionally a pharmaceutically acceptable carrier or diluent in which the cells of the invention remain viable. The use of such carriers and diluents is well known in the art. The solution includes without limitation physiologically compatible buffers such as Hank's solution, Ringer' solution, or physiologically buffered saline. The cells can be kept in the solution or pharmaceutical composition for short term storage without losing viability. In certain particular embodiments, the cells are frozen for long term storage without losing viability according to cryopreservation methods well-known in the art.

[0060] Aqueous injection suspensions may contain substances which increase the viscosity of the suspension, such as sodium carboxymethyl cellulose, sorbitol, or dextran, but still fluid to the extent that can be easily delivered by syringe injection. The solution is preferably sterile, stable under the conditions of manufacture and storage and is free of microorganism contamination through the use of, for example, parabens, chlorobutanol, phenol, ascorbic acid, thimerosal, and the like. The cells contained in the solution can be stem cells or differentiated cells as described herein, in a pharmaceutically acceptable carrier or diluent and, as required, other ingredients indicated above.

[0061] The cells may be administered systemically (e.g., intravenously) or locally (e.g., directly into a myocardial defect under the guidance of echocardiogram, or by direct application to damaged tissues or organs accessible during open surgery). For injections, the cells may be in an injectable liquid suspension preparation or in a biocompatible medium which is injectable in liquid form and becomes semi-solid at the site of damaged tissue. A syringe, a controllable endoscopic delivery device or other similar devices can be used so long as the needle lumen is of sufficient diameter (e.g. at least 30 gauge or larger) to avoid physical damages to the cells during delivery.

[0062] In certain other embodiments, the cells for use in transplantation can be transplanted via a solid support, e.g., a planar surface or three-dimensional matrix. The matrix or planar surface is surgically implanted into the appropriate site in a patient. For example, a patient needing a pancreatic graft can have differentiated cells on a solid support surgically implanted in the pancreas tissue. Exemplary solid support includes without limitation a patch, a gel matrix (such as GELFOAM® from Pharmacia-Upjohn), polyvinyl alcohol sponge (PVA)-collagen gel implants (such as IVALON, Unipoint Industries, High Point, NC) and other similar or equivalent devices. A variety of other encapsulation technologies can be used with the cells of the invention, for example, WO 91/10470; WO 91/10425; U.S. Pat. No. 5,837,234; U.S. Pat. No. 5,011,472; U.S. Pat. No. 4,892,538).

[0063] The cells of the invention can be differentiated into various cell types of all three lineages, including without limitation hematopoietic, mesenchymal, pancreatic endoderm, cardiac and keratinocytes cells. In certain embodiments, the differentiated cell further expresses a single chain fusion HLA class I protein. In general, each cell type can be analyzed for HLA class I protein expression, reactivity with human T cells and NK cells, appropriate differentiation markers, and xenotransplantation in immunodeficient mice to examine *in vivo* developmental potential. See Figure 4. A brief discussion of each differentiated cell type follows.

[0064] In certain embodiments, the cells of the invention can be differentiated to hematopoietic cells for the use in treating various hematopoietic diseases currently treated by bone marrow transplantation. Patients receiving transfusion can become refractory to platelet transfusions due to HLA mismatches. Anemic or cytopenic patients can be treated by delivering the cells of the invention-derived erythrocytes, platelets or neutrophils to treat bleeding or infection.

[0065] Further, stem cells of the invention-derived dendritic cells are antigen-presenting cells that can be used as cellular vaccines when properly engineered. In certain embodiments, the cells of the invention engineered to express a single chain fusion HLA class I protein and a unique peptide antigen are used to vaccinate against specific pathogen or tumor antigens. In certain other embodiments, differentiated *B2M*^{-/-} cytotoxic lymphocytes with HLA-restricted reactivity against specific antigens are used to eliminate infected cells or tumor cells.

[0066] To obtain hematopoietic cells, the pluripotent cells are first allowed to form embryoid bodies, thereafter non-adherent cells were cultured in the presence of hematopoietic cytokines to develop into specific cell lineages. The differentiation of hematopoietic cells from the cells of the invention that express a single chain fusion HLA class I protein expressers can be analyzed by flow cytometry and colony assays. The different cell populations are sorted based on their surface markers, and used to monitor the expression of HLA genes and reactivity with human NK cells and T cells as measured by Elispot, mixed lymphocyte reactions, and cytotoxicity assays. The effectiveness of the single chain fusion HLA constructs on suppression of NK cell-mediated killing can be examined at different stages of differentiation and transplantation. See Bix et al., 1991, Nature 349, 329-331. The hematopoietic stem cells can also be assayed using xenotransplantation models in, for example, immunodeficient mice (SCID-repopulating cells or

SRCs).

[0067] The cells of the invention can be differentiated into hematopoietic cell either before or after the cells are administered to a patient. In certain preferred embodiments, the cell is a human cell and the patient is a human. *In vitro* hematopoietic differentiation can be performed according to established protocols. See for example, Slukvin et al., 2006, J Immunol 176:2924-32, and Chang et al., 2006, Blood 108:1515-23.

[0068] In certain other embodiments, the cells of the invention can be differentiated into mesenchymal stem cells. In certain embodiments, the cells of the invention express one or more single chain fusion HLA class I proteins. MSCs have the potential to form several differentiated cell types, including marrow stromal cells, adipocytes, osteoblasts, and chondrocytes. Thus, inducing pluripotent stem cells to form MSCs (iMSCs) is useful in treating skeletal and joint conditions. The iMSCs can be further differentiated into osteoblasts and formed bone *in vivo*. Deyle et al., 2012, Mol Ther. 20(1):204-13. Cellular responses of T cells and NK cells to ESCs, iMSCs, and their more terminally differentiated derivatives such as osteoblasts can be examined.

[0069] In certain particular embodiments, the mesenchymal stem cells are capable of differentiating into non-limiting examples of cell types such as marrow stromal cells, adipocytes, osteoblasts, osteocytes and chondrocytes. The cells of the invention are differentiated into mesenchymal stem cells either before or after the cells are administered to a patient. In certain preferred embodiments, the cell is a human cell and the patient is a human. *In vitro* mesenchymal differentiation can be performed according to established protocols. See for example, Deyle et al., *supra*.

[0070] In yet other particular embodiments, the cells of the invention can be differentiated into insulin-producing pancreatic islet cells. In certain embodiments, the cells of the invention express one or more single chain fusion HLA class I proteins. The cells of the invention can be used to treat insulin-dependent diabetes mellitus. Advantageously, the transplanted cells do not need to reconstitute a functioning pancreas: they just need to secrete insulin in response to glucose levels. Therefore the treatment can succeed with different cell doses, with cells that are not perfectly differentiated into adult cell types, and when cells are transplanted into an ectopic location. Specific auto-antigens such as those derived from GAD65 or Insulin can cause autoimmune destruction of β cells in diabetes (Di Lorenzo et al., 2007, Clin Exp Immunol 148, 1-16). Thus, *B2M*^{-/-}-cells or *B2M*^{-/-}-cells expressing a single chain fusion HLA class I protein presenting a predetermined peptide antigen provide additional advantages in that they do not present these auto-antigens and can avoid autoimmune rejection and prevent a relapse of diabetes after transplantation.

[0071] The cells of the invention can be differentiated into pancreatic cells as described previously, which employs exposure of cells to different cytokines and drugs to promote sequential formation of mesendoderm, definitive endoderm, and pancreatic progenitors (Kroon et al., 2008, Nat Biotechnol 26, 443-452). These cells can be further cultured in implants in

immunodeficient mice. The cells of the invention with or without expressing a single chain fusion HLA class I protein and wild-type cell lines can be analyzed at different developmental stages for their reactivity with T cells and NK cells.

[0072] The cells of the invention are differentiated into pancreatic islet cell either before or after patient administration. In certain preferred embodiments, the cell is a human cell and the patient is a human. *In vitro* hematopoietic differentiation can be performed according to established protocols. See for example, Kroon et al., 2008, Nat Biotechnol 26, 443-452.

[0073] In certain other particular embodiments, the cells of the invention can be differentiated into cardiomyocytes. In certain embodiments, the cells of the invention further express one or more single chain fusion HLA class I proteins. The common clinical problems of myocardial infarction and congestive heart failure can be treated by transplanting healthy stem cell-derived cardiomyocytes that engraft and re-establish functional myocardium. The use of cells of the invention-derived cardiomyocytes allow these treatments to proceed with pre-packaged cells and avoid the immunosuppression currently required for allogeneic heart transplants. Physiologically relevant tests can be performed on the cardiomyocytes derived from the cells of the invention, such as electrical conduction and contraction studies. *B2M*^{-/-} stem cells or differentiated cardiomyocytes with or without expressing a single chain fusion HLA class I protein can be tested to determine their immunological reactivity when expressing cardiomyocyte genes, and to establish which HLA modifications minimize these immune responses.

[0074] The cells of the invention can be differentiated into cardiomyocytes either before or after the cells are administered to a patient. In certain preferred embodiments, the cell is a human cell and the patient is a human. In certain embodiments, the cells of the invention are differentiated into cardiomyocytes for the use in treating diseases including without limitation myocardial infarction and congestive heart failure. *In vitro* cardiomyocyte differentiation can be performed according to established protocols. See for example, Laflamme et al., 2007, Nat Biotechnol 25, 1015-1024.

[0075] In yet other particular embodiments, the cells of the invention can be differentiated into keratinocytes. In certain embodiments, the cells of the invention used for differentiation into keratinocytes express one or more single chain fusion HLA class I proteins. Severe burns and genetic skin conditions require treatment with skin grafts, and this is currently done with a variety of cell sources such as porcine skin grafts and cultured autologous human keratinocytes. Keratinocytes derived from the cells of the invention can provide a major clinical advance, since burns could be treated as an emergency with pre-packaged cells, and genetic diseases such as epidermolysis bullosa can be treated with normal cells (albeit with the *B2M*^{-/-} background in the cellular chromosome) that do not require correction of the responsible genetic mutations. In many cases the cells only need to engraft long enough for neighboring host cells to repopulate the affected area. Figure 5 shows *in vitro* differentiation of Keratin 5+ and Keratin 14+ keratinocyte colonies from the cells of the invention. The cells of the invention were cultured in matrigel cultures, followed by expansion in serum-free

keratinocyte medium containing all-trans retinoic acid and BMP4 as described previously (Itoh et al., 2011, PNAS USA 108, 8797-8802). For *in vivo* differentiation, the cells of the invention for use in transplantation can be embedded in polyvinyl alcohol sponge (PVA)-collagen gel implants for transplantation into a recipient. The cells of the invention can be differentiated into keratinocytes either before or after transplantation. In certain preferred embodiments, the cell is a human cell and the patient is a human.

[0076] In yet another aspect, the invention provides a use of the cells of the invention for the preparation for a medicament for transplantation. In a related aspect, the invention provides a use of the cells of the invention for the preparation for a medicament for treating a disease condition.

[0077] Further, the cells of the invention can serve as a research tool to provide a system for studying the functions of immunoregulatory proteins in a *B2M*^{-/-} genetic background. In certain embodiments, the cells of the invention further express one or more single chain fusion HLA class I proteins. Accordingly, in a related aspect, the invention provides a method of determining the function of an immunoregulatory protein comprising the steps of introducing one or more immunoregulatory genes into the cells of the invention and assaying for the activities of the immunoregulatory genes. In certain preferred embodiments, the cell is a human cell. For example, the cells of the invention can be used to study the function of an immune regulatory gene, or to study an immune response, in the absence of unwanted class I antigens. In certain embodiments, the cells of the invention express HLA-F or a single chain fusion HLA class I protein comprising B2M and HLA-F, wherein the function of the HLA-F can be studied in the *B2M*^{-/-} background. In a further related aspect, the invention provides a method of identifying a compound or molecule that modulates the function of the immunoregulatory protein comprising the steps of contacting the *B2M*^{-/-} cells comprising the one or more immunoregulatory genes with a compound or molecule of interest and assaying for the activities of the immunoregulatory genes. In certain preferred embodiments, the cell is a human cell.

[0078] In yet another related aspect, the invention provides an *in vivo* research tool in a mammal, particular in a non-human primate, that are administered the cells of the invention, for studying the functions of immunoregulatory genes, or identifying a compound that modulates the function of an immunoregulatory gene in the administered cells in a *B2M*^{-/-} genetic background. In certain embodiments, the cells of the invention further express one or more single chain fusion HLA class I proteins.

[0079] Mice, especially immune deficient mice, have been used as a model system for studying human cells *in vivo*. Human stem cells can behave differently in mice. In addition, the mouse and human immune systems have different NK cell receptors and non-classical MHC class I genes (e.g. HLA-E, F and G). Therefore, a *Macaca nemestrina* (Mn, pigtailed macaque) model can be developed to study the cells of the invention. The *Macaca mulatta* genome has been sequenced, which is highly homologous to the *nemestrina* genome. Further, the organization of macaque MHC loci is similar to human HLA, including the non-classical genes.

Homologs of the human HLA-E and HLA-G genes have been identified in macaques. The macaque MHC loci also contain homologs of many human NK cell receptors. Human *B2M*^{-/-} ESCs as well as Mn *B2M*^{-/-} ESCs can be used for transplantation in macaques.

[0080] MHC class I-deficient (*B2M*^{-/-}) macaque ESCs can be developed using the same AAV-mediated gene targeting strategy described for human cells. *Mn* versions of the single-chain HLA class I fusion proteins are expressed in the *B2M*^{-/-} macaques ESCs using the analogous viral vectors as described above.

[0081] Cells can be expanded *in vitro* and labeled with a vector expressing GFP for subsequent identification of transplanted cells. The cells can be embedded in polyvinyl alcohol sponge (PVA)-collagen gel implants, and placed subdermally into macaques. The implants can be harvested, sectioned and stained to determine the cell types that are present. Specific antibodies can be used to identify the differentiated cell types formed by the transplanted cells.

[0082] Any and every embodiment described above applies to any and every aspect of the invention, unless the context clearly indicates otherwise. All embodiments within and between different aspects can be combined unless the context clearly dictates otherwise.

[0083] The Examples, which follow, are illustrative of specific embodiments of the invention, and various uses thereof. They are set forth for explanatory purposes only, and are not to be taken as limiting the invention.

EXAMPLES

Reference Example 1 Construction of Human Pluripotent Stem Cells with Knockout Mutations in B2M Genes

[0084] Human pluripotent stem cells were created with knockout mutations in both alleles of the beta-2 microglobulin (*B2M*) genes that encodes the common subunit required for surface expression of all HLA class I heterodimers (HLA-A, B, C, E, F and G). Adeno-associated virus (AAV) gene targeting vectors were used to construct *B2M*^{-/-} (class I-negative) H1 human ESCs (University of Wisconsin). Human pluripotent stem cells were infected with AAV gene targeting vectors and the *B2M* gene was inactivated by homologous recombination. AAV mediated gene targeting methodology has been described previously in for example, Khan et al., 2011, Protocol, 482:482-501 and Khan et al., 1990, Science 248:1227-30.

[0085] Figure 1 describes the construction of HLA class I-negative human H1 ESCs cells using the adeno-associated virus (AAV) gene targeting vectors. The two AAV vectors used contain homologous arms surrounding exon 1 of the human *B2M* gene, and are designed to insert either a *TKNeo* or *HyTK* fusion gene encoding G418 or hygromycin resistance respectively into

exon 1 (Figure 1A). The H1 ESCs were infected with the AAV-B2M-ETKNpA vector and 30% of G418-resistant cells were targeted at one *B2M* allele based on Southern blot analysis. One of these clones was then infected with the AAV-B2M-EHyTKpA vector and 10% of hygromycin-resistant cells were targeted at *B2M*. Southern blot analysis of a representative clone that had deletions in both *B2M* alleles (*B2M*^{-/-}) is shown in Figure 1B (HyTK/TKN). None of the targeted clones analyzed contained random integrants. The sequences of the targeting vector plasmid pA2-B2METKMpA and pA2-B2MEHuTKpA are shown in SEQ ID NO:21 and SEQ ID NO:22, respectively.

[0086] Cre recombinase was then used to remove the floxed *TKNeo* and *HyTK* transgenes from the *B2M* loci. Cre was delivered transiently by a non-integrating foamy virus vector, which is a type of retroviral vector previously described that efficiently infects human ESCs. See Deyle, et al., 2010, J. Virol 84, 9341-9 and Gharwan et al., 2007, Mol Ther 15, 1827-1833. Four clones lacking the *TKNeo* and *HyTK* transgenes were selected by gancyclovir selection that kills cells expressing thymidine kinase (TK). The results shown by Southern blot analysis demonstrated transgene-free double knockouts (Figure 1B).

[0087] Karyotypes were checked on two of these clones and found to be normal (data not shown), and teratoma assays conducted in immunodeficient mice showed that these cells had trilineage developmental potential (Figure 2). Flow cytometry with antibodies against B2M (anti-B2M-01- PE from SantaCruz Biotechnology) and pan-HLA class I antigens (W6/32 from Sigma-Aldrich) confirmed that these cells did not express HLA class I proteins on the cell surface (Figure 1C).

Reference Example 2 Expression of Single Chain Fusion HLA class I Proteins in *B2M* Knockout Cells

[0088] In mice, HLA class I-negative cells can be destructed by Natural Killer (NK) cells through the "missing self" mechanism. Bix et al., 1991, Nature 349, 329-331. Human NK cells have different receptors, but an analogous inhibition of NK cell killing is mediated through interactions of NK cell receptors with HLA-C, E and G. The "missing self" phenomenon has largely been described for class I-deficient hematopoietic cells, and the mouse transplantation data reported previously showing that many types of *B2M*^{-/-} organs survived in *B2M*^{+/+} hosts suggests that it may be less important when transplanting cells form solid organs. However, given that it could significantly affect donor cell survival in some settings, specific HLA class I genes as single chain fusion proteins that suppress NK cell killing were introduced to the *B2M*^{-/-}-cells.

[0089] The strategy for expressing specific HLA class I genes in a *B2M*^{-/-} background is shown in Figure 3. The B2M chain was fused to the specific HLA class I heavy chain, thereby allowing surface expression of the class I chain even in *B2M*^{-/-} cells. Integrating foamy virus vectors were used to express these single chain fusion proteins. Foamy virus vectors are a type of retroviral vector with a large packaging capacity that can efficiently infect human pluripotent

stem cells (Gharwan *at al.*, *supra*). One such representative single chain fusion HLA class I protein foamy virus construct is shown in Figure 3A. The $\Delta\Phi$ -EGP-PHLA-SC foamy vectors included a GFP-Puro fusion protein gene driven by an EF1 alpha promoter to allow for puromycin selection and GFP expression in transduced cells, and a separate expression cassette with a ubiquitously expressed PGK promoter driving an HLA single chain fusion (HLA-SC) construct (Figure 3A). The vector design produced constitutive expression of both transgenes, but many other vector designs and internal promoters can also be used. For example, the GFP-Pur gene can be driven by the pGK promoter, and the EF1 alpha promoter controls the expression of the SC HLA gene.

[0090] As shown in Figure 3B, the HLA-bGBE trimeric single chain fusion construct included a covalently attached HLA-G peptide (SEQ ID NO:23) in the HLA-E peptide binding cleft, while the HLA-gBE dimeric construct included an HLA-G signal peptide that was cleaved off but still bound non-covalently to the HLA-E molecule. See Crew et al., 2005, Mol Immunol 42, 1205-1214. *B2M*^{-/-} cells were transduced with these vectors. Puromycin-resistant clones were selected and HLA-E surface expression was analyzed by flow cytometry in pluripotent cells expressing these constructs (Figure 3C).

[0091] Further, a specific classical HLA class I allele single chain fusion protein was constructed and expressed in *B2M*^{-/-} H1 ESCs to create a "semi-universal" donor cell to facilitate compatibility with recipients. For example, in the U.S. the HLA-A0201 allele is present in 48% of Caucasians, 46% of Hispanics, and 24% of African-Americans, all of which should accept HLA-A0201+ stem cells. See www.allelfrequencies.net and Storkus et al., 1989, PNAS USA 86:2361-2364. The HLA-bBA0201 dimeric single chain fusion construct was introduced in *B2M*^{-/-} H1 ESCs by foamy virus vectors (Figure 3B) and the expression of the single chain fusion protein was analyzed by flow cytometry (Figure 3D).

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ctgacctgtg ttccctcccc gatcattctt cctgttccag agaggtgggg ctggatgtct			1406
ccatctctgt ctcaaattca tgggtgcactg agctgcaact tcttacttcc ctaatgaagt			1466
taagaacctg aatataaatt tgtgtttotca aatatttgct atgaagcgtt gatggattaa			1526
ttaaataagt caattcctag aagttgagag agcaaataaa gacctgagaa ccttccagaa			1586

<211> 366

<212> PRT

<213> Homo sapiens

<400> 8

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Met Arg Val Met Ala Pro Arg Ala Leu Leu Leu Leu Leu Ser Gly Gly
1          5          10          15

Leu Ala Leu Thr Glu Thr Trp Ala Cys Ser His Ser Met Arg Tyr Phe
20          25          30

Asp Thr Ala Val Ser Arg Pro Gly Arg Gly Glu Pro Arg Phe Ile Ser
35          40          45

Val Gly Tyr Val Asp Asp Thr Gln Phe Val Arg Phe Asp Ser Asp Ala
50          55          60

Ala Ser Pro Arg Gly Glu Pro Arg Ala Pro Trp Val Glu Gln Glu Gly
65          70          75          80

Pro Glu Tyr Trp Asp Arg Glu Thr Gln Lys Tyr Lys Arg Gln Ala Gln
85          90          95

Ala Asp Arg Val Ser Leu Arg Asn Leu Arg Gly Tyr Tyr Asn Gln Ser
100         105         110

Glu Asp Gly Ser His Thr Leu Gln Arg Met Ser Gly Cys Asp Leu Gly
115         120         125

Pro Asp Gly Arg Leu Leu Arg Gly Tyr Asp Gln Ser Ala Tyr Asp Gly
130         135         140

Lys Asp Tyr Ile Ala Leu Asn Glu Asp Leu Arg Ser Trp Thr Ala Ala
145         150         155         160

Asp Thr Ala Ala Gln Ile Thr Gln Arg Lys Leu Glu Ala Ala Arg Ala
165         170         175

Ala Glu Gln Leu Arg Ala Tyr Leu Glu Gly Thr Cys Val Glu Trp Leu
180         185         190

Arg Arg Tyr Leu Glu Asn Gly Lys Glu Thr Leu Gln Arg Ala Glu Pro
195         200         205

Pro Lys Thr His Val Thr His His Pro Leu Ser Asp His Glu Ala Thr
210         215         220

Leu Arg Cys Trp Ala Leu Gly Phe Tyr Pro Ala Glu Ile Thr Leu Thr
225         230         235         240

Trp Gln Arg Asp Gly Glu Asp Gln Thr Gln Asp Thr Glu Leu Val Glu
245         250         255

Thr Arg Pro Ala Gly Asp Gly Thr Phe Gln Lys Trp Ala Ala Val Val
260         265         270

Val Pro Ser Gly Gln Glu Gln Arg Tyr Thr Cys His Met Gln His Glu
275         280         285

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Gly Leu Gln Glu Pro Leu Thr Leu Ser Trp Glu Pro Ser Ser Gln Pro
290 295 300

Thr Ile Pro Ile Met Gly Ile Val Ala Gly Leu Ala Val Leu Val Val
305 310 315 320

Leu Ala Val Leu Gly Ala Val Val Thr Ala Met Met Cys Arg Arg Lys
325 330 335

Ser Ser Gly Gly Lys Gly Gly Ser Cys Ser Gln Ala Ala Cys Ser Asn
340 345 350

Ser Ala Gln Gly Ser Asp Glu Ser Leu Ile Thr Cys Lys Ala
355 360 365

<210> 9

<211> 2679

<212> DNA

<213> Homo sapiens

<220>

<221> CDS

<222> (127)..(1203)

<400> 9

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cacgactccc gactataaag tccccatccg gactcaagaa gttctcagga ctcagaggct 120

gggatac atg gta gat gga acc ctc ctt tta ctc ctc tcg gag gcc ctg 168
Met Val Asp Gly Thr Leu Leu Leu Leu Leu Ser Glu Ala Leu
1 5 10

gcc ctt acc cag acc tgg gcg ggc tcc cac tcc ttg aag tat ttc cac 216
Ala Leu Thr Gln Thr Trp Ala Gly Ser His Ser Leu Lys Tyr Phe His
15 20 25 30

act tcc gtg tcc cgg ccc ggc cgc ggg gag ccc cgc ttc atc tct gtg 264
Thr Ser Val Ser Arg Pro Gly Arg Gly Glu Pro Arg Phe Ile Ser Val
35 40 45

ggc tac gtg gac gac acc cag ttc gtg cgc ttc gac aac gac gcc gcg 312
Gly Tyr Val Asp Asp Thr Gln Phe Val Arg Phe Asp Asn Asp Ala Ala
50 55 60

agt ccg agg atg gtg ccg cgg gcg ccg tgg atg gag cag gag ggg tca 360
Ser Pro Arg Met Val Pro Arg Ala Pro Trp Met Glu Gln Glu Gly Ser
65 70 75

gag tat tgg gac cgg gag aca cgg agc gcc agg gac acc gca cag att 408
Glu Tyr Trp Asp Arg Glu Thr Arg Ser Ala Arg Asp Thr Ala Gln Ile

80

85

90

ttc cga gtg aat ctg cgg acg ctg cgc ggc tac tac aat cag agc gag 456
Phe Arg Val Asn Leu Arg Thr Leu Arg Gly Tyr Tyr Asn Gln Ser Glu
95 100 105 110

gcc ggg tct cac acc ctg cag tgg atg cat ggc tgc gag ctg ggg ccc 504
Ala Gly Ser His Thr Leu Gln Trp Met His Gly Cys Glu Leu Gly Pro
115 120 125

gac ggg cgc ttc ctc cgc ggg tat gaa cag ttc gcc tac gac gcc aag 552
Asp Gly Arg Phe Leu Arg Gly Tyr Glu Gln Phe Ala Tyr Asp Gly Lys
130 135 140

gat tat ctc acc ctg aat gag gac ctg cgc tcc tgg acc gcg gtg gac Asp Tyr Leu Thr Leu Asn Glu Asp Leu Arg Ser Trp Thr Ala Val Asp 145 150 155	600
acg gcg gct cag atc tcc gag caa aag tca aat gat gcc tct gag gcg Thr Ala Ala Gln Ile Ser Glu Gln Lys Ser Asn Asp Ala Ser Glu Ala 160 165 170	648
gag cac cag aga gcc tac ctg gaa gac aca tgc gtg gag tgg ctc cac Glu His Gln Arg Ala Tyr Leu Glu Asp Thr Cys Val Glu Trp Leu His 175 180 185 190	696
aaa tac ctg gag aag ggg aag gag acg ctg ctt cac ctg gag ccc cca Lys Tyr Leu Glu Lys Gly Lys Glu Thr Leu Leu His Leu Glu Pro Pro 195 200 205	744
aag aca cac gtg act cac cac ccc atc tct gac cat gag gcc acc ctg Lys Thr His Val Thr His His Pro Ile Ser Asp His Glu Ala Thr Leu 210 215 220	792
agg tgc tgg gcc ctg ggc ttc tac cct gcg gag atc aca ctg acc tgg Arg Cys Trp Ala Leu Gly Phe Tyr Pro Ala Glu Ile Thr Leu Thr Trp 225 230 235	840
cag cag gat ggg gag ggc cat acc cag gac acg gag ctc gtg gag acc Gln Gln Asp Gly Glu Gly His Thr Gln Asp Thr Glu Leu Val Glu Thr 240 245 250	888
agg cct gca ggg gat gga acc ttc cag aag tgg gca gct gtg gtg gtg Arg Pro Ala Gly Asp Gly Thr Phe Gln Lys Trp Ala Ala Val Val Val 255 260 265 270	936
cct tct gga gag gag cag aga tac acg tgc cat gtg cag cat gag ggg Pro Ser Gly Glu Glu Gln Arg Tyr Thr Cys His Val Gln His Glu Gly 275 280 285	984
cta ccc gag ccc gtc acc ctg aga tgg aag ccg gct tcc cag ccc acc Leu Pro Glu Pro Val Thr Leu Arg Trp Lys Pro Ala Ser Gln Pro Thr 290 295 300	1032
atc ccc atc gtg ggc atc att gct ggc ctg gtt ctc ctt gga tct gtg Ile Pro Ile Val Gly Ile Ile Ala Gly Leu Val Leu Leu Gly Ser Val 305 310 315	1080
gtc tct gga gct gtg gtt gct gct gtg ata tgg agg aag aag agc tca Val Ser Gly Ala Val Val Ala Ala Val Ile Trp Arg Lys Lys Ser Ser 320 325 330	1128
ggt gga aaa gga ggg agc tac tct aag gct gag tgg agc gac agt gcc	1176
Gly Gly Lys Gly Gly Ser Tyr Ser Lys Ala Glu Trp Ser Asp Ser Ala 335 340 345 350	
cag ggg tct gag tct cac agc ttg taa agcctgagac agctgccttg Gln Gly Ser Glu Ser His Ser Leu 355	1223
tgtgcgactg agatgcacag ctgccttgtg tgcgactgag atgcaggatt tcctcacgcc	1283
tcccctatgt gtcttagggg actctggctt ctctttttgc aagggcctct gaatctgtct	1343
gtgtccctgt tagcacaatg tgaggaggta gagaaacagt ccacctctgt gtctaccatg	1403
acccccttcc tcacactgac ctgtgttctt tccctgttct cttttctatt aaaaataaga	1463
acctgggcag agtgcggcag ctcatgctg taatccacgc acttagggag gccgaggag	1523
gcagatcacg aggtcaggag atcgaaacca tcctggctaa cacggtgaaa ccccgctctt	1583
actaaaaaat acaaaaaatt agctgggcgc agaggcacgg gcctgtagtc ccagctactc	1643
aggaggcgga ggcaggagaa tggcgtcaac ccgggaggcg gaggttgacg tgagccagga	1703
ttgtgcgact gcactccagc ctgggtgaca ggggtgaaacg ccattctcaa aaataaaaat	1763
tgaaaaataa aaaaagaacc tggatctcaa tttaattttt catattcttg caatgaaatg	1823
gacttgagga agctaagatc atagctagaa atacagataa ttccacagca catctctagc	1883

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aaatttagcc tattcctatt ctctagccta ttccttacca cctgtaatct tgaccatata      1943
ccttggaggtt gaatattggt ttcatactgc tgtgggttga atgttccctc caacactcat      2003
gttgagactt aatccctaata gtggcaatac tgaaagggtgg ggcctttgag atgtgattgg      2063
atcgtaaggc tgtgccttca ttcattgggtt aatggattaa tgggttatca caggaatggg      2123
actggtggct ttataagaag aggaaaagag aactgagcta gcatgccacag cccacagaga      2183
gcctccacta gagtgatgct aagtggaaat gtgaggtgca gctgccacag agggccccc      2243
ccagggaat gtctagtgtc tagtggatcc aggccacagg agagagtgcc ttgtggagcg      2303
ctgggagcag gacctgacca ccaccaggac cccagaactg tggagtcagt ggcagcatgc      2363
agcgccccct tgggaaagct ttaggcacca gcctgcaacc cattcgagca gccacgtagg      2423
ctgcaccacag caaagccaca ggcacggggc tacctgaggc cttggggggc caatccctgc      2483
tccagtgtgt ccgtgaggca gcacacgaag tcaaaagaga ttattctctt cccacagata      2543
ccttttctct cccatgaccc tttaacagca tctgcttcat tcccctcacc ttcccaggct      2603
gatctgaggt aaactttgaa gtaaaataaa agctgtgttt gagcatcatt tgtatttcaa      2663
aaaaaaaaaa aaaaaa      2679

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<210> 10

<211> 358

<212> PRT

<213> Homo sapiens

<400> 10

```

Met Val Asp Gly Thr Leu Leu Leu Leu Leu Ser Glu Ala Leu Ala Leu
1          5          10          15

```

```

Thr Gln Thr Trp Ala Gly Ser His Ser Leu Lys Tyr Phe His Thr Ser
20          25          30

```

```

Val Ser Arg Pro Gly Arg Gly Glu Pro Arg Phe Ile Ser Val Gly Tyr
35          40          45

```

```

Val Asp Asp Thr Gln Phe Val Arg Phe Asp Asn Asp Ala Ala Ser Pro
50          55          60

```

```

Arg Met Val Pro Arg Ala Pro Trp Met Glu Gln Glu Gly Ser Glu Tyr
65          70          75          80

```

```

Trp Asp Arg Glu Thr Arg Ser Ala Arg Asp Thr Ala Gln Ile Phe Arg
85          90          95

```

```

Val Asn Leu Arg Thr Leu Arg Gly Tyr Tyr Asn Gln Ser Glu Ala Gly
100         105         110

```

```

Ser His Thr Leu Gln Trp Met His Gly Cys Glu Leu Gly Pro Asp Gly
115         120         125

```

```

Arg Phe Leu Arg Gly Tyr Glu Gln Phe Ala Tyr Asp Gly Lys Asp Tyr
130         135         140

```

```

Leu Thr Leu Asn Glu Asp Leu Arg Ser Trp Thr Ala Val Asp Thr Ala
145         150         155         160

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Ala Gln Ile Ser Glu Gln Lys Ser Asn Asp Ala Ser Glu Ala Glu His
165         170         175         180

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[illegible]

<210> 11
<211> 1301
<212> DNA
<213> Homo sapiens

<220>
<221> CDS
<222> (125)..(1165)

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<400> 11
tttctcactc ccattgggcg tcgcgtttct agagaagcca atcagtgtcg ccgcagttcc      60
caggttctaa agtcccacgc accccgcggg actcatattt ttcccagacg cggaggttgg      120
ggtc atg gcg ccc cga agc ctc ctc ctg ctg ctc tca ggg gcc ctg gcc      169
Met Ala Pro Arg Ser Leu Leu Leu Leu Leu Ser Gly Ala Leu Ala
      1              5              10              15

ctg acc gat act tgg gcg ggc tcc cac tcc ttg agg tat ttc agc acc      217
Leu Thr Asp Thr Trp Ala Gly Ser His Ser Leu Arg Tyr Phe Ser Thr

```

20	40	60	
gct gtg tgg cgg ccc ggc cgc ggg gag ccc cgc tac atc gcc gtg gag			265
Ala Val Ser Arg Pro Gly Arg Gly Glu Pro Arg Tyr Ile Ala Val Glu			
35	40	45	
tac gta gac gac acg caa ttc ctg cgg ttc gac agc gac gcc gcg att			313
Tyr Val Asp Asp Thr Gln Phe Leu Arg Phe Asp Ser Asp Ala Ala Ile			
50	55	60	
ccg agg atg gag ccg cgg gag ccg tgg gtg gag caa gag ggg ccg cag			361
Pro Arg Met Glu Pro Arg Glu Pro Trp Val Glu Gln Glu Gly Pro Gln			
65	70	75	
tat tgg gag tgg acc aca ggg tac gcc aag gcc aac gca cag act gac			409
Tyr Trp Glu Trp Thr Thr Gly Tyr Ala Lys Ala Asn Ala Gln Thr Asp			
80	85	90	95
cga gtg gcc ctg agg aac ctg ctc cgc cgc tac aac cag agc gag gct			457
Arg Val Ala Leu Arg Asn Leu Leu Arg Arg Tyr Asn Gln Ser Glu Ala			
100	105	110	
ggg tct cac acc ctc cag gga atg aat ggc tgc gac atg ggg ccc gac			505
Gly Ser His Thr Leu Gln Gly Met Asn Gly Cys Asp Met Gly Pro Asp			
115	120	125	
gga cgc ctc ctc cgc ggg tat cac cag cac gcg tac gac ggc aag gat			553
Gly Arg Leu Leu Arg Gly Tyr His Gln His Ala Tyr Asp Gly Lys Asp			
130	135	140	
tac atc tcc ctg aac gag gac ctg cgc tcc tgg acc gcg gcg gac acc			601
Tyr Ile Ser Leu Asn Glu Asp Leu Arg Ser Trp Thr Ala Ala Asp Thr			
145	150	155	
gtg gct cag atc acc cag cgc ttc tat gag gca gag gaa tat gca gag			649
Val Ala Gln Ile Thr Gln Arg Phe Tyr Glu Ala Glu Glu Tyr Ala Glu			
160	165	170	175
gag ttc agg acc tac ctg gag ggc gag tgc ctg gag ttg ctc cgc aga			697
Glu Phe Arg Thr Tyr Leu Glu Gly Glu Cys Leu Glu Leu Leu Arg Arg			
180	185	190	
tac ttg gag aat ggg aag gag acg cta cag cgc gca gat cct cca aag			745
Tyr Leu Glu Asn Gly Lys Glu Thr Leu Gln Arg Ala Asp Pro Pro Lys			
195	200	205	
gca cac gtt gcc cac cac ccc atc tct gac cat gag gcc acc ctg agg			793
Ala His Val Ala His His Pro Ile Ser Asp His Glu Ala Thr Leu Arg			
210	215	220	
tgc tgg gcc ctg ggc ttc tac cct gcg gag atc acg ctg acc tgg cag			841
Cys Trp Ala Leu Gly Phe Tyr Pro Ala Glu Ile Thr Leu Thr Trp Gln			
225	230	235	
cgg gat ggg gag gaa cag acc cag gac aca gag ctt gtg gag acc agg			889
Arg Asp Gly Glu Glu Gln Thr Gln Asp Thr Glu Leu Val Glu Thr Arg			
240	245	250	255
cct gca ggg gat gga acc ttc cag aag tgg gcc gct gtg gtg gtg cct			937
Pro Ala Gly Asp Gly Thr Phe Gln Lys Trp Ala Ala Val Val Val Pro			
260	265	270	
cct gga gag gaa cag aga tac aca tgc cat gtg cag cac gag ggg ctg			985
Pro Gly Glu Glu Gln Arg Tyr Thr Cys His Val Gln His Glu Gly Leu			
275	280	285	
ccc cag ccc ctc atc ctg aga tgg gag cag tct ccc cag ccc acc atc			1033
Pro Gln Pro Leu Ile Leu Arg Trp Glu Gln Ser Pro Gln Pro Thr Ile			
290	295	300	
ccc atc gtg ggc atc gtt gct ggc ctt gtt gtc ctt gga gct gtg gtc			1081
Pro Ile Val Gly Ile Val Ala Gly Leu Val Val Leu Gly Ala Val Val			
305	310	315	
act gga gct gtg gtc gct gct gtg atg tgg agg aag aag agc tca gat			1129
Thr Glu Ala Val Val Ala Ala Val Met Trp Arg Lys Lys Ser Ser Asn			

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320          325          330          335
aga aac aga ggg agc tac tct cag gct gca gtg tga gacagcttcc      1175
Arg Asn Arg Gly Ser Tyr Ser Gln Ala Ala Val
          340          345

ttgtgtggga ctgagaagca agatatcaat gtagcagaat tgcacttgtg cctcacgaac      1235
atacataaat tttaaaaata aagaataaaa atatattcttt ttatagataa aaaaaaaaaa      1295
aaaaaa      1301

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<210> 12
 <211> 346
 <212> PRT
 <213> Homo sapiens

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<400> 12
Met Ala Pro Arg Ser Leu Leu Leu Leu Leu Ser Gly Ala Leu Ala Leu
1          5          10          15

Thr Asp Thr Trp Ala Gly Ser His Ser Leu Arg Tyr Phe Ser Thr Ala
          20          25          30

Val Ser Arg Pro Gly Arg Gly Glu Pro Arg Tyr Ile Ala Val Glu Tyr
          35          40          45

Val Asp Asp Thr Gln Phe Leu Arg Phe Asp Ser Asp Ala Ala Ile Pro
          50          55          60

Arg Met Glu Pro Arg Glu Pro Trp Val Glu Gln Glu Gly Pro Gln Tyr
65          70          75          80

Trp Glu Trp Thr Thr Gly Tyr Ala Lys Ala Asn Ala Gln Thr Asp Arg
          85          90          95

Val Ala Leu Arg Asn Leu Leu Arg Arg Tyr Asn Gln Ser Glu Ala Gly
          100          105          110

Ser His Thr Leu Gln Gly Met Asn Gly Cys Asp Met Gly Pro Asp Gly
          115          120          125

Arg Leu Leu Arg Gly Tyr His Gln His Ala Tyr Asp Gly Lys Asp Tyr
          130          135          140

Ile Ser Leu Asn Glu Asp Leu Arg Ser Trp Thr Ala Ala Asp Thr Val
145          150          155          160

Ala Gln Ile Thr Gln Arg Phe Tyr Glu Ala Glu Glu Tyr Ala Glu Glu
          165          170          175

Phe Arg Thr Tyr Leu Glu Gly Glu Cys Leu Glu Leu Leu Arg Arg Tyr
          180          185          190

Leu Glu Asn Gly Lys Glu Thr Leu Gln Arg Ala Asp Pro Pro Lys Ala
          195          200          205

His Val Ala His His Pro Ile Ser Asp His Glu Ala Thr Leu Arg Cys
210          215          220

```

Trp Ala Leu Gly Phe Tyr Pro Ala Glu Ile Thr Leu Thr Trp Gln Arg
225 230 235 240

Asp Gly Glu Glu Gln Thr Gln Asp Thr Glu Leu Val Glu Thr Arg Pro
245 250 255

Ala Gly Asp Gly Thr Phe Gln Lys Trp Ala Ala Val Val Val Pro Pro
260 265 270

Gly Glu Glu Gln Arg Tyr Thr Cys His Val Gln His Glu Gly Leu Pro
275 280 285

Gln Pro Leu Ile Leu Arg Trp Glu Gln Ser Pro Gln Pro Thr Ile Pro
290 295 300

Ile Val Gly Ile Val Ala Gly Leu Val Val Leu Gly Ala Val Val Thr
305 310 315 320

Gly Ala Val Val Ala Ala Val Met Trp Arg Lys Lys Ser Ser Asp Arg
325 330 335

Asn Arg Gly Ser Tyr Ser Gln Ala Ala Val
340 345

<210> 13

<211> 1578

<212> DNA

<213> Homo sapiens

<220>

<221> CDS

<222> (179)..(1195)

<400> 13

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atgaagttct cactccatt aggtgacagg tttttagaga agccaatcag cgtcgccgcg 120

gtcctggttc taaagtcctc gtcacccac ccgactcat tctccccaga cgccaagg 178

atg gtg gtc atg gcg ccc cga acc ctc ttc ctg ctg ctc tcg ggg gcc 226
Met Val Val Met Ala Pro Arg Thr Leu Phe Leu Leu Leu Ser Gly Ala
1 5 10 15

ctg acc ctg acc gag acc tgg gcg ggc tcc cac tcc atg agg tat ttc 274
Leu Thr Leu Thr Glu Thr Trp Ala Gly Ser His Ser Met Arg Tyr Phe
20 25 30

agc gcc gcc gtg tcc cgg ccc ggc cgc ggg gag ccc cgc ttc atc gcc 322
Ser Ala Ala Val Ser Arg Pro Gly Arg Gly Glu Pro Arg Phe Ile Ala
35 40 45

atg ggc tac gtg gac gac acg cag ttc gtg cgg ttc gac agc gac tcg 370
Met Gly Tyr Val Asp Asp Thr Gln Phe Val Arg Phe Asp Ser Asp Ser
50 55 60

gcg tgt ccg agg atg gag ccg cgg gcg ccg tgg gtg gag cag gag ggg 418
Ala Cys Pro Arg Met Glu Pro Arg Ala Pro Trp Val Glu Gln Glu Gly
65 70 75 80

ccg gag tat tgg gaa gag gag aca cgg aac acc aag gcc cac gca cag 466
Pro Glu Trp Trp Glu Glu Glu Thr Arg Asn Thr Lys Ala His Ala Gln

85	90	95	
act gac aga atg aac ctg cag acc ctg cgc ggc tac tac aac cag agc Thr Asp Arg Met Asn Leu Gln Thr Leu Arg Gly Tyr Tyr Asn Gln Ser 100 105 110			514
gag gcc agt tct cac acc ctc cag tgg atg att ggc tgc gac ctg ggg Glu Ala Ser Ser His Thr Leu Gln Trp Met Ile Gly Cys Asp Leu Gly 115 120 125			562
tcc gac gga cgc ctc ctc cgc ggg tat gaa cag tat gcc tac gat ggc Ser Asp Gly Arg Leu Leu Arg Gly Tyr Glu Gln Tyr Ala Tyr Asp Gly 130 135 140			610
aag gat tac ctc gcc ctg aac gag gac ctg cgc tcc tgg acc gca gcg Lys Asp Tyr Leu Ala Leu Asn Glu Asp Leu Arg Ser Trp Thr Ala Ala 145 150 155 160			658
gac act gcg gct cag atc tcc aag cgc aag tgt gag gcg gcc aat gtg Asp Thr Ala Ala Gln Ile Ser Lys Arg Lys Cys Glu Ala Ala Asn Val 165 170 175			706
gct gaa caa agg aga gcc tac ctg gag ggc acg tgc gtg gag tgg ctc Ala Glu Gln Arg Arg Ala Tyr Leu Glu Gly Thr Cys Val Glu Trp Leu 180 185 190			754
cac aga tac ctg gag aac ggg aag gag atg ctg cag cgc gcg gac ccc His Arg Tyr Leu Glu Asn Gly Lys Glu Met Leu Gln Arg Ala Asp Pro 195 200 205			802
ccc aag aca cac gtg acc cac cac cct gtc ttt gac tat gag gcc acc Pro Lys Thr His Val Thr His His Pro Val Phe Asp Tyr Glu Ala Thr 210 215 220			850
ctg agg tgc tgg gcc ctg ggc ttc tac cct gcg gag atc ata ctg acc Leu Arg Cys Trp Ala Leu Gly Phe Tyr Pro Ala Glu Ile Ile Leu Thr 225 230 235 240			898
tgg cag cgg gat ggg gag gac cag acc cag gac gtg gag ctc gtg gag Trp Gln Arg Asp Gly Glu Asp Gln Thr Gln Asp Val Glu Leu Val Glu			946
245	250	255	
acc agg cct gca ggg gat gga acc ttc cag aag tgg gca gct gtg gtg Thr Arg Pro Ala Gly Asp Gly Thr Phe Gln Lys Trp Ala Ala Val Val 260 265 270			994
gtg cct tct gga gag gag cag aga tac acg tgc cat gtg cag cat gag Val Pro Ser Gly Glu Glu Gln Arg Tyr Thr Cys His Val Gln His Glu 275 280 285			1042
ggg ctg ccg gag ccc ctc atg ctg aga tgg aag cag tct tcc ctg ccc Gly Leu Pro Glu Pro Leu Met Leu Arg Trp Lys Gln Ser Ser Leu Pro 290 295 300			1090
acc atc ccc atc atg ggt atc gtt gct ggc ctg gtt gtc ctt gca gct Thr Ile Pro Ile Met Gly Ile Val Ala Gly Leu Val Val Leu Ala Ala 305 310 315 320			1138
gta gtc act gga gct gcg gtc gct gct gtg ctg tgg aga aag aag agc Val Val Thr Gly Ala Ala Val Ala Ala Val Leu Trp Arg Lys Lys Ser 325 330 335			1186
tca gat tga aaaggaggga gctactctca ggctgcaatg tgaaacagct Ser Asp			1235
gccctgtgtg ggactgagtg gcaagtcctt ttgtgacttc aagaaccctg actcctcttt			1295
gtgcagagac cagcccaccc ctgtgccac catgaccctc ttctcatgc tgaactgcat			1355
tccttcccca atcacctttc ctgttccaga aaaggggctg ggatgtctcc gtctctgtct			1415
caaatttgtg gtccactgag ctataactta cttctgtatt aaaattagaa tctgagtata			1475
aatttacttt ttcaaattat ttccaagaga gattgatggg ttaattaaag gagaagattc			1535
ctgaaatttt aagacacaaa taaatggaag acatggaac ttt			1578

<210> 14

<211> 338

<212> PRT

<213> Homo sapiens

<400> 14

Met Val Val Met Ala Pro Arg Thr Leu Phe Leu Leu Leu Ser Gly Ala
 1 5 10 15

Leu Thr Leu Thr Glu Thr Trp Ala Gly Ser His Ser Met Arg Tyr Phe
 20 25 30

Ser Ala Ala Val Ser Arg Pro Gly Arg Gly Glu Pro Arg Phe Ile Ala
 35 40 45

Met Gly Tyr Val Asp Asp Thr Gln Phe Val Arg Phe Asp Ser Asp Ser
 50 55 60

Ala Cys Pro Arg Met Glu Pro Arg Ala Pro Trp Val Glu Gln Glu Gly

65 70 75 80

Pro Glu Tyr Trp Glu Glu Glu Thr Arg Asn Thr Lys Ala His Ala Gln
 85 90 95

Thr Asp Arg Met Asn Leu Gln Thr Leu Arg Gly Tyr Tyr Asn Gln Ser
 100 105 110

Glu Ala Ser Ser His Thr Leu Gln Trp Met Ile Gly Cys Asp Leu Gly
 115 120 125

Ser Asp Gly Arg Leu Leu Arg Gly Tyr Glu Gln Tyr Ala Tyr Asp Gly
 130 135 140

Lys Asp Tyr Leu Ala Leu Asn Glu Asp Leu Arg Ser Trp Thr Ala Ala
 145 150 155 160

Asp Thr Ala Ala Gln Ile Ser Lys Arg Lys Cys Glu Ala Ala Asn Val
 165 170 175

Ala Glu Gln Arg Arg Ala Tyr Leu Glu Gly Thr Cys Val Glu Trp Leu
 180 185 190

His Arg Tyr Leu Glu Asn Gly Lys Glu Met Leu Gln Arg Ala Asp Pro
 195 200 205

Pro Lys Thr His Val Thr His His Pro Val Phe Asp Tyr Glu Ala Thr
 210 215 220

Leu Arg Cys Trp Ala Leu Gly Phe Tyr Pro Ala Glu Ile Ile Leu Thr
 225 230 235 240

Trp Gln Arg Asp Gly Glu Asp Gln Thr Gln Asp Val Glu Leu Val Glu
 245 250 255

Thr Arg Pro Ala Gly Asp Gly Thr Phe Gln Lys Trp Ala Ala Val Val
260 265 270

Val Pro Ser Gly Glu Glu Gln Arg Tyr Thr Cys His Val Gln His Glu
275 280 285

Gly Leu Pro Glu Pro Leu Met Leu Arg Trp Lys Gln Ser Ser Leu Pro
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Val Asp Leu Leu Lys Asn Gly Glu Arg Ile Glu Lys Val Glu His Ser
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Glu Phe Thr Pro Thr Glu Lys Asp Glu Tyr Ala Cys Arg Val Asn His
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Val Thr Leu Ser Gln Pro Lys Ile Val Lys Trp Asp Arg Asp Met Gly
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Ile Ser Glu Gln Lys Ser Asn Asp Ala Ser Glu Ala Glu His Gln Arg
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Ala Tyr Leu Glu Asp Thr Cys Val Glu Trp Leu His Lys Tyr Leu Glu
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Lys Gly Lys Glu Thr Leu Leu His Leu Glu Pro Pro Lys Thr His Val
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REFERENCES CITED IN THE DESCRIPTION

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Patentkrav

1. En isoleret celle omfattende en genetisk modificeret forstyrrelse i et beta-2-mikroglobulin(*B2M*)-gen, hvor cellen er en primatcelle og er en ikke-transformeret celle, hvor cellen yderligere omfatter et eller flere rekombinante immunomodulerende gener, der hver er i stand til at eksprimere et immunomodulatorisk polypeptid i cellen, hvor den ene eller flere immunomodulerende gener omfatter et polynukleotid der er i stand til at kode et enkeltkædet-fusion-human-leukocyt-antigen (HLA) klasse I protein omfattende mindst en del af B2M-proteinet kovalent bundet, enten direkte eller via en linkersekvens til mindst en del af en HLA I α kæde, hvor det enkeltkædede-fusion-human HLA klasse I protein er i stand til normal HLA klasse I funktion med hensyn til dannelse af korrekt sekundær struktur af enkeltkæde-fusions heterodimerer på celleoverfladen, præsensation af peptider i HLA I peptidbindende kløft og interagering med de inhiberende receptorer på overfladen af NK-celler.
2. Isoleret celle ifølge krav 1, hvor det enkeltkædede-fusion-human-leukocytantigen (HLA) klasse I-protein omfatter et B2M-protein uden ledersekvens.
3. Isoleret celle ifølge krav 1, hvor det enkeltkædede-fusion-human-leukocyt-antigen (HLA) klasse I-protein omfatter et HLA klasse I-protein eller variant deraf eller et lederløst HLA klasse I α protein.
4. Celle ifølge et hvilket som helst af kravene 1-3, hvor cellen omfatter genetisk modificerede forstyrrelser af alle kopier af *B2M* genet.
5. Celle ifølge et hvilket som helst af kravene 1-4, hvor cellen er en human celle.
6. Celle ifølge et hvilket som helst af kravene 1-5, hvor det enkeltkædede-fusion-HLA klasse I protein omfatter
 - a. mindst en del af B2M kovalent bundet til mindst en del af et HLA klasse I α kæde udvalgt blandt gruppen bestående af HLA-A, HLA-B, HLA-C, HLA-E, HLA-F og HLA-G;
 - b. mindst en del af B2M og mindst en del af HLA klasse I α kæde er udvalgt blandt gruppen bestående af HLA-E, HLA-G og HLA-A;
 - c. mindst en del af B2M og mindst en del af HLA-A;
 - d. mindst en del af B2M og mindst en del af HLA-A0201;
 - e. mindst en del af B2M og mindst en del af HLA-E;
 - f. mindst en del af B2M og mindst en del af HLA-G;
 - g. mindst en del af B2M og mindst en del af HLA-B;
 - h. mindst en del af B2M og mindst en del af HLA-C; eller
 - i. mindst en del af B2M og mindst en del af HLA-F.
7. Celle ifølge et hvilket som helst af kravene 1-6, hvor cellen yderligere eksprimere et target peptidantigen, der er præsenteret af det enkeltkædede-fusion-HLA klasse I protein på celleoverfladen.
8. Celle ifølge krav 7, hvor cellen yderligere omfatter et eller flere rekombinante gener, der er i stand til at kode for et selvmordsgenprodukt.

9. Celle ifølge et hvilket som helst af kravene 1-8, hvor cellen

- 5 a. har en normal karyotype;
 b. er en stamcelle udvalgt blandt gruppen bestående af en hæmatopoietisk stamcelle, en induceret pluripotent stamcelle, en leverstamcelle, en neural stamcelle, en pankreatisk stamcelle og en mesenkym stamcelle; eller
 c. er en pluripotent stamcelle;

10

10. Celle ifølge krav 9, hvor stamcellen er differentieret, og hvor den differentierede celle er udvalgt blandt gruppen bestående af en dendritisk celle, en pankreatisk ø-celle, en levercelle, en muskelcelle, en keratinocyt, neuronal celle, hæmatopoietisk celle, lymfocyt, rødt blodlegeme, blodplade, skeletmuskelcelle, okularcelle, mesenkymcelle, fibroblast, lungecelle, tarmkanalscelle, vaskulær celle, endokrin celle, adipocyt og en cardiomyocyt.

15

11. Vaccine omfattende cellen ifølge krav 7, hvor vaccinen er i stand til fremkaldelse af et immunrespons specifikt for target-peptidantigenet i et primat.

20

12. Vaccinen ifølge krav 11, hvor primatet er et menneske og cellen er en human celle.

13. Celle ifølge et hvilket som helst af kravene 1-10 til anvendelse ved transplantation hos en patient med behov dertil, hvorved cellen administreres til patienten i en effektiv mængde, hvor

25

- 30 a. cellen er en differentieret celle;
 b. patienten er menneske, og cellen er en human celle; og/eller
 c. cellen yderligere eksprimere et enkeltkædet-fusion-HLA klasse I protein.

14. Celle ifølge et hvilket som helst af kravene 1-10 til anvendelse til behandling af en sygdomstilstand hos en patient med behov dertil, hvorved cellen administreres til patienten i en effektiv mængde, og hvor sygdomstilstanden er diabetes, en autoimmun sygdom, cancer, infektion, anæmi, cytopeni, myokardieinfarkt, hjerteinsufficiens, skelet- eller ledtilstand, osteogenese imperfecta eller forbrændinger.

35

15. Celle til anvendelse ifølge krav 14, hvor

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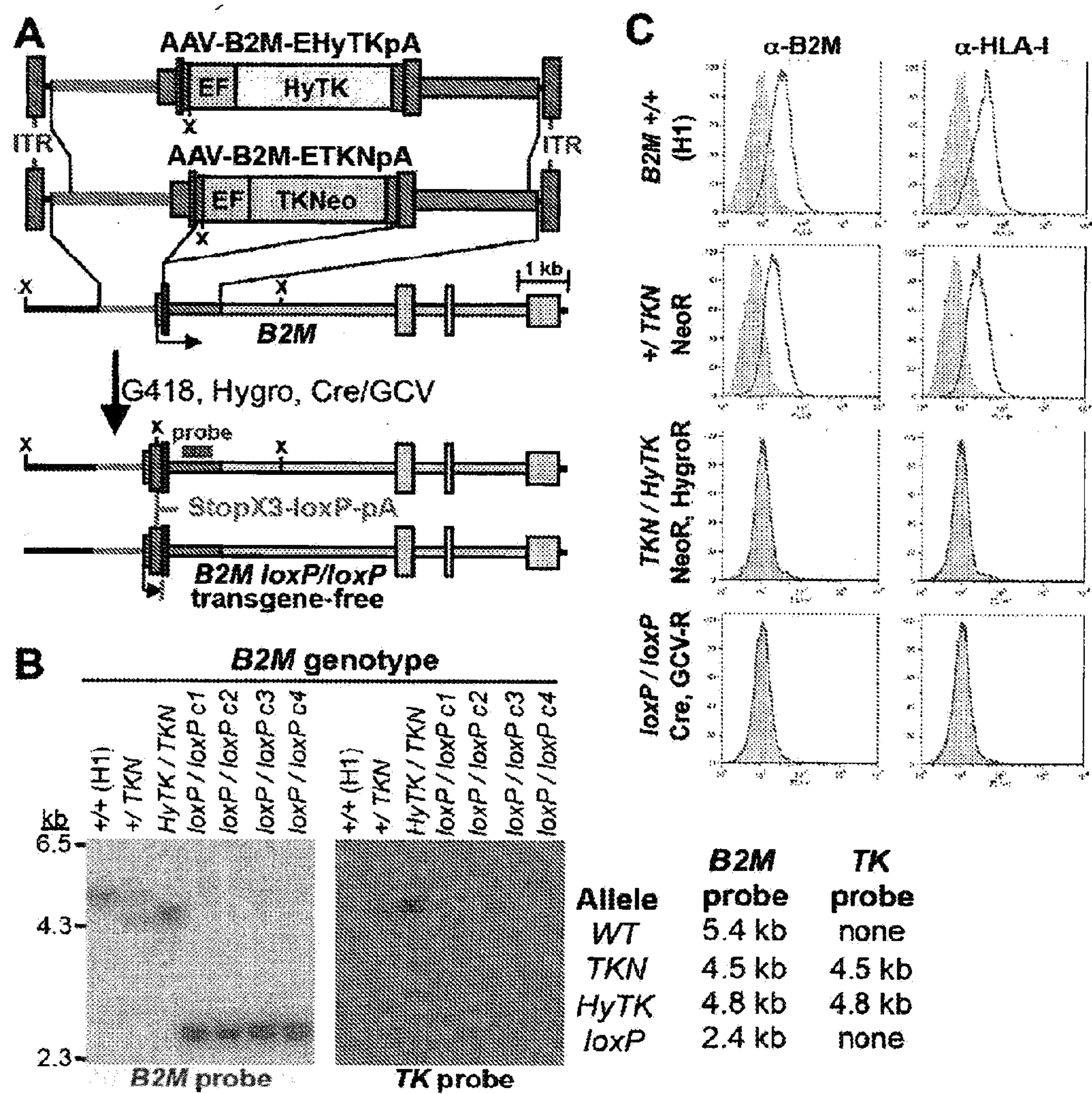
- a. cellen er en differentieret celle;
 b. patienten er et menneske, og cellen er en human celle;
 c. sygdomstilstanden er diabetes, og cellen er en pankreatisk ø-celle; og/eller
 d. cellen yderligere eksprimere et enkeltkædet-fusion-HLA klasse I protein.

45

16. Et kit omfattende

- a. cellen ifølge et hvilket som helst af kravene 1-10;
 b. et implantat omfattende cellen ifølge et hvilket som helst af kravene 1-10; eller
 50 c. vaccinen ifølge krav 11, yderligere omfattende en immun-adjuvans.

DRAWINGS



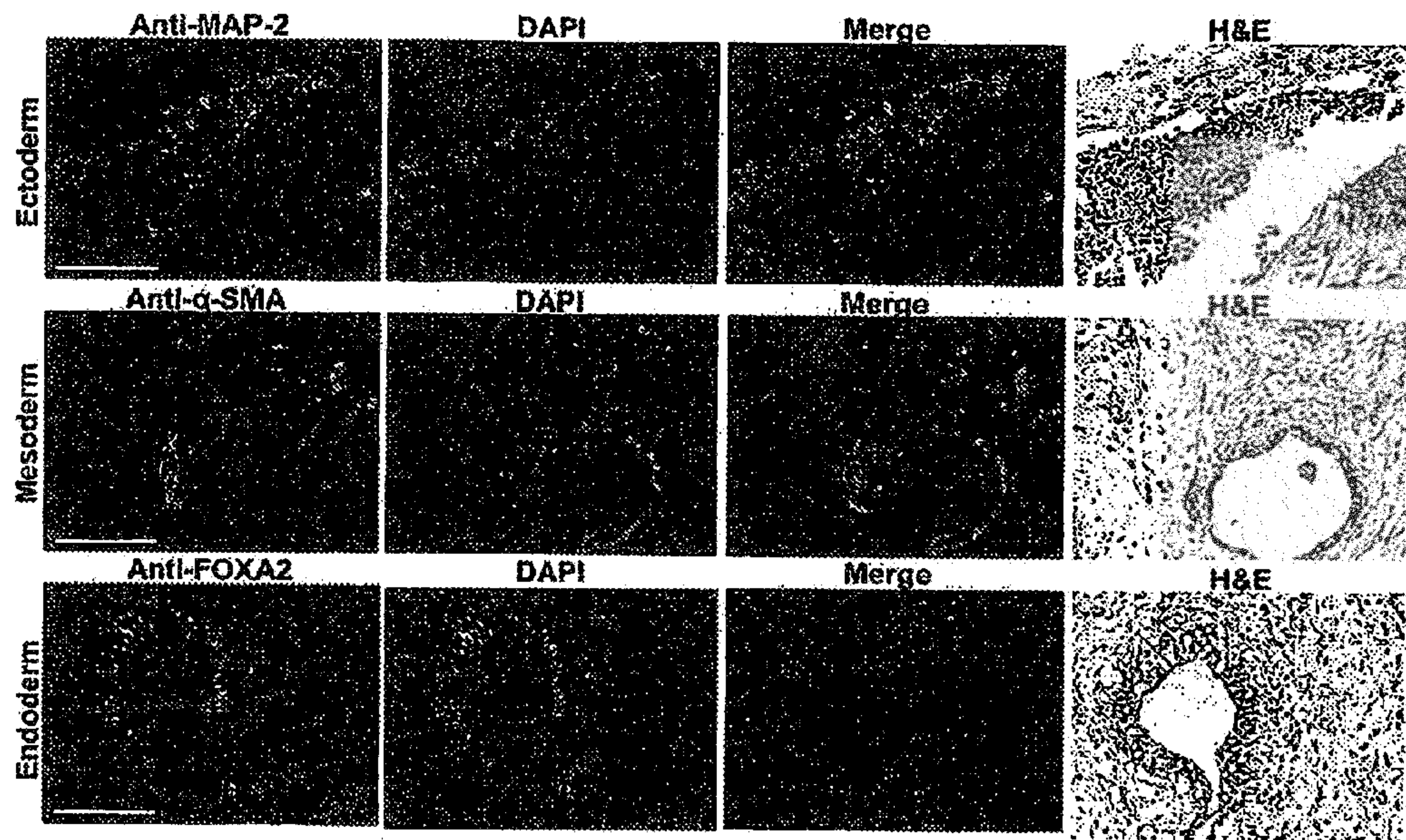


Figure 2

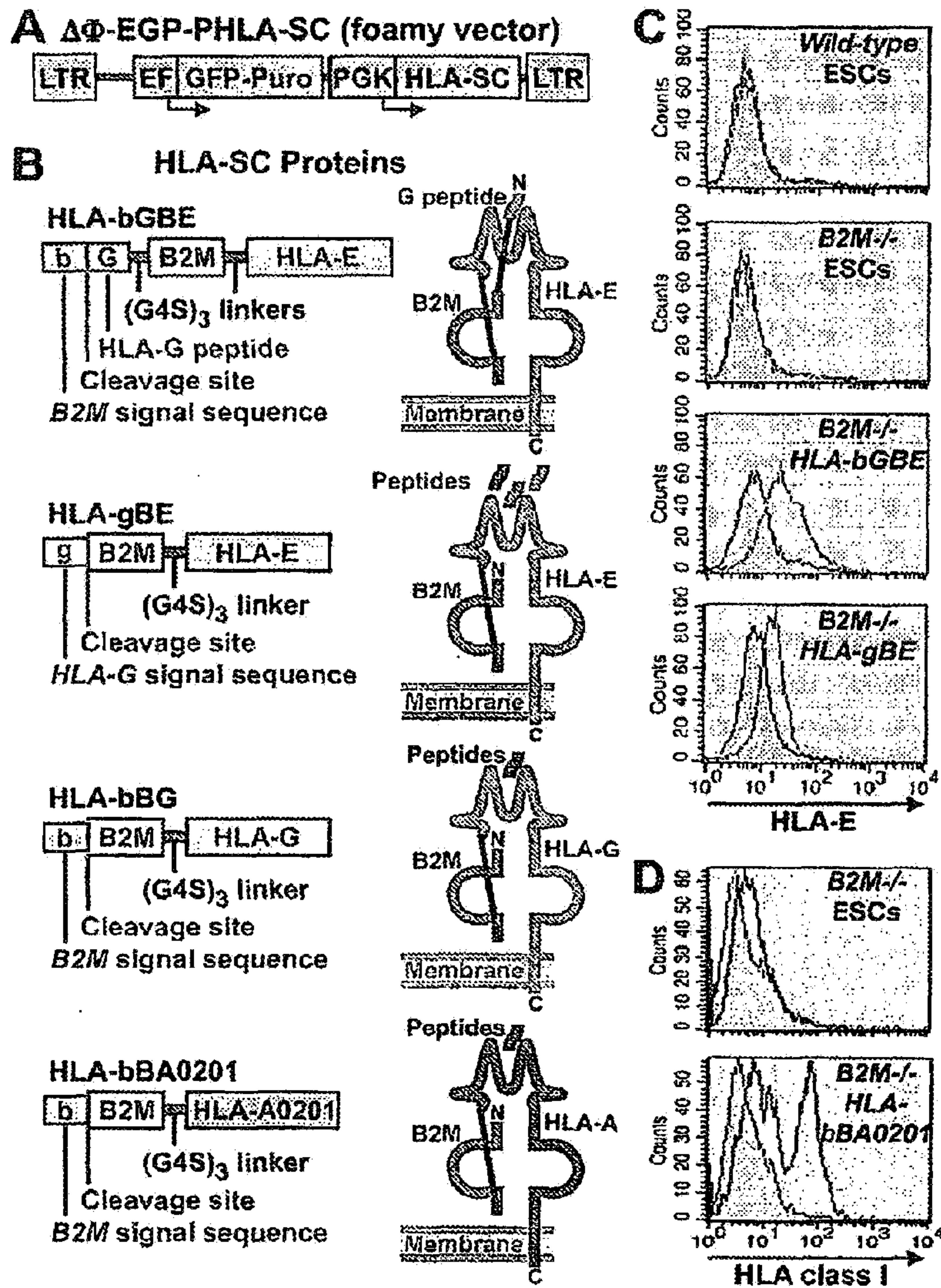


Figure 3

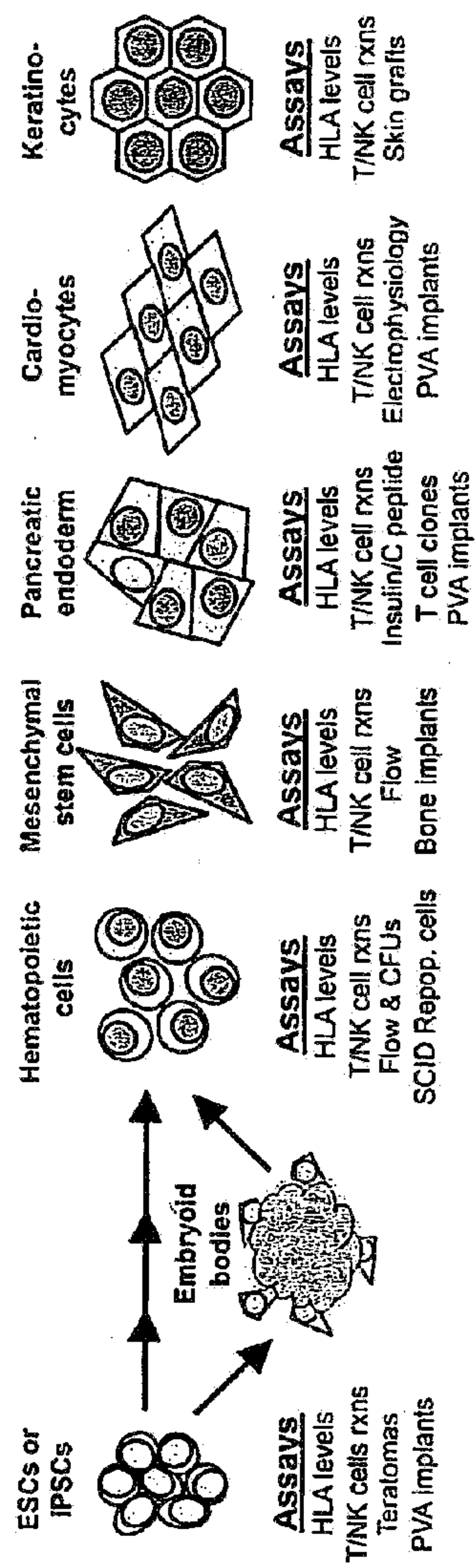
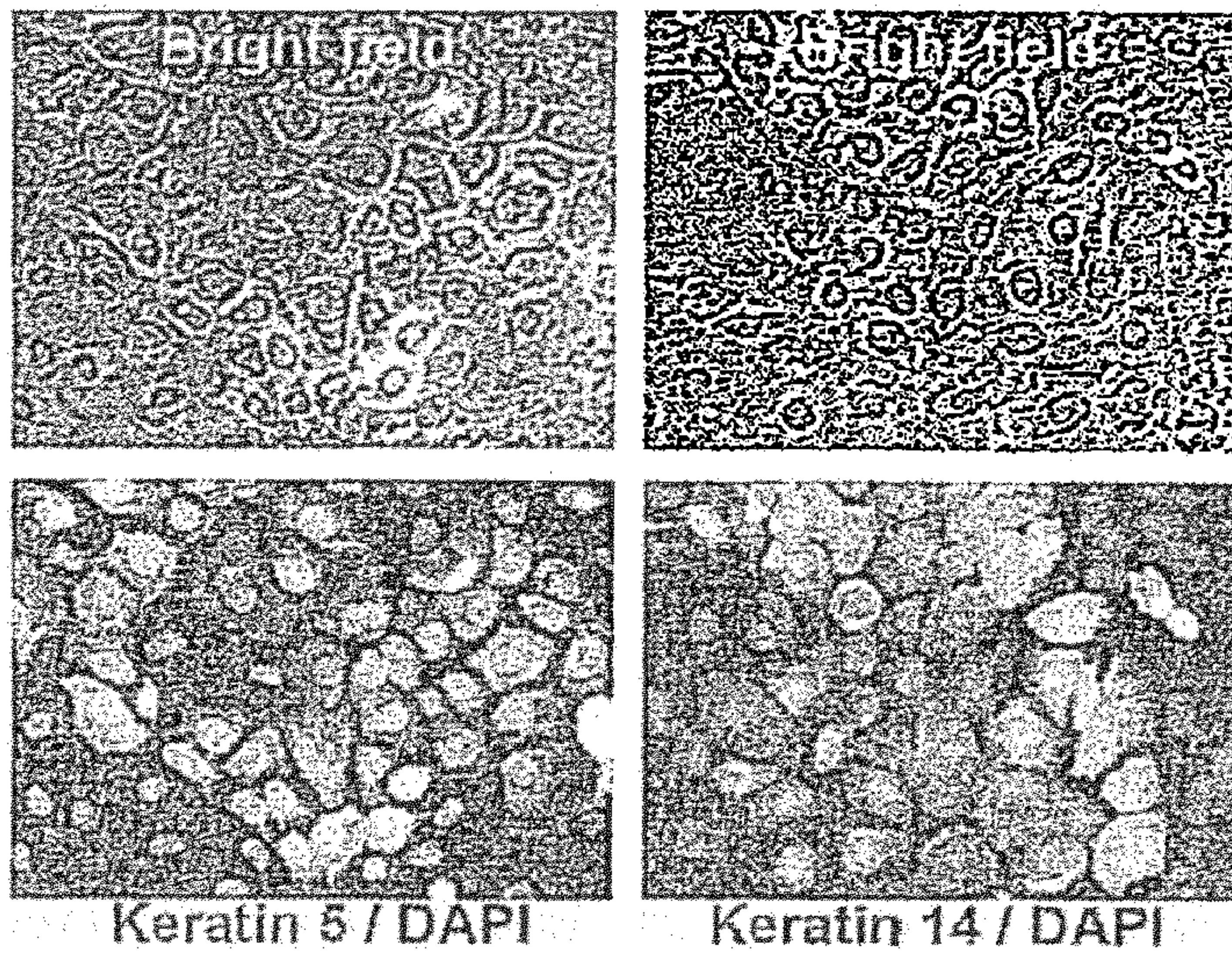


Figure 4

Skin



In vitro differentiation of *B2M*^{-/-} ESCs

Figure 5