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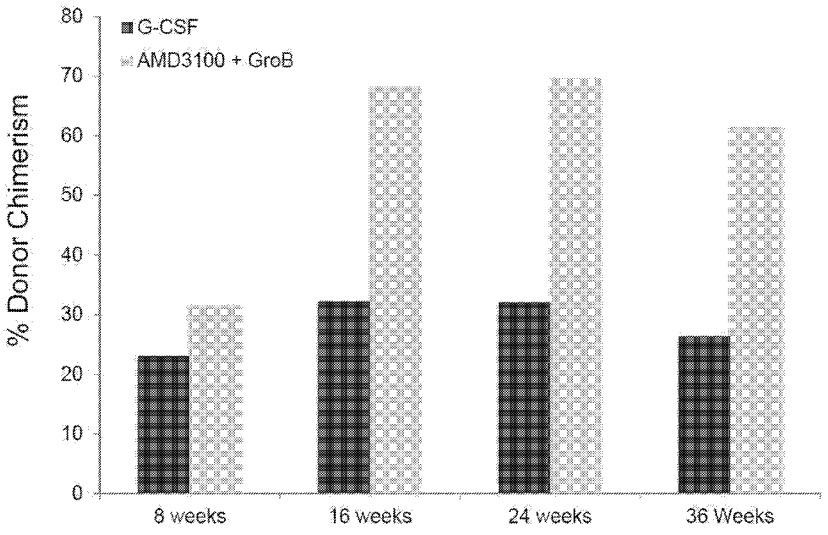

FIG. 1

(57) Abstract: The present inventions relates to highly engraftable hematopoietic stem cell (heHSC) and related methods of production and use for the treatment of stem cell and progenitor cell disorders.

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HIGHLY ENGRAFTABLE HEMATOPOIETIC STEM CELLS

CROSS-REFERENCE TO RELATED APPLICATIONS

This application claims the benefit of U.S. Provisional Application Serial No. 62/413,821, filed October 27, 2016 and U.S. Provisional Application No. 62/300,694, filed February 26, 2016, the contents of which are incorporated herein by reference in their entireties.

BACKGROUND OF THE INVENTION

Hematopoietic stem cell (HSC) transplantation is currently the only curative treatment modality for a number of stem cell disorders, including both malignant and non-malignant hematologic conditions. Yet, despite the fact that hematopoietic transplant is the only curative option for patients having such stem cell disorders, transplant-related morbidity and mortality remains high, and only a fraction of the patients that could benefit from an HSC transplant actually receive one.

Sources of HSCs for transplantation include the bone marrow itself, umbilical cord blood, and mobilized peripheral blood. Under steady state conditions, HSCs and hematopoietic progenitor cells (HPCs) normally reside within the bone marrow niches, while the mature cells produced by these populations of HSCs and HPCs ultimately exit the bone marrow and enter the peripheral blood. Considerable evidence over the last several decades, however, clearly demonstrates that HSCs and

HPCs (collectively referred to as "HSPCs") also exit the bone marrow niche and traffic to the peripheral blood and we now know that this natural egress into the periphery can be enhanced, allowing for "mobilization" of these cells from the bone marrow to the peripheral blood. Mobilized adult HSCs and HPCs are widely used for autologous and allogeneic transplantation and have improved patient outcomes when compared to bone marrow grafts.

The hematopoietic growth factor, granulocyte-colony stimulating factor (G-CSF) is widely used clinically to mobilize HSC and HPC for transplantation. G-CSF-mobilized peripheral blood stem cells (PBSCs) are associated with more rapid engraftment, shorter hospital stays, and in some circumstances, superior overall survival compared to bone marrow grafts, though the use of G-CSF-mobilized grafts over bone marrow in some allogeneic settings is under scrutiny.

While successful, G-CSF mobilization regimens involve repeated subcutaneous injections and are often associated with morbidity from bone pain (an often severe and debilitating complication), nausea, headache, and fatigue. These can be lifestyle disruptive in normal volunteers and particularly distressing for patients who are enduring the rigors of cancer chemotherapy. In a small population of normal donors, G-CSF has also been associated with serious toxicity, including enlargement of the spleen and splenic rupture, and the pro-coagulant effects of G-CSF can increase the risk of myocardial infarction and cerebral ischemia in high-risk individuals. Despite its success for most patients and donors, poor mobilization in response to G-CSF occurs in 15% of normal, healthy donors, and often those who do achieve sufficient numbers of CD34+ cells require more than one apheresis procedure. Repeated, prolonged sessions of apheresis are particularly common among autologous donors, which is particularly troubling for them given their ongoing ordeals associated with their underlying cancer and its treatment. Up to 60% of patients that fail to mobilize an optimal CD34+ cell dose for autologous transplantation often requiring tandem cycles of high dose chemotherapy. This is particularly an issue for patients with lymphoma and multiple myeloma, who often require extended aphereses and comprise the largest group of transplant recipients.

The availability of alternative methods for mobilizing HSPC could have high impact on the foregoing obstacles associated with HSC transplantation. Needed are novel therapeutics and methods that are capable of enhancing graft acquisition and hematopoietic recovery and engraftment. Also needed are highly engraftable cells

that may be used to treat stem cell and/or progenitor cell disorders, such as malignant and non-malignant hematologic diseases.

SUMMARY OF THE INVENTION

There remains a need for novel compositions, methods and therapies that are capable of reducing hematopoietic stem cell (HSC) transplant-related morbidity and mortality and enhancing engraftment of transplanted HSCs in subjects in need of a stem cell transplant. The present inventions are directed toward further solutions to address these unmet needs, in addition to having other desirable characteristics. Accordingly, disclosed herein is an isolated, highly engraftable hematopoietic stem cell (heHSC), as well as related methods of preparing such heHSCs and related methods of using such heHSCs for the treatment of stem cell and/or progenitor cell disorders and other diseases for which a stem cell transplant may be indicated.

In certain aspects, the present inventions are directed to an isolated, heHSC, wherein the heHSC is Sca-1+ and c-kit+ and is negative for Lineage markers (e.g., B220-, CD3-, Gr-1-, Mac-1-, TER119-) (e.g., a Sca-1+, c-kit+ and Lin- (SKL) cell). In certain aspects, the isolated heHSC is CD48-. In certain aspects the heHSC is not naturally occurring, i.e., differs from a naturally occurring HSC in one or more ways including but not limited to functionality (e.g., engraftability) and gene expression. In certain aspects, the isolated heHSC is CD150+. In certain aspects, the isolated heHSC is a Signaling lymphocytic activation molecule (SLAM) SKL cell, which is CD150+, CD48-, Sca-1+, c-kit+ and lineage negative. In certain aspects, the isolated heHSC does not express an immunophenotypic means of identifying human hematopoietic stem cells (e.g., the isolated heHSC does not express antigens, markers or other characteristics that may be useful for distinguishing such heHSC from other cell types). In some embodiments, the isolated heHSC comprises a unique transcriptome relative to hematopoietic stem cells contacted with granulocyte colony-stimulating factor (G-CSF), a chemotherapeutic agent, or any combination thereof. For example, in some aspects, the isolated heHSCs disclosed herein are characterized based on their differential expression of one or more of the genes selected from the group consisting of Fos, CD93, Fosb, Dusp1, Jun, Dusp6, Cdk1, Fignl1, Plk2, Rsad2, Sgk1, Sdc1, Serpine2, Spp1, Cdca8, Nrp1, Mcam, Pbk, Akr1cl and Cyp11a1 (e.g., relative to the expression of one or more genes by hematopoietic stem cells mobilized using G-

CSF). In some embodiments, the isolated heHSC expresses osteopontin (e.g., the heHSC is OPN+). In some embodiments, the isolated heHSC expresses CD93 (e.g., the heHSC is CD93+) than an HSC obtained from a subject subjected to a conventional mobilization regimen. In some embodiments, the isolated heHSC does not express CD34 or is CD34-. In some embodiments, the isolated heHSC is CD93+ and CD34-. In some embodiments, the heHSC is a non-native or non-naturally occurring cell, i.e., possesses one or more genotypic or phenotypic characteristics not present in native or naturally occurring HSC. In some embodiments, the isolated heHSC is from in a population of cells not present in a non-treated host and/or a host treated with a conventional mobilization regimen (e.g., a cell population with a different gene expression profile or a different phenotype profile). In some embodiments, the heHSC is from in a population of heHSC with a higher proportion of CD93+ cells than a HSC population obtained from a host treated with a conventional mobilization regimen.

Conventional procedures using G-CSF are known in the art. See Schmitt, M et al. "Mobilization of PBSC for Allogeneic Transplantation by the Use of the G-CSF Biosimilar XM02 in Healthy Donors." *Bone Marrow Transplantation* 48.7 (2013): 922–925. *PMC*. Web. 24 Feb. 2017, incorporated herein by reference.

As used herein, "differentially expresses", when used in reference to a cell population means an expression that is at least 10% higher than or lower than a reference value (e.g., an heHSC population differentially expresses CD93 from an HSC population obtained by a conventional immobilization technique if the heHSC population expresses at least 10% more or less CD93). As used herein, "differentially expresses," when used in reference to a cell, means that the cell has a different expression pattern of one or more phenotypes than a reference cell.

In certain aspects of the present inventions, the isolated heHSCs disclosed herein may be transformed to express a polynucleotide (e.g., an exogenous polynucleotide). For example, in certain embodiments, an isolated heHSC is transformed with an expression vector to express a polynucleotide (e.g., an exogenous polynucleotide). In some embodiments, the expression vector comprises a viral vector selected from the group consisting of a retrovirus, a herpes simplex, an adenovirus,a lentivirus, and an adeno-associated virus. In some embodiments, the isolated heHSC is transfected with an expression vector that comprises the

polynucleotide. In some embodiments, the polynucleotide comprises an exogenous polynucleotide.

Also disclosed herein is the use of isolated heHSCs to deliver an exogenous polynucleotide to a subject in need thereof. For example, the isolated heHSCs disclosed herein may be transformed to express an exogenous polynucleotide and, upon engraftment in the subject's tissues (e.g., bone marrow tissues), the engrafted heHSC expresses the exogenous polynucleotide, thereby delivering the expression product (e.g., a protein, enzyme or amino acid) to the subject.

Also disclosed herein are methods of transforming an isolated heHSC, wherein such methods comprise a step of contacting the heHSC with an expression vector under conditions sufficient for the vector to integrate into the heHSC genome. In yet other embodiments, the isolated heHSC of the present inventions are genetically modified to shut off expression of an endogenous polynucleotide.

In certain embodiments, the isolated heHSC is substantially pure (e.g., at least 10%, 20%, 30%, 40%, 50%, 60%, 70%, 80%, 90%, 95%, 97.5%, 98%, 99% or more pure). In certain aspects, the isolated heHSC is non-quiescent.

Also disclosed herein are methods of preparing an isolated, heHSC. For example, in some embodiments, the isolated heHSC disclosed herein is prepared by contacting a hematopoietic stem cell and/or a progenitor cell with at least one CXCR2 agonist and at least one CXCR4 antagonist, VLA-4 antagonist, $\alpha_9\beta_1$ antagonist, $\alpha_9\beta_1$ integrin/VLA-4 antagonist or combination thereof. In some embodiments, the isolated heHSC disclosed herein is prepared by contacting a hematopoietic stem cell and/or a progenitor cell with at least one CXCR2 agonist and at least one CXCR4 antagonist. In some embodiments, such contacting is performed *in vivo,* for example by administering GROβ or an analog or derivative thereof and plerixafor or an analog or derivative thereof to a human subject. In some embodiments, such contacting is performed *in vitro*. In some in vivo embodiments, such contacting mobilizes an amount of circulating peripheral blood stem cells in the subject sufficient to harvest a cell dose of between about 1 x 10^6/kg body weight and 10 x 10^6/kg body weight in a single apheresis session. In some in vivo embodiments, such contacting mobilizes an amount of circulating peripheral blood stem cells in the subject sufficient to harvest a cell dose of between about 2 x 10^6/kg body weight and 8 x 10^6/kg body weight in a single apheresis session. In some in vivo embodiments, such contacting mobilizes an amount of circulating peripheral blood stem cells in the subject sufficient to harvest a cell dose of

between about 3 x 10^6/kg body weight and 6 x 10^6/kg body weight in a single apheresis session. In some in vitro embodiments, isolated HSC are contacted with sufficient amount of at least one CXCR2 agonist and at least one CXCR4 antagonist, VLA-4 antagonist, $\alpha_9\beta_1$ antagonist, $\alpha_9\beta_1$ integrin/VLA-4 antagonist or combination thereof to obtain between 1 x 10^6 and 1.2 x 10^9 heHSC cells.

In some embodiments, the at least one CXCR2 agonist comprises GROβ or an analog or derivative thereof. In some embodiments the at least one CXCR2 agonist comprises GROβ-Δ4 or an analog or derivative thereof. In some embodiments, the at least one CXCR4 antagonist comprises plerixafor (AMD-3100) or an analog or derivative thereof. In some embodiments, the at least one CXCR4 antagonist comprises ALT1188, ALT1187, ALT1128, ALT1228, or TG-0054 or an analog or derivative thereof. In some embodiments, the CXCR4 antagonist comprises at least one inhibitor described in Debnath B, et al., "Small Molecule Inhibitors of CXCR4,"*Theranostics* 2013; 3(1):47-75, incorporated herein by reference. In some embodiments, the $\alpha_9\beta_1$ integrin/VLA-4 antagonist is N-(benzenesulfonyl)-L-prolyl-L-O-(1-pyrrolidinylcarbonyl)tyrosine (BOP) or an analog or derivative thereof (e.g., R-BC154). In some embodiments, the VLA-4 antagonist is BIO 5192, Natalizumab, firategrast, or an analog or derivative thereof. In still other embodiments, the at least one CXCR2 agonist is GROβ or an analog or derivative thereof and the at least one CXCR4 antagonist is plerixafor or an analog or derivative thereof. In some embodiments, a Gro-beta analog or derivative is the desamino Gro-beta protein (also known as MIP-2alpha), which comprises the amino acid sequence of mature gro-S protein truncated at its N terminus between amino acid positions 2 and 8, as described in PCT International Application Publication WO/1994/029341, incorporated herein by reference in its entirety. In other embodiments, the Gro-beta analog or derivative is the dimeric modified Gro-beta protein described in U.S. Pat. No. 6,413,510, incorporated herein by reference in its entirety. In some embodiments, the Gro-beta analog or derivative is SB-251353, a Gro-beta analog involved in directing movement of stem cells and other leukocytes, as described by Bensinger et al. (Bone Marrow Transplantation (2009), 43, 181-195, incorporated by reference herein).

The isolated heHSCs disclosed herein are characterized by their enhanced ability to engraft in a target tissue of a subject (e.g., the bone marrow tissue of a subject). Accordingly, in some embodiments upon administration or transplant of the heHSC in a subject such heHSC demonstrates increased engrafting ability, for

example, relative to engraftment of the same quantity of hematopoietic stem cells that are contacted or mobilized with granulocyte colony-stimulating factor (G-CSF), chemotherapeutic agents (e.g., mobilizing chemotherapeutic agents), or any combinations thereof. In certain embodiments, such engrafting ability is increased by at least about two-fold, three-fold, four-fold, five-fold, six-fold, or more.

In some embodiments, the heHSC is a non-native cell, i.e., possesses one or more genotypic or phenotypic characteristics not present in native HSC. In some embodiments, the isolated heHSC is from in a population of cells not present in a non-treated host and/or a host treated with a conventional mobilization regimen (e.g., a cell population with a different gene expression profile or a different phenotype profile). In some embodiments, the heHSC is from in a population of heHSC with a higher proportion of CD93+ cells than a HSC population obtained from a host treated with a conventional mobilization regimen.

The isolated heHSCs disclosed herein are also characterized by their ability to produce or cause improved or increased donor chimerism following their engraftment. In some embodiments, upon engraftment of the heHSCs in a subject the heHSCs demonstrate increased donor chimerism, for example, relative to the donor chimerism observed following engraftment of the same quantity of hematopoietic stem cells contacted or mobilized with G-CSF, chemotherapeutic agents (e.g., mobilizing chemotherapeutic agents), or any combinations thereof. In certain embodiments, such donor chimerism is increased by at least about two fold, three-fold, four-fold, five-fold, six-fold, or more. In some embodiments, such donor chimerism is at least about 10%, 20%, 25%, 30%, 40%, 50%, 60%, 70%, 75%, 80%, 85%, 90%, 95%, 97%, 99%, or more.

In certain aspects, the present inventions are directed to methods of treating a stem cell or progenitor cell disorder. Such methods comprise a step of administering an isolated heHSC (e.g., a SLAM SKL heHSC) to a subject in need thereof, wherein the administered heHSC engrafts in the subject's tissues (e.g., the subject's bone marrow compartment), thereby treating the stem cell or progenitor cell disorder. In some embodiments, the methods described herein comprise administering a population of cells comprising at least about 20%, 25%, 30%, 35%, 40%, 45%, 50%, 55%, 60%, 65%, 70%, 75%, 80%, 85%, 90%, or 95% heHSC cells.

In certain aspects, upon engraftment in a subject, the engrafted heHSCs demonstrate enhanced hematopoietic function relative to engraftment of the same

quantity of hematopoietic stem cells contacted or mobilized with G-CSF, chemotherapeutic agents (e.g., mobilizing chemotherapeutic agents), or any combinations thereof. In some embodiments, upon engraftment in a subject the engrafted heHSCs demonstrate an enhanced CD34+ number relative to engraftment of the same quantity of hematopoietic stem cells contacted or mobilized with G-CSF, chemotherapeutic agents, or any combinations thereof. In certain embodiments, upon engraftment in a subject the engrafted heHSCs demonstrate enhanced hematopoietic function relative to engraftment of the same quantity of hematopoietic stem cells contacted or mobilized with granulocyte colony-stimulating factor (G-CSF), chemotherapeutic agents, or any combinations thereof.

In some embodiments, the subject (e.g., a human subject) is conditioned for engraftment prior to administering the isolated heHSCs disclosed herein. In some embodiments, the subject (e.g., a human subject) exhibits poor mobilization in response to a conventional mobilization regimen, such as G-CSF.

Also disclosed herein are methods of treating a stem cell and/or progenitor cell disorder in a subject, the method comprising: (a) depleting an endogenous hematopoietic stem cell or progenitor cell population in a bone marrow compartment of the subject; and (b) administering an isolated, non-native heHSC to the subject, wherein the heHSC is Sca-1+, c-kit+ and Lin- (SKL), and where the administered heHSC engrafts in the bone marrow compartment of the subject. In certain embodiments, the heHSC is a SLAM SKL heHSC.

The heHSCs disclosed herein may be used for the treatment of stem cell and/or progenitor cell disorders or any diseases for which a stem cell transplant may be indicted. In some embodiments, such a stem cell or progenitor cell disorder is a malignant hematologic disease. For example, in some embodiments, the malignant hematologic disease may be selected from the group consisting of acute lymphoid leukemia, acute myeloid leukemia, chronic lymphoid leukemia, chronic myeloid leukemia, diffuse large B-cell non-Hodgkin's lymphoma, mantle cell lymphoma, lymphoblastic lymphoma, Burkitt's lymphoma, follicular B-cell non-Hodgkin's lymphoma, lymphocyte predominant nodular Hodgkin's lymphoma, multiple myeloma, and juvenile myelomonocytic leukemia. In some embodiments, the stem cell or progenitor cell disorder is a non-malignant disease. For example, in some embodiments the non-malignant disease may be selected from the group consisting of myelofibrosis, myelodysplastic syndrome, amyloidosis, severe aplastic anemia,

paroxysmal nocturnal hemoglobinuria, immune cytopenias, systemic sclerosis, rheumatoid arthritis, multiple sclerosis, systemic lupus erythematosus, Crohn's disorder, chronic inflammatory demyelinating polyradiculoneuropathy, human immunodeficiency virus (HIV), Fanconi anemia, sickle cell disorder, beta thalassemia major, Hurler's syndrome (MPS-IH), adrenoleukodystrophy, metachromatic leukodystrophy, familial erythrophagocytic lymphohistiocytosis and other histiocytic disorders, severe combined immunodeficiency (SCID), and Wiskott-Aldrich syndrome.

Also disclosed herein is an isolated, non-native heHSC, wherein the heHSC is Sca-1+, c-kit+ and Lin- (SKL); wherein the heHSC is prepared by mobilizing hematopoietic stem cells and/or progenitor cells from a bone marrow compartment of a subject to a peripheral compartment of the subject by administering at least one CXCR2 agonist and at least one CXCR4 antagonist, VLA-4 antagonist, $\alpha_9\beta_1$ antagonist, $\alpha_9\beta_1$ integrin/VLA-4 antagonist or combination thereof to the subject, and isolating the mobilized hematopoietic stem cells and/or progenitor cells from the peripheral compartment of the subject. In some embodiments, the isolated heHSC does not express CD48 or is CD48-. In some embodiments, the isolated heHSC expresses CD150 or is CD150+. In some embodiments, the isolated heHSC expresses CD93 or is CD93+. In certain aspects, the isolated heHSC does not express an immunophenotypic means of identifying human hematopoietic stem cells. In some embodiments the heHSC is a SLAM SKL heHSC. In some embodiments, the at least one CXCR2 agonist comprises GROβ or an analog or derivative thereof. In some embodiments the at least one CXCR2 agonist comprises GROβ-Δ4 or an analog or derivative thereof. In some embodiments, the at least one CXCR4 antagonist comprises plerixafor (AMD-3100) or an analog or derivative thereof. In still other embodiments, the at least one CXCR2 agonist is GROβ or an analog or derivative thereof and the at least one CXCR4 antagonist is plerixafor or an analog or derivative thereof. In some embodiments, the at least one CXCR4 antagonist comprises ALT1188, ALT1187, ALT1128, ALT1228, or TG-0054. In some embodiments, the $\alpha_9\beta_1$ integrin/VLA-4 antagonist is N-(benzenesulfonyl)-L-prolyl-L-O-(1-pyrrolidinylcarbonyl)tyrosine (BOP) or an analog or derivative thereof (e.g., R-BC154). In some embodiments, the VLA-4 antagonist is BIO 5192 or Natalizumab, or an analog or derivative thereof.

In some embodiments, the isolated heHSC comprises a unique transcriptome relative to hematopoietic stem cells contacted with granulocyte colony-stimulating factor (G-CSF), a chemotherapeutic agent, or any combination thereof. For example, in some aspects, the isolated heHSCs disclosed herein are characterized based on their differential expression of one or more of the genes selected from the group consisting of Fos, CD93, Fosb, Dusp1, Jun, Dusp6, Cdk1, Fignl1, Plk2, Rsad2, Sgk1, Sdc1, Serpine2, Spp1, Cdca8, Nrp1, Mcam, Pbk, Akr1cl and Cyp11a1, relative to, for example the expression of one or more genes in HSCs mobilized using G-CSF. In certain aspects, the isolated heHSC is non-quiescent. In some embodiments, the isolated heHSC is OPN+ (e.g., the isolated heHSC express osteopontin). In some embodiments, the isolated heHSC differentially expresses CD93 (e.g., the heHSC is CD93+). In some embodiments, the isolated heHSC does not express CD34 or is CD34-. In some embodiments, the isolated heHSC is CD93+ and CD34-.

In certain aspects of the present inventions, the isolated heHSCs disclosed herein are transformed to express a polynucleotide (e.g., an isolated heHSC may be transformed with an expression vector to express an exogenous polynucleotide). In some embodiments, the expression vector comprises a viral vector selected from the group consisting of a retrovirus, a herpes simplex, a lentivirus, an adenovirus, and an adeno-associated virus. In some embodiments, the isolated heHSC is transfected with an expression vector that comprises the polynucleotide. In some embodiments, the polynucleotide comprises an exogenous polynucleotide.

Also disclosed herein is the use of the isolated heHSC to effect or otherwise facilitate the delivery of an exogenous polynucleotide to a subject in need thereof. For example, the isolated heHSC disclosed herein may be transformed to express an exogenous polynucleotide and, upon engraftment in the subject's tissues (e.g., bone marrow tissues), the engrafted heHSC expresses the exogenous polynucleotide, thereby delivering the expression product of the exogenous polynucleotide (e.g., a protein or amino acid) to the subject.

In some embodiments, also disclosed herein are methods of transforming an isolated heHSC, wherein such methods comprise a step of contacting the heHSC with an expression vector under conditions sufficient for the vector to integrate into the heHSC genome. In yet other embodiments, the isolated heHSC of the present inventions are genetically modified to shut off expression of an endogenous polynucleotide.

In certain embodiments, the isolated heHSC is substantially pure.

The above discussed, and many other features and attendant advantages of the present inventions will become better understood by reference to the following detailed description of the invention.

BRIEF DESCRIPTION OF THE DRAWINGS

The patent or application file contains at least one drawing executed in color. Copies of this patent or patent application publication with color drawings will be provided by the Office upon request and payment of the necessary fee.

FIG. 1 illustrates that relative to G-CSF, the combination of the CXCR2 agonist GROβ and the CXCR4 antagonist plerixafor (AMD-3100) mobilized a highly engraftable hematopoietic stem cell (heHSC). As shown in **FIG. 1**, relative to G-CSF mobilized cells, an increase in donor chimerism was observed following engraftment with the heHSCs that were mobilized with GROβ and AMD-3100. In this demonstration, 195 CD150+, CD48-, SKL cells were transplanted per mouse.

FIG. 2 illustrates that relative to G-CSF, the combination of the CXCR2 agonist GROβ and the CXCR4 antagonist plerixafor (AMD-3100) mobilized a highly engraftable hematopoietic stem cell (heHSC), in a separate, independent demonstration from that shown in **FIG. 1**. As shown in **FIG. 2**, relative to G-CSF mobilized cells, an increase in donor chimerism was observed following engraftment of the heHSCs that were mobilized with GROβ and AMD-3100. In this demonstration, 50 CD150+CD48-SKL cells were transplanted per mouse.

FIG. 3 illustrates that certain genes showed higher expression in the heHSCs that were mobilized using the combination of the CXCR2 agonist GROβ and the CXCR4 antagonist plerixafor (AMD-3100), relative to the cells mobilized using G-CSF.

FIG. 4 illustrates a heat map showing the top twenty discriminating genes between hematopoietic stem cells (HSCs) that were mobilized using G-CSF mobilized (the two Tube B replicates), relative to the heHSCs (Tube C) mobilized using the combination of the CXCR2 agonist GROβ and the CXCR4 antagonist plerixafor (AMD-3100). Spp1 corresponds to osteopontin marker I.

DETAILED DESCRIPTION OF THE INVENTION

The present disclosure relates to a non-native, highly engraftable hematopoietic stem cell (heHSC) that is useful in connection with stem cell transplantation and the treatment of stem cell and/or progenitor cell disorders. Disclosed herein are isolated, non-native heHSCs, methods of their use and manufacture, and kits that comprise such heHSCs for use in connection with stem cell transplantation or the treatment of stem cell and/or progenitor cell disorders. The heHSCs disclosed herein are useful, for example, for transplantation and/or engraftment in a subject in connection with the treatment of any disease requiring stem cell transplantation.

The work described herein relates to the surprising discovery that heHSCs that are prepared by contacting or mobilizing with a combination of a CXCR2 agonist (e.g., GROβ) and a CXCR4 antagonist (e.g., plerixafor) exhibit superior engrafting ability, for example, superior engrafting ability relative to HSCs or peripheral blood stem cells (PBSCs) that are mobilized using traditional mobilizing regimens (e.g., granulocyte-colony stimulating factor (G-CSF) or chemotherapeutic agents). Accordingly, certain aspects of the present inventions relate to non-native, isolated heHSCs that are prepared by contacting or mobilizing hematopoietic stem cells and/or progenitor cells using a combination of one or more CXCR2 agonists (e.g., GROβ) and one or more CXCR4 antagonists (e.g., plerixafor). An exemplary method of mobilizing hematopoietic stem cells and/or progenitor cells in a subject comprises administering to the subject a combination of at least one CXCR2 agonist and at least one CXCR4 antagonist in amounts sufficient to mobilize such hematopoietic stem cells and/or progenitor cells into the subject's peripheral blood. The isolated heHSCs disclosed herein and the related methods of their preparation by mobilizing hematopoietic stem cells and/or progenitor cells have a variety of useful applications, for example for the treatment of stem cell and/or progenitor cell disorders.

In some embodiments, aspects of the present inventions relate to non-native, isolated heHSCs that are prepared by contacting or mobilizing hematopoietic stem cells and/or progenitor cells using a combination of at least one CXCR2 agonist (e.g., GROβ) and at least one CXCR4 antagonist, VLA-4 antagonist, $\alpha_9\beta_1$ antagonist, $\alpha_9\beta_1$ integrin/VLA-4 antagonist or combination thereof.

As used herein, the term "mobilizing" refers to the act of inducing the migration of hematopoietic stem cells and/or progenitor cells (e.g., heHSCs) from a

first location (e.g., the stem cell niche or bone marrow tissues of a subject) to a second location (e.g., the peripheral blood or an organ, such as the spleen, of a subject). For example, in certain embodiments, the non-native, isolated heHSCs disclosed herein may be prepared by mobilizing hematopoietic stem cells and/or progenitor cells from the stem cell niche of a human subject into the subject's peripheral tissue by administering to the subject a combination of one or more CXCR2 agonists (e.g., GROβ) and one or more CXCR4 antagonists (e.g., plerixafor), following which the mobilized heHSCs may be harvested or isolated (e.g., by apheresis), as further described herein. With regard to the heHSCs disclosed herein, the term "isolated" means that the heHSC is substantially free of other cell types or cellular materials with which may be present when the heHSC is isolated from a treated subject. In some embodiments, an isolated heHSC or an isolated population of heHSCs is a substantially pure population of heHSCs, for example, as compared to the heterogeneous population from which the cells were isolated or enriched from (e.g., substantially pure as compared to the population of mobilized cells). In some embodiments, the heHSCs are enriched from a biological sample that is obtained from a subject following treatment with a combination of a CXCR2 agonist (e.g., GROβ) and a CXCR4 antagonist (e.g., plerixafor). In one embodiment, the mobilized and harvested heHSCs disclosed herein may be used in connection with an allogeneic or an autologous transplant. The terms "enriching" or "enriched" are used interchangeably herein and mean that the yield (fraction) of heHSCs is increased by at least about 10%, 15%, 20%, 25%, 30%, 40%, 50%, 60%, 70%, 80%, 90%, 95%, 99% or more over the fraction of mobilized cells.

As used herein with respect to a population of heHSCs, term "substantially pure", refers to a population of heHSCs that is at least about 75%, preferably at least about 85%, more preferably at least about 90%, and most preferably at least about 95% pure, and still more preferably at least about 99% pure with respect to the cells making up a total population of mobilized cells. Recast, the terms "substantially pure" or "essentially purified", with regard to a population of heHSCs, refers to a population of cells that contain fewer than about 20%, more preferably fewer than about 15%, 12%, 10%, 8%, 7%, most preferably fewer than about 5%, 4%, 3%, 2%, 1%, or less than 1%, of cells that are not heHSCs as defined by the terms herein. In some embodiments, the present invention encompasses methods to expand a

population of heHSCs, wherein the expanded population of heHSCs is a substantially pure population.

While certain embodiments disclosed herein contemplate the *in vivo* preparation of the heHSCs by mobilizing hematopoietic stem cells and/or progenitor cells, it should be understood that the present inventions are not limited to such *in vivo* methods. Rather, also contemplated are *in vitro* methods of preparing heHSCs, for example by contacting hematopoietic stem cells and/or progenitor cells with a combination of a CXCR2 agonist (e.g., GROβ) and a CXCR4 antagonist (e.g., plerixafor) , VLA-4 antagonist, $\alpha_9\beta_1$ antagonist, $\alpha_9\beta_1$ integrin/VLA-4 antagonist or combination thereof. As used herein, the term "contacting" means bringing two or more moieties together, or within close proximity of one another such that the moieties may interact with each other. For example, in one embodiment of the present invention, a hematopoietic stem cell and/or a progenitor cell is contacted with a CXCR2 agonist and/or a CXCR4 antagonist to produce and/or mobilize a heHSC.

Contemplated CXCR2 agonists include any compounds or agents that are capable of activating the CXCR2 receptor (e.g., the human CXCR2 receptor). Exemplary CXCR2 agonists include chemokines, cytokines, biologic agents, antibodies and small organic molecules. For example, contemplated chemokines acting via the CXCR2 receptor include without limitation GROβ, GROα, GROγ, GCP-2 (granulocyte chemo-attractant protein 2), IL-8, NAP-2 (neutrophil activating peptide 2), ENA-78 (epithelial-cell derived neutrophil activating protein 78), and modified forms of any of the foregoing. In some embodiments, the CXCR2 agonist is selected from the group of compounds or agents consisting of small organic or inorganic molecules; oligosaccharides; polysaccharides; biological macromolecules selected from the group consisting of peptides, proteins, peptide analogs and derivatives; peptidomimetics; nucleic acids selected from the group consisting of siRNAs, shRNAs, antisense RNAs, ribozymes, and aptamers; and any combination thereof.

In certain aspects, the CXCR2 agonist comprises GROβ.

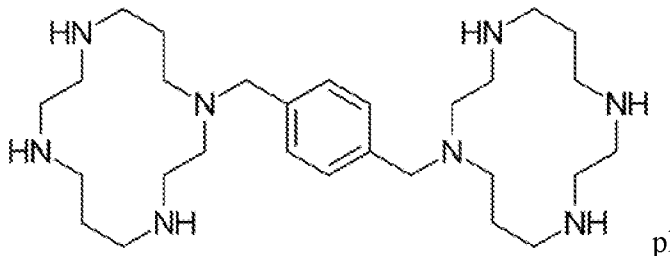
In some embodiments, the at least one CXCR2 agonist is the chemokine GROβ or an analog or derivative thereof. An exemplary form of GROβ is the human GROβ polypeptide (GenBank Accession: AAP13104; SEQ ID NO: 1). In certain aspects, an exemplary form of GROβ is the human GROβ (UniProt ID No. P19875; SEQ ID NO: 2).

An exemplary GROβ analog or derivative is the desamino GROβ protein (also known as MIP-2alpha), which comprises the amino acid sequence of mature gro-S protein truncated at its N terminus between amino acid positions 2 and 8, as described in PCT International Application Publication WO/1994/029341, the contents of which are incorporated herein by reference in their entirety. Another GROβ analog or derivative is the dimeric modified GROβ protein described in U.S. Patent No. 6,413,510, the contents of which are incorporated herein by reference in their entirety. Still another exemplary GROβ analog or derivative is SB-251353, a GROβ analog involved in directing movement of stem cells and other leukocytes, as described by Bensinger, *et al.*, *Bone Marrow Transplantation* (2009), 43, 181-195, the entire contents of which are incorporated by reference herein.

In some embodiments of the present inventions, the at least one CXCR2 agonist is or comprises GROβ-Δ4 (e.g., SEQ ID NO: 3) or an analog or derivative thereof. In some embodiments, the at least one CXCR2 agonist is selected from the group consisting of GROβ or an analog or derivative thereof and GROβ-Δ4 or an analog or derivative thereof.

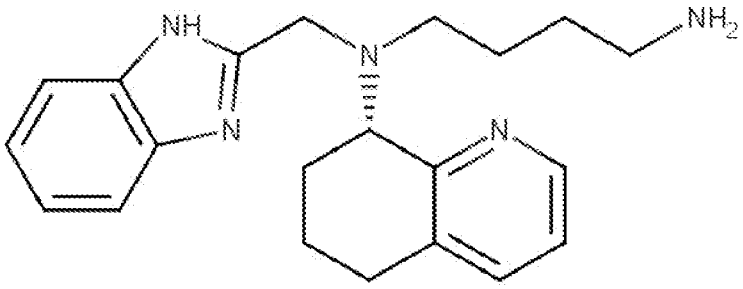
Contemplated CXCR4 antagonists include any compounds or agents that are capable of blocking the CXCR4 receptor or preventing its activation. For example, contemplated are compounds and agents that block or otherwise interfere with the binding or interaction of the CXCR4 receptor with such receptor's ligand. Also contemplated are compounds or agents that block the downstream effects of the activated CXCR4 receptor. In some embodiments, the CXCR4 antagonist is selected from the group of compounds or agents consisting of small organic or inorganic molecules; oligosaccharides; polysaccharides; biological macromolecules selected from the group consisting of peptides, proteins, peptide analogs and derivatives; peptidomimetics; nucleic acids selected from the group consisting of siRNAs, shRNAs, antisense RNAs, ribozymes, and aptamers; and any combination thereof.

In some embodiments of the present inventions, the at least one CXCR4 antagonist is plerixafor (formerly known as AMD-3100), the structure of which is depicted below (I), or an analog or derivative thereof.

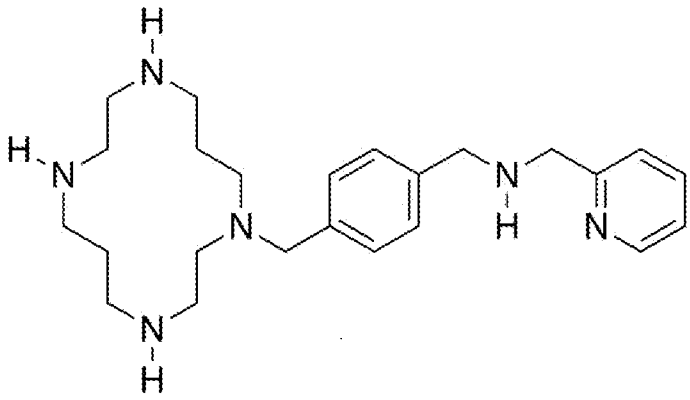


plerixafor (I)

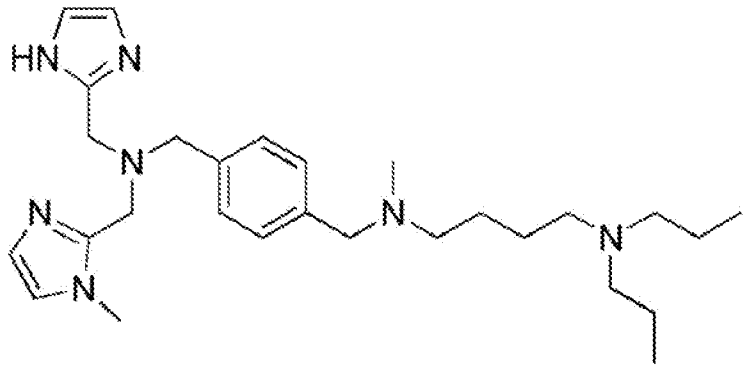
In some embodiments, the at least one CXCR4 antagonist is MOZOBIL® or an analog or derivative thereof. Exemplary analogs of plerixafor include, but are not limited to, AMD11070, AMD3465, KRH-3955, T-140, and 4F-benzoyl-TN14003, as depicted below (II-VI, respectively) and described by De Clercq, *Pharmacol Ther.* (2010) 128(3):509-18, the contents of which are incorporated by reference herein in their entirety.



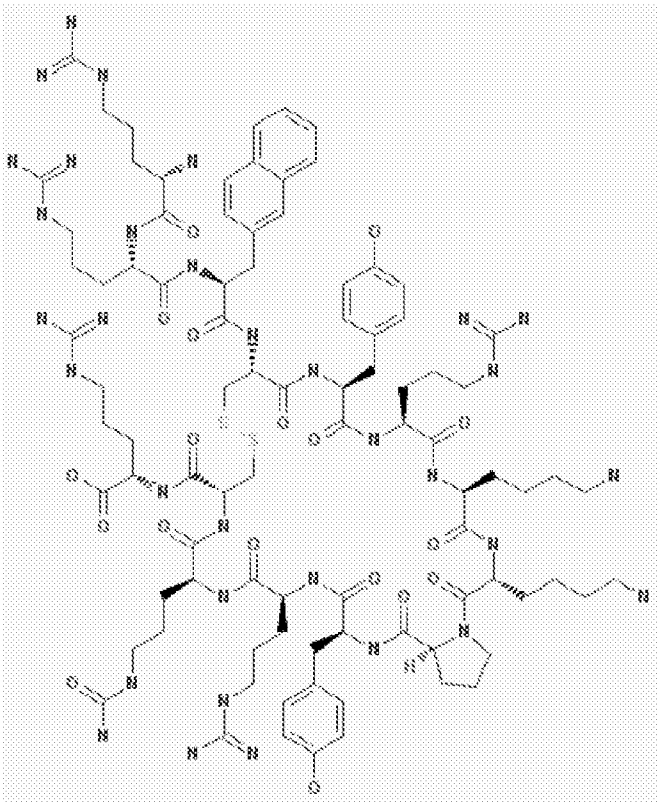
AMD11070 (II)



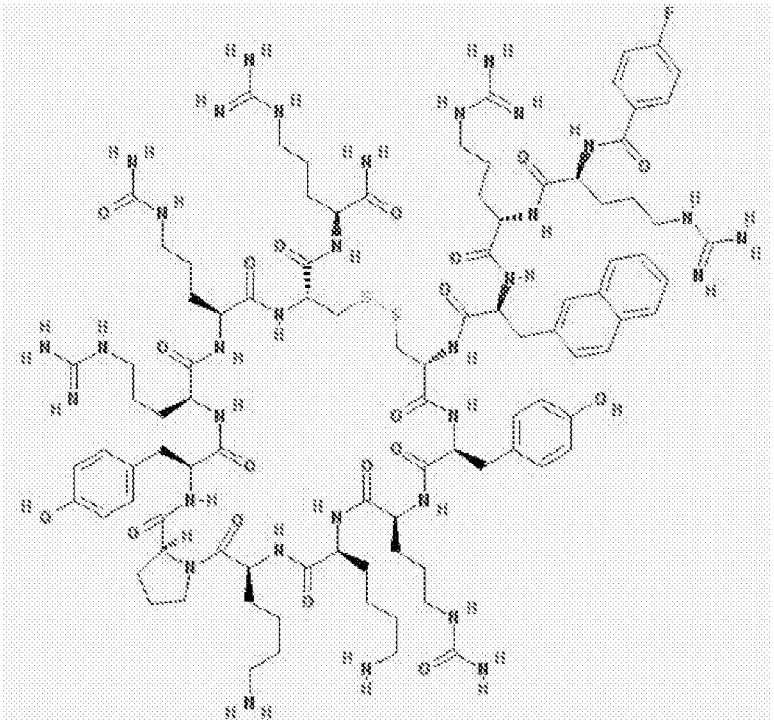
AMD3465 (III)



KRH-3955 (IV)



T-140 (V)



4F-benzoyl-TN14003

(VI)

In some embodiments, the at least one CXCR4 antagonist comprises ALT1188, ALT1187, ALT1128, ALT1228, or TG-0054 or an analog or derivative thereof. In some embodiments, the CXCR4 antagonist comprises at least one inhibitor described in Debnath B, et al., "Small Molecule Inhibitors of CXCR4,"*Theranostics* 2013; 3(1):47-75, incorporated herein by reference.

In some embodiments, non-native, isolated heHSCs are prepared by contacting or mobilizing hematopoietic stem cells and/or progenitor cells using a combination of at least one CXCR2 agonist (e.g., GROβ) and at least one $\alpha_9\beta_1$ integrin/VLA-4 antagonist. In some embodiments, the $\alpha_9\beta_1$ integrin/VLA-4 antagonist is N-(benzenesulfonyl)-L-prolyl-L-O-(1-pyrrolidinylcarbonyl)tyrosine (BOP) or an analog or derivative thereof (e.g., R-BC154). In some embodiments, non-native, isolated heHSCs are prepared by contacting or mobilizing hematopoietic stem cells and/or progenitor cells using a combination of at least one CXCR2 agonist (e.g., GROβ) and at least one VLA-4 antagonist. In some embodiments, the VLA-4 antagonist is BIO 5192, Natalizumab, or an analog or derivative thereof.

In some embodiments, the at least one CXCR2 agonist is or comprises GROβ or an analog or derivative thereof, and the at least one CXCR4 antagonist is or comprises plerixafor (AMD-3100) or an analog or derivative thereof. In some

embodiments, the at least one CXCR2 agonist is selected from the group consisting of GROβ-Δ4 or an analog or derivative thereof and the at least one CXCR4 antagonist is selected from the group consisting of plerixafor or an analog or derivative thereof.

The combination of at least one CXCR2 agonist and at least one CXCR4 antagonist, VLA-4 antagonist, $\alpha_9\beta_1$ antagonist, $\alpha_9\beta_1$ integrin/VLA-4 antagonist or combination thereof may be administered directly to a subject in combination or, in certain aspects, may be administered independently. For example, the at least one CXCR2 agonist and the at least one CXCR4 antagonist, VLA-4 antagonist, $\alpha_9\beta_1$ antagonist, $\alpha_9\beta_1$ integrin/VLA-4 antagonist or combination thereof can be, but need not be, administered (e.g., administered intravenously) to a subject at the same time. In one embodiment, the at least one CXCR2 agonist is administered in one or more doses, followed by the administration of the at least one CXCR4 antagonist in one or more doses.

In addition to inducing a faster mobilization (e.g., about two-fold, three-fold ,four-fold, five-fold, six-fold, seven-fold, eight-fold, nine-fold, ten-fold, twelve-fold, fifteen-fold, twenty-fold or more faster relative to traditional mobilization regimens that are performed using, for example, G-CSF or, alternatively, within one hour, within 45 minutes, within 30 minutes, within 15 minutes within 10 minutes, within 5 minutes or faster) and producing a greater quantity of mobilized stem cells (e.g., heHSCs), the combination of at least one CXCR2 agonist (e.g., GROB-Δ4 or an analog or derivative thereof) and at least one CXCR4 antagonist (e.g., plerixafor or an analog or derivative thereof) , VLA-4 antagonist, $\alpha_9\beta_1$ antagonist, $\alpha_9\beta_1$ integrin/VLA-4 antagonist or combination thereof mobilizes a non-native stem cell that is characterized by its enhanced engrafting ability and its unique genetic signatures, as illustrated in **FIG. 3**. As used herein to describe the stem cells that are mobilized using the combination of at least one CXCR2 agonist and at least one CXCR4 antagonist, VLA-4 antagonist, $\alpha_9\beta_1$ antagonist, $\alpha_9\beta_1$ integrin/VLA-4 antagonist or combination thereof the term “unique” refers to one or more distinguishing characteristics of such mobilized stem cells relative to those cells that are mobilized using traditional mobilization regiments using, for example, G-CSF alone. For example, stem cells that are mobilized using the combination of at least one CXCR2 agonist and at least one CXCR4 antagonist, VLA-4 antagonist, $\alpha_9\beta_1$ antagonist, $\alpha_9\beta_1$ integrin/VLA-4 antagonist or combination thereof may be characterized by their

expression of one or more unique markers or antigens (e.g., CD93+) or by their unique transcriptome.

One such marker, CD93, is expressed in hematopoietic cells at the apex of hematopoiesis. These early hematopoietic CD93 expressing cells in humans may also be negative for CD34. heHSC populations generated upon treatment with combination of at least one CXCR2 agonist and at least one CXCR4 antagonist which also exhibit CD93 expression are indicative of early lineage stem cells and may serve to support improved transplantation and/or engraftment.

Similarly, in certain embodiments, stem cells that are mobilized using the combination of at least one CXCR2 agonist and at least one CXCR4 antagonist, VLA-4 antagonist, $\alpha_9\beta_1$ antagonist, $\alpha_9\beta_1$ integrin/VLA-4 antagonist or combination thereof may be characterized by improved function. In particular, the engrafting ability of the heHSCs mobilized using the combination of at least one CXCR2 agonist and at least one CXCR4 antagonist, VLA-4 antagonist, $\alpha_9\beta_1$ antagonist, $\alpha_9\beta_1$ integrin/VLA-4 antagonist or combination thereof is surprisingly increased or enhanced relative to the engrafting ability of stem cells or PBSCs that are mobilized following the contacting of hematopoietic stem cells and/or progenitor cells with traditional mobilizing agents, such as G-CSF.

In certain aspects, the heHSCs are characterized by their increased or enhanced engrafting ability relative to stem cells or PBSCs that are mobilized following the contacting of hematopoietic stem cells and/or progenitor cells with one or more chemotherapeutic agents (e.g., chemotherapeutic mobilization agents). Exemplary chemotherapeutic agents include paclitaxel, etoposide, vinblastine, doxorubicin, bleomycin, methotrexate, 5-fluorouracil, 6-thioguanine, cytarabine, cyclophosphamide, cisplatinum and combinations thereof. In certain aspects, such chemotherapeutic agents mobilize hematopoietic stem cells and/or progenitor cells. For example, such a chemotherapeutic mobilization agent may comprise EPO. In some embodiments, such a chemotherapeutic mobilization agent is or comprises stem cell factor. In some embodiments, such a chemotherapeutic mobilization agent is or comprises TPO. In still other embodiments, such a chemotherapeutic mobilization agent is or comprises parathyroid hormone.

As used herein, the term “hematopoietic stem cells” or “HSC” refers to stem cells that can differentiate into the hematopoietic lineage and give rise to all blood cell types such as white blood cells and red blood cells, including myeloid (e.g.,

monocytes and macrophages, neutrophils, basophils, eosinophils, erythrocytes, megakaryocytes/platelets, dendritic cells), and lymphoid lineages (e.g., T-cells, B-cells, NK-cells). Stem cells are defined by their ability to form multiple cell types (multipotency) and their ability to self-renew. Hematopoietic stem cells can be identified, for example by cell surface markers such as CD34-, CD133+, CD48-, CD150+, CD244-, cKit+, Sca1+, and lack of lineage markers (negative for B220, CD3, CD4, CD8, Mac1, Gr1, and Ter119, among others).

As used herein, the term "hematopoietic progenitor cells" encompasses pluripotent cells which are committed to the hematopoietic cell lineage, generally do not self-renew, and are capable of differentiating into several cell types of the hematopoietic system, such as granulocytes, monocytes, erythrocytes, megakaryocytes, B-cells and T-cells, including, but not limited to, short term hematopoietic stem cells (ST-HSCs), multi-potent progenitor cells (MPPs), common myeloid progenitor cells (CMPs), granulocyte-monocyte progenitor cells (GMPs), megakaryocyte-erythrocyte progenitor cells (MEPs), and committed lymphoid progenitor cells (CLPs). The presence of hematopoietic progenitor cells can be determined functionally as colony forming unit cells (CFU-Cs) in complete methylcellulose assays, or phenotypically through the detection of cell surface markers (e.g., CD45-, CD34+, Ter119-, CD16/32, CD127, cKit, Sca1) using assays known to those of skill in the art.

In some embodiments, the mobilized hematopoietic stem cells and/or progenitor cells comprise SKL cells. In certain aspects, the mobilized hematopoietic stem cells and/or progenitor cells comprise SKL SLAM cells. In certain aspects, the mobilized hematopoietic stem cells and/or progenitor cells exhibit a SLAM (Signaling lymphocyte activation molecule) expression pattern which is CD150+, CD48-. A SLAM expression pattern (SLAM code) is an expression pattern of specific markers (SLAM markers) that are used to identify subpopulations of hematopoietic stem cells and multipotent progenitors. See Oguro, et al. (2013) "SLAM family markers resolve functionally distinct subpopulations of hematopoietic stem cells and multipotent progenitors," *Cell Stem Cell*, 13(1), 102–116, and references cited therein.

In some embodiments, the mobilized hematopoietic stem cells and/or progenitor cells comprise CD34-, CD133+ cells. In some embodiments, the mobilized hematopoietic stem cells and/or progenitor cells comprise common myeloid progenitor cells. In some embodiments, the mobilized hematopoietic stem cells

and/or progenitor cells comprise granulocyte/monocyte progenitor cells. In some embodiments, the mobilized hematopoietic stem cells and/or progenitor cells comprise megakaryocyte/erythroid progenitor cells. In some embodiments, the mobilized hematopoietic stem cells and/or progenitor cells comprise committed lymphoid progenitor cells. In some embodiments, the mobilized hematopoietic stem cells and/or progenitor cells comprise a combination of common myeloid progenitor cells, granulocyte/monocyte progenitor cells, megakaryocyte/erythroid progenitor cells. In some embodiments, the mobilized hematopoietic stem cells and/or progenitor cells comprise CD150-, CD48-, CD244+ cells. In some embodiments, the mobilized hematopoietic stem cells and/or progenitor cells comprise CD150-, CD48+, CD244+ cells. In some embodiments, the mobilized hematopoietic stem cells and/or progenitor cells comprise Sca-1-, c-kit+, Lin-, CD34+, CD16/32^{mid} cells. In some embodiments, the mobilized hematopoietic stem cells and/or progenitor cells comprise Sca-1-, c-kit+, Lin-, CD34-, CD16/32^{low} cells. In some embodiments, the isolated heHSC does not express an immunophenotypic means of identifying human hematopoietic stem cells.

In some embodiments, the isolated heHSCs disclosed herein comprise a unique transcriptome relative to hematopoietic stem cells contacted with G-CSF, a chemotherapeutic agent, or a combination thereof. For example, in certain aspects, the isolated heHSCs disclosed herein are characterized based on their differential expression of one or more of the genes identified in **FIG. 4**, relative to, for example the expression of one or more genes in hematopoietic stem cells (HSCs) that were mobilized using G-CSF. In some aspects, the isolated heHSCs disclosed herein are characterized based on their differential expression of one or more of the genes selected from the group consisting of Fos (e.g., SEQ ID NO: 4), CD93 (e.g., SEQ ID NO: 5), Fosb (e.g., SEQ ID NO: 6), Dusp1 (e.g., SEQ ID NO: 7), Jun (e.g., SEQ ID NO: 8), Dusp6 (e.g., SEQ ID NO: 9), Cdk1 (e.g., SEQ ID NO: 10), Fignl1 (e.g., SEQ ID NO: 11), Plk2 (e.g., SEQ ID NO: 12), Rsad2 (e.g., SEQ ID NO: 13), Sgk1 (e.g., SEQ ID NO: 14), Sdc1 (e.g., SEQ ID NO: 15), Serpine2 (e.g., SEQ ID NO: 16), Spp1 (e.g., SEQ ID NO: 17), Cdca8 (e.g., SEQ ID NO: 18), Nrp1 (e.g., SEQ ID NO: 19), Mcam (e.g., SEQ ID NO: 20), Pbk (e.g., SEQ ID NO: 21), Akr1cl (e.g., SEQ ID NO: 22) and Cyp11a1 (e.g., SEQ ID NO: 23), relative to, for example the expression of one or more genes by hematopoietic stem cells (HSCs) that were mobilized using G-CSF. In some embodiments, the isolated heHSC is OPN+ (e.g., the isolated heHSC

express osteopontin). In some embodiments, the isolated heHSC differentially expresses CD93 (e.g., the heHSC is CD93+). In certain aspects, the isolated heHSC disclosed herein is non-quiescent. In some embodiments, the heHSC is CD34-.

The heHSCs disclosed herein are prepared by mobilizing or contacting hematopoietic stem cells and/or progenitor cells with a combination of a CXCR2 agonist and a CXCR4 antagonist, VLA-4 antagonist, $\alpha_9\beta_1$ antagonist, $\alpha_9\beta_1$ integrin/VLA-4 antagonist or combination thereof. As used herein, the terms "highly engraftable hematopoietic stem cell" and "heHSC" refer to the isolated population or fraction of stem cells or PBSCs that are, for example, mobilized from the stem cell niche or bone marrow of a subject into the peripheral blood or organs of the subject following the administration of one or more CXCR2 agonists (e.g., GROβ or an analog or derivative thereof) and one or more CXCR4 antagonists (e.g., plerixafor or an analog or derivative thereof), VLA-4 antagonist, $\alpha_9\beta_1$ antagonist, $\alpha_9\beta_1$ integrin/VLA-4 antagonist or combination thereof. In certain aspects, such heHSCs are substantially pure.

In some embodiments, the isolated heHSCs disclosed herein are immunophenotypically unique relative to cells or stem cells mobilized using traditional mobilization regimens (e.g., stem cells mobilized using G-CSF). For example, as illustrated in **FIG. 3**, certain genes showed higher expression in the heHSCs that were mobilized using the combination of the CXCR2 agonist GROβ and the CXCR4 antagonist plerixafor (AMD-3100), relative to the cells mobilized using G-CSF. In certain aspects, the heHSCs disclosed herein express osteopontin or are osteopontin positive (OPN+). In some embodiments, the isolated heHSC differentially expresses CD93 (e.g., the heHSC is CD93+). In some embodiments, the isolated heHSC does not express CD34 or is CD34-. In some embodiments, the isolated heHSC is CD93+ and CD34-. In some embodiments, the isolated heHSC differentially expresses one or more genes shown in FIG. 3 or FIG. 4 as compared to an isolated HSC mobilized using traditional mobilization regimens (e.g., stem cells mobilized using G-CSF).

In some embodiments, a population of cells (i.e., a cell population comprising or consisting of heHSC) isolated by the methods disclosed herein (e.g., by contacting cells with a combination of at least one CXCR2 agonist (e.g., GROβ) and at least one CXCR4 antagonist, VLA-4 antagonist, $\alpha_9\beta_1$ antagonist, $\alpha_9\beta_1$ integrin/VLA-4 antagonist or combination thereof) has an increased or decreased proportion of cells

exhibiting one or more cell surface markers or one or more expression profiles disclosed herein as compared to cells isolated by conventional methods. The one or more cell surface markers or cell expression profiles may be increased or decreased by about 10%, 15%, 20%, 25%, 30%, 35%, 40%, 45%, 50%, 55%, 60%, 65%, 70%, 75%, 80%, 85%, 90%, 95%, or more. In some embodiments, the one or more cell surface marker is CD93. In some embodiments, after performing the methods disclosed herein, an obtained cell population may be assayed to determine whether the prevalence of one or more cell surface markers or cell expression profiles has increased or decreased to determine whether the obtained cell population is suitable as heHSC for transplantation. In some embodiments, the obtained cell population is assayed to determine if at least about 10%, 15%, 20%, 25%, 30%, 35%, 40%, 45%, 50%, 55%, 60%, 65%, 70%, 75%, 80%, 85%, 90%, 95%, or more of the cells are CD93+. Any suitable assay (e.g., FACS analysis) may be used for the determination.

In some embodiments, the obtained cell population may be further enriched for a desired cell surface marker or gene expression pattern to obtain a desired heHSC population for transplantation. In some embodiments, the obtained cell population may be enriched for CD93+ cells or CD93+ and CD34- cells. In some embodiments, the cell population may be enriched by about 1.5-fold, 2-fold, 2.5-fold, 3-fold, 4-fold, 5-fold or more. In some embodiments, the cell population may be enriched to contain at least 40%, 45%, 50%, 55%, 60%, 65%, 70%, 75%, 80%, 85%, 90%, 95%, or more of cells containing a desired cell surface marker or cell expression pattern (e.g., enriched for CD93+ cells or CD93+/CD34- cells). Any suitable procedure (e.g., FACS sorting) may be used for the enrichment.In some embodiments, the isolated heHSCs disclosed herein are not immunophenotypically unique relative to cells or stem cells mobilized using traditional mobilization regimens (e.g., stem cells mobilized using G-CSF). Such isolated heHSC may be functionally unique relative to cells or stem cells mobilized using traditional mobilization regimens.

Upon mobilization, which in certain instances may occur within 15-30 minutes of having administered a CXCR2 agonist and a CXCR4 antagonist, VLA-4 antagonist, $\alpha_9\beta_1$ antagonist, $\alpha_9\beta_1$ integrin/VLA-4 antagonist or combination thereof, the mobilized heHSCs can be harvested or isolated (e.g., via apheresis) as disclosed herein and are useful for subsequent transplantation in a subject in need thereof. For example, such mobilized heHSCs may be harvested or isolated for autologous transplantation into a subject or for allogeneic transplantation into a recipient subject.

In some instances, the harvesting or isolation of the mobilized hematopoietic stem cells and/or progenitor cells can be initiated within as little as 15 minutes following the administration of the at least one CXCR2 agonist and the at least one CXCR4 antagonist, VLA-4 antagonist, $\alpha_9\beta_1$ antagonist, $\alpha_9\beta_1$ integrin/VLA-4 antagonist or combination thereof. In some embodiments, the harvesting or isolating procedure can begin in as little as 10 minutes, 12 minutes, 15 minutes, 18 minutes, 20 minutes, 22 minutes, 25 minutes, 30 minutes, 35 minutes, 40 minutes, 47 minutes, 52 minutes, 58 minutes, or an hour after administration of the at least one CXCR2 agonist and the at least one CXCR4 antagonist, VLA-4 antagonist, $\alpha_9\beta_1$ antagonist, $\alpha_9\beta_1$ integrin/VLA-4 antagonist or combination thereof.

The disclosure contemplates the use of any suitable method of harvesting and/or collecting mobilized hematopoietic stem cells and/or progenitor cells to prepare the isolated heHSCs disclosed herein. In some embodiments harvesting the mobilized hematopoietic stem cells and/or progenitor cells comprises apheresis. In some embodiments, the combination of at least one CXCR2 agonist (e.g., GROβ or GROβ-Δ4) and at least one CXCR4 antagonist (e.g., plerixafor), VLA-4 antagonist, $\alpha_9\beta_1$ antagonist, $\alpha_9\beta_1$ integrin/VLA-4 antagonist or combination thereof rapidly and efficiently mobilizes mobilized hematopoietic stem cells and/or progenitor cells, and exhibits increased efficiencies compared to traditional mobilizing regimens. As a result, in some embodiments an apheresis procedure may be performed on the same day that the at least one CXCR2 agonist and the at least one CXCR4 antagonist, VLA-4 antagonist, $\alpha_9\beta_1$ antagonist, $\alpha_9\beta_1$ integrin/VLA-4 antagonist or combination thereof are administered to the subject. In other words, harvesting mobilized heHSCs from a subject (e.g., a donor) via apheresis can be performed on the same day that the mobilization agents are administered to the subject (e.g., during a single visit to a healthcare facility). In some embodiments, an apheresis procedure may be performed on the same day that at least one CXCR2 agonist (e.g., GROβ or GROβ-Δ4) and at least one CXCR4 antagonist, VLA-4 antagonist, $\alpha_9\beta_1$ antagonist, $\alpha_9\beta_1$ integrin/VLA-4 antagonist or combination thereof is administered to the subject.

In some embodiments, administration of the at least one CXCR2 agonist (e.g., GROβ or GROβ-Δ4) and the at least one CXCR4 antagonist, VLA-4 antagonist, $\alpha_9\beta_1$ antagonist, $\alpha_9\beta_1$ integrin/VLA-4 antagonist or combination thereof mobilizes an amount of hematopoietic stem cells and/or progenitor cells in the subject to harvest a heHSC cell dose of between about 1 x 10^6/kg body weight and 10 x 10^6/kg body

weight in a single apheresis session. In some embodiments, a single session of apheresis collects enough heHSCs for a cell dose of between about 1 x 10^6/kg and 10 x 10^6/kg of the recipient's body weight. In some embodiments, administration of the at least one CXCR2 agonist (e.g., GROβ or GROβ-Δ4) and the at least one CXCR4 antagonist, VLA-4 antagonist, $\alpha_9\beta_1$ antagonist, $\alpha_9\beta_1$ integrin/VLA-4 antagonist or combination thereof mobilizes an amount of hematopoietic stem cells and/or progenitor cells in the subject to harvest enough heHSCs for a cell dose of between about 2 x 10^6/kg body weight and 8 x 10^6/kg body weight in a single apheresis session. In some embodiments, a single session of apheresis collects enough heHSCs for a cell dose of between about 2 x 10^6/kg and 8 x 10^6/kg of the recipient's body weight. In some embodiments, administration of the at least one CXCR2 agonist (e.g., GROβ or GROβ-Δ4) and the at least one CXCR4 antagonist, VLA-4 antagonist, $\alpha_9\beta_1$ antagonist, $\alpha_9\beta_1$ integrin/VLA-4 antagonist or combination thereof mobilizes an amount of hematopoietic stem cells and/or progenitor cells in the subject to harvest a heHSC cell dose of between about 3 x 10^6/kg body weight and 6 x 10^6/kg body weight in a single apheresis session. In some embodiments, a single session of apheresis collects enough heHSCs for a cell dose of between about 1 x 10^6/kg and 10 x 10^6/kg of the recipient's body weight.

Following harvesting, the isolated heHSCs disclosed herein may be administered to or transplanted in the donor subject (e.g., an autologous transplant), or alternatively may be donated to a different subject in need thereof (e.g., allogeneic transplant). In certain aspects, the administration or transplant of the isolated heHsCs occurs following or in combination with radiation or chemotherapy.

The mobilized heHSC disclosed herein are characterized by their increased engrafting ability (e.g., a two-fold increased engrafting ability), which makes such heHSCs suitable for use in connection with gene therapy. For example, where genetic manipulation of cells is associated with a corresponding reduction in their engrafting ability and, due to the improved or enhanced engrafting ability of the heHSCs disclosed herein, such heHSCs are rendered more tolerant to genetic manipulation, following which only limited reductions in their engrafting ability may be observed.

Gene therapy can be used to transform a heHSC, modify a heHSC to replace a gene product, to treat disease, or to improve engraftment of the heHSC following implantation into a subject. For example, in certain embodiments, the heHSCs disclosed herein may be transformed with an expression vector (e.g., a viral vector

selected from the group consisting of a retrovirus, a herpes simplex, a lentivirus, an adenovirus, and an adeno-associated virus). In some embodiments, the isolated heHSC is transformed or transfected with an expression vector that comprises a polynucleotide. In some embodiments, the polynucleotide comprises an exogenous polynucleotide. In some embodiments, the expression product of a polynucleotide is a protein that is not endogenously expressed or is under expressed by the subject's cells.

As used herein, the term "transform" means to introduce into a heHSC an exogenous polynucleotide (e.g., a nucleic acid or nucleic acid analog) which replicates within that heHSC, that encodes a gene product (e.g., an amino acid, polypeptide sequence, protein or enzyme) which is expressed in that heHSC, and/or that is integrated into the genome of that heHSC so as to affect the expression of a genetic locus within the genome. The term "transform" is used to embrace all of the various methods of introducing such polynucleotides (e.g., nucleic acids or nucleic acid analogs), including, but not limited to the methods referred to in the art as transformation, transfection, transduction, or gene transfer, and including techniques such as microinjection, DEAE-dextran-mediated endocytosis, calcium phosphate coprecipitation, electroporation, liposome-mediated transfection, ballistic injection, viral-mediated transfection, and the like.

In some embodiments, also disclosed herein are methods of transforming an isolated heHSC, wherein such methods comprise a step of contacting the heHSC with an expression vector under conditions sufficient for the vector to integrate into the heHSC genome. In yet other embodiments, the isolated heHSC of the present inventions are genetically modified to shut off expression of an endogenous polynucleotide.

As used herein, the term "vector" means any genetic construct, such as for example, a plasmid, phage, transposon, cosmid, chromosome, virus and/or virion, which is capable transferring nucleic acids between cells. Vectors may be capable of one or more of replication, expression, and insertion or integration, but need not possess each of these capabilities. Thus, the term includes cloning, expression, homologous recombination, and knock-out vectors.

In certain aspects, prior to engraftment, a mobilized hematopoietic stem cell and/or progenitor cell can be manipulated to express one or more desired polynucleotides or gene products (e.g., one or more of a polypeptide, amino acid

sequence protein and/or enzyme). Gene therapy can be used to either modify a mobilized hematopoietic stem cell and/or progenitor cell to replace a polynucleotide or gene product or to add or knockdown a gene product. In some embodiments the genetic engineering is done, for example, to treat disease, following which the genetically engineered heHSC would be transplanted and engraft into a subject. For example, a mobilized heHSC may be manipulated to express one or more polynucleotides or genes that would enhance the engrafting ability of the transplanted heHSC.

Techniques for transfecting cells are known in the art. In an exemplary embodiment, gene therapy can be used to insert a polynucleotide (e.g., DNA) into a mobilized hematopoietic stem cell from a patient or subject with a genetic defect to correct such genetic defect, following which the corrected or genetically engineered mobilized hematopoietic stem cell may be transplanted into a subject.

In some other embodiments, the heHSCs disclosed herein can be used as carriers for gene therapy.

In some embodiments, the isolated heHSCs and the related methods of mobilizing such heHSCs are useful for treating subjects that have demonstrated poor mobilization in response to a conventional hematopoietic stem cell and/or progenitor cell mobilization regimen (e.g., subjects that have failed to mobilize a sufficient numbers of stem cells following a mobilization regimen comprising or consisting of G-CSF). For example, such heHSCs and the related methods disclosed herein may be used to enhance hematopoietic stem cell and/or progenitor cell mobilization in individuals exhibiting stem cell and/or progenitor cell mobilopathy. Accordingly, in certain embodiments, any of the methods and compositions disclosed herein may be suitable for use in mobilizing hematopoietic stem cell and/or progenitor stem cells in a subject having an underlying disease that impairs egress of such hematopoietic stem cells and/or progenitor stem cells from bone marrow and into the peripheral circulation, including, for example, subjects that have or are at risk of developing diabetic stem cell mobilopathy. In certain aspects, subjects that have failed to mobilize a sufficient number of hematopoietic stem cells and/or progenitor cells in response to a mobilization regimen comprising G-CSF (e.g., subjects that have failed to mobilize a sufficient number of stem cells about five days after receiving a G-CSF mobilization regimen) are candidates for mobilization using the methods and compositions disclosed herein. In certain embodiments, the isolated heHSCs may be

administered to a subject exhibiting mobilopathy for the treatment of a stem cell or progenitor cell disorder.

As used herein to describe a mobilization regimen, the term "conventional" generally refers to those mobilization regimens that have traditionally been used to mobilize stem cells. For example, conventional mobilization regimens include those comprising or consisting of G-CSF and that have historically been used to mobilize stem cells from the bone marrow compartment. Such convention mobilization regimens are frequently associated with poor mobilization results, which may often occur over an extended period of time (e.g., over about 5 days), and subjecting the patient to repeated and prolonged apheresis procedures.

In addition to being phenotypically unique relative to stem cells mobilized using traditional mobilization regimens, the heHSCs disclosed herein are characterized by their improved functional properties. For example, in certain embodiments, the heHSCs disclosed herein are characterized by their improved engrafting ability. Accordingly, certain aspects of the methods disclosed herein comprise administering or otherwise transplanting the isolated, non-native heHSCs to a subject in need, such that the administered heHSCs engraft in the tissues (e.g., the bone marrow tissue) of the recipient subject. As used herein, the terms "engrafting" and "engraftment" refer to placing or administration of the heHSCs into an animal (e.g., by injection), wherein following such placement or administration, the heHSCs persist *in vivo*. Engraftment may be readily measured by the ability of the transplanted heHSCs to, for example, contribute to the ongoing blood cell formation or by assessing donor chimerism following the transplant of such heHSCs.

Successful stem cell transplantation depends on the ability to engraft sufficient quantities of transplanted stem cells in the tissues of the subject (e.g., the bone marrow tissues of the subject). The heHSCs disclosed herein are characterized by their improved engrafting ability and accordingly, certain aspects of the present invention relate to methods of treating stem cell and/or progenitor cell disorders or other diseases requiring transplantation of hematopoietic stem cells and/or progenitor cells by administering to a subject the non-native, isolated heHSCs disclosed herein.

The heHSCs disclosed herein are also characterized by their ability to achieve enhanced or improved donor chimerism following their engraftment in the tissues of a subject. For example, as illustrated in **FIG. 1,** relative to G-CSF-mobilized stem cells, in certain embodiments, an increase in donor chimerism is observed following

engraftment of heHSCs that were mobilized with the combination of one or more CXCR2 agonists (e.g., GROβ and analogs or derivatives thereof) and one or more CXCR4 antagonist (e.g., AMD-3100 and analogs or derivatives thereof). As used herein, the term "donor chimerism" refers to the fraction or percentage of bone marrow cells that originate from the donor heHSCs following engraftment of such heHSCs in a subject. In certain embodiments, donor chimerism following engraftment of the heHSCs is increased relative to, for example, donor chimerism observed following engraftment of the same or a similar quantity of stem cells that are mobilized using conventional mobilization regimens (e.g., conventional mobilization regimens comprising or consisting of G-CSF or other chemotherapeutic agents). In certain embodiments, donor chimerism following engraftment of the heHSCs is increased by at least about two fold, three-fold, four-fold, five-fold, six-fold, or more. In some embodiments, such donor chimerism is at least about 10%, 20%, 25%, 30%, 40%, 50%, 60%, 70%, 75%, 80%, 85%, 90%, 95%, 97%, 99%, or more.

In certain aspects, the heHSCs disclosed herein are also characterized by their ability to achieve an enhanced or improved CD34+ number upon engraftment in a subject. For example, such engrafted heHSCs demonstrate an enhanced or improved CD34+ number relative to an engraftment of the same quantity of hematopoietic stem cells contacted with G-CSF or one or more chemotherapeutic agents described herein. In some embodiments, such CD34+ number is increased by at least about 10%, 20%, 25%, 30%, 40%, 50%, 60%, 70%, 75%, 80%, 85%, 90%, 95%, 97%, 99%, 100%, 150%, 200%, 300%, or more relative to, for example, the CD34+ number observed following engraftment of a G-CSF-mobilized stem cell. In some embodiments, such CD34+ number is increased by at least about 1.2-fold, 1.3-fold, 1.4-fold, 1.5-fold, 1.6-fold, 1.7-fold, 1.8-fold, 1.9-fold, 2-fold, 2.5-fold, 3-fold, 3.5-fold, 4-fold, or more relative to, for example, the CD34+ number observed following engraftment of a G-CSF-mobilized stem cell.

In some embodiments, also disclosed herein are methods of treating a stem cell or progenitor cell disorder or a disease requiring transplantation of stem cells, the methods comprising administering the isolated, non-native heHSCs to a subject, wherein the administered heHSCs engrafts in the subject's tissues (e.g., the subject's bone marrow compartment), thereby treating the stem cell or progenitor cell disorder.

As used herein, the terms "treat," "treatment," "treating," or "amelioration" when used in reference to a stem cell disorder, progenitor cell disorder or any disease

requiring stem cell transplantation, generally refer to therapeutic treatments for a condition, wherein the object is to reverse, alleviate, ameliorate, inhibit, slow down or stop the progression or severity of a symptom or condition. The term "treating" also includes reducing or alleviating at least one adverse effect or symptom of a condition, disease or disorder. Treatment is generally effective if one or more symptoms or clinical markers of the condition or disease are reduced. Alternatively, treatment is effective if the progression of a condition is reduced or halted. That is, treatment includes not just the improvement of symptoms or markers, but also a cessation or at least slowing of progress or worsening of symptoms that would be expected in the absence of treatment. Beneficial or desired clinical results include, but are not limited to, alleviation of one or more symptom(s), diminishment of extent of the deficit, stabilized state of, for example, a condition, disease, or disorder described herein, or delaying or slowing onset of a condition, disease, or disorder described herein, and an increased lifespan as compared to that expected in the absence of treatment.

As used herein, the term "administering," generally refers to the placement of the heHSCs described herein into a subject (e.g., the parenteral placement of heHSCs into a subject) by a method or route which results in delivery of such heHSCs to an intended target tissue or site of action (e.g., the bone marrow tissue of a subject). In certain aspects, the term "administering" refers to the placement of at least one CXCR2 agonist and at least one CXCR4 antagonist, VLA-4 antagonist, $\alpha_9\beta_1$ antagonist, $\alpha_9\beta_1$ integrin/VLA-4 antagonist or combination thereof to a subject to mobilize hematopoietic stem cells and/or progenitor cells from, for example, the subject's bone marrow tissues and into the subject's peripheral tissues (e.g., mobilizing such hematopoietic stem cells and/or progenitor cells out of the bone marrow compartment and into one or more of the peripheral compartments, such as the peripheral blood compartment).

The isolated, non-native heHSCs disclosed herein are useful for the treatment of any disease, disorder, condition, or complication associated with a disease, disorder, or condition, in which transplantation of hematopoietic stem cells and/or progenitor cells is desirable. In some embodiments, the present inventions relate to methods of treating diseases that require peripheral blood stem cell transplantation. In some embodiments, the disclosure provides method of treating stem cell disorders and progenitor cell disorders in a subject in need of such treatment. Examples of such

stem cell and progenitor disorders include hematological malignancies and non-malignant hematological diseases.

In some embodiments, the disease, stem cell disorder or progenitor cell disorder is a hematological malignancy. Exemplary hematological malignancies which can be treated with the heHSCs and methods described herein include, but are not limited to, acute lymphoid leukemia, acute myeloid leukemia, chronic lymphoid leukemia, chronic myeloid leukemia, diffuse large B-cell non-Hodgkin's lymphoma, mantle cell lymphoma, lymphoblastic lymphoma, Burkitt's lymphoma, follicular B-cell non-Hodgkin's lymphoma, T-cell non-Hodgkin's lymphoma, lymphocyte predominant nodular Hodgkin's lymphoma, multiple myeloma, and juvenile myelomonocytic leukemia.

In some embodiments, the disease, stem cell disorder or progenitor cell disorder is a non-malignant disorder. Exemplary non-malignant diseases which can be treated with the methods and heHSCs described herein include, but are not limited to, myelofibrosis, myelodysplastic syndrome, amyloidosis, severe aplastic anemia, paroxysmal nocturnal hemoglobinuria, immune cytopenias, systemic sclerosis, rheumatoid arthritis, multiple sclerosis, systemic lupus erythematosus, Crohn's disease, chronic inflammatory demyelinating polyradiculoneuropathy, human immunodeficiency virus (HIV), Fanconi anemia, sickle cell disease, beta thalassemia major, Hurler's syndrome (MPS-IH), adrenoleukodystrophy, metachromatic leukodystrophy, familial erythrophagocytic lymphohistiocytosis and other histiocytic disorders, severe combined immunodeficiency (SCID), and Wiskott-Aldrich syndrome.

As used herein, the term "subject" means any human or animal. In certain aspects, the animal is a vertebrate such as a primate, rodent, domestic animal or game animal. Primates include chimpanzees, cynomologous monkeys, spider monkeys, and macaques, e.g., Rhesus. Rodents include mice, rats, woodchucks, ferrets, rabbits and hamsters. Domestic and game animals include cows, horses, pigs, deer, bison, buffalo, feline species, e.g., domestic cat, canine species, e.g., dog, fox, wolf, avian species, e.g., chicken, emu, ostrich, and fish, e.g., trout, catfish and salmon. Patient or subject includes any subset of the foregoing (e.g., all of the above), but excluding one or more groups or species such as humans, primates or rodents. In certain embodiments, the subject is a mammal (e.g., a primate or human). In some embodiments, the subject is a mammal. In some embodiments, the mammal is a human, a non-human primate, a

mouse, a rat, a dog, a cat, a horse, or a cow, and is not limited to these examples. Mammals other than humans can be advantageously used, for example, as subjects that represent animal models of, for example, a hematological malignancy. In addition, the methods described herein can be used to treat domesticated animals and/or pets. A subject can be male or female.

In certain embodiments, a subject can be one who has been previously diagnosed with or otherwise identified as suffering from or having a condition, disease, stem cell disorder or progenitor cell disorder described herein in need of treatment (e.g., of a hematological malignancy or non-malignant disease described herein) or one or more complications related to such a condition, and optionally, but need not have already undergone treatment for a condition or the one or more complications related to the condition. Alternatively, a subject can also be one who has not been previously diagnosed as having a condition in need of treatment or one or more complications related to such a condition. Rather, a subject can include one who exhibits one or more risk factors for a condition or one or more complications related to a condition.

A "subject in need" of treatment for a particular condition (e.g., a stem cell or progenitor cell disorder) can be a subject having that condition, diagnosed as having that condition, or at increased risk of developing that condition relative to a given reference population. In some embodiments, the methods of treatment described herein comprise selecting a subject diagnosed with, suspected of having, or at risk of developing a hematological malignancy, for example a hematological malignancy described herein. In some embodiments, the methods described herein comprise selecting a subject diagnosed with, suspected of having, or at risk of developing a non-malignant disease, for example a non-malignant disease described herein.

In other aspects of the invention, heHSC described herein may be produced by obtaining a HSC cell population by any conventional method disclosed in the art and enriching the HSC cell population for one or more cell surface markers or gene expression profiles for heHSC disclosed herein. In some embodiments, the obtained HSC cell population is enriched for CD93+ cells. In some embodiments, the HSC cell population is enriched for CD93+/CD34- cells. In some embodiments, the HSC cell population is enriched by about 1.5-fold, 2-fold, 2.5-fold, 3-fold, 4-fold, 5-fold or more. In some embodiments, the cell population may be enriched to contain at least 40%, 45%, 50%, 55%, 60%, 65%, 70%, 75%, 80%, 85%, 90%, 95%, or more of cells

containing a desired cell surface marker or cell expression pattern (e.g., enriched for CD93+ cells or CD93+/CD34- cells). Any suitable procedure (e.g., FACS sorting) may be used for the enrichment.

Some aspects of the invention are directed towards a method of making an HSC product comprising: i) contacting hematopoietic stem cells and/or progenitor cells with at least one CXCR2 agonist and at least one CXCR4 antagonist, VLA-4 antagonist, α9β1 antagonist, α9β1 integrin/VLA-4 antagonist or combination thereof to produce a candidate product; ii) providing a target expression profile for an heHSC product; iii) determining whether the candidate product meets the target expression profile of an heHSC product; and iv) releasing the candidate product as an heHSC product if the candidate product meets the target expression profile of an heHSC product.

In some embodiments, the target expression profile comprises Sca-1+, c-kit+ and Lin- (SKL) cells. In some embodiments, the the target expression profile comprises CD48- cells. . In some embodiments, the target expression profile comprises CD150+ cells. In some embodiments, the target expression profile comprises CD93+ cells. In some embodiments, the target expression profile comprises CD34- cells. In some embodiments, the target expression profile comprises OPN+ cells.

"The target expression profile" refers to a transcriptome and/or cell surface marker profile indicating the presence of heHSC cells or a certain percentage of heHSC cells in a cell population. In some embodiments, the target expression profile comprises at least 40%, 45%, 50%, 55%, 60%, 65%, 70%, 75%, 80%, 85%, 90%, 95%, or more of cells in the candidate product or enriched candidate product having one or more cell surface markers. In some embodiments, the target expression profile can be a transcriptome profile of the candidate product or enriched candidate product indicating an heHSC product. In some embodiments, the transcriptome profile can be similar or substantially similar to the profiles shown in FIG. 3 or FIG. 4.

In some embodiments, the contacting of the hematopoietic stem cells and/or progenitor cells with at least one CXCR2 agonist and at least one CXCR4 antagonist, VLA-4 antagonist, α9β1 antagonist, α9β1 integrin/VLA-4 antagonist or combination thereof is performed in vivo. In some embodiments, the contacting is performed in vitro.

In some embodiments, the at least one CXCR2 agonist comprises GROβ or an analog or derivative thereof. In some embodiments, the at least one CXCR2 agonist comprises GROβ-Δ4 or an analog or derivative thereof. In some embodiments, the at least one CXCR4 antagonist comprises plerixafor or an analog or derivative thereof. In some embodiments, the at least one CXCR2 agonist is GROβ or an analog or derivative thereof, and wherein the at least one CXCR4 antagonist is plerixafor or an analog or derivative thereof.

In some embodiments of the invention, the heHSC product, upon transplant into a subject, demonstrates increased engrafting ability relative to engraftment of the same quantity of hematopoietic stem cells contacted with granulocyte colony-stimulating factor (G-CSF), a chemotherapeutic agent, or a combination thereof. In some embodiments, the engrafting ability is increased by at least about two-fold. In certain embodiments, such engrafting ability is increased by at least about two-fold, three-fold, four-fold, five-fold, six-fold, or more.

In some embodiments of the invention, upon engraftment in a subject the heHSC product demonstrates increased donor chimerism relative to engraftment of the same quantity of hematopoietic stem cells contacted with G-CSF, a chemotherapeutic agent, or a combination thereof. In some embodiments, the donor chimerism is increased by at least about two fold. . In certain embodiments, such donor chimerism is increased by at least about two-fold, three-fold, four-fold, five-fold, six-fold, or more. In some embodiments, donor chimerism is increased by at least about 50%.

In some embodiments, the heHSC product is non-quiescent.

In some embodiments, the method of making an HSC product additionally comprises a step of enriching the candidate product for one or more cell surface markers and/or one or more gene expression profiles. Any suitable method of enrichment may be employed. In some embodiments, the method is FACS.

In some embodiments, the heHSC product comprises a unique transcriptome relative to hematopoietic stem cells contacted with granulocyte colony-stimulating factor (G-CSF), a chemotherapeutic agent, or a combination thereof. In some embodiments, the heHSC product differentially express one or more of genes selected from the group consisting of Fos, CD93, Fosb, Dusp1, Jun, Dusp6, Cdk1, Fignl1, Plk2, Rsad2, Sgk1, Sdc1, Serpine2, Spp1, Cdca8, Nrp1, Mcam, Pbk, Akr1cl and Cyp11a1, relative to one or more genes expressed by hematopoietic stem cells

mobilized using G-CSF. In some embodiments, the heHSC product comprises at least a unique transcriptome or a unique phenotype as compared to a naturally occurring HSC.

In some aspects of the invention, the heHSC product is transformed to express a polynucleotide. In some embodiments, the heHSC product is transformed with an expression vector to express a polynucleotide. In some embodiments, the expression vector comprises a viral vector selected from the group consisting of a retrovirus, a herpes simplex, a lentivirus, an adenovirus, and an adeno-associated virus. In some embodiments, the heHSC product is transfected with an expression vector that comprises the polynucleotide. In some embodiments, polynucleotide comprises an exogenous polynucleotide.

In some embodiments, the heHSC product comprises at least 40% CD93+ cells. In some embodiments, the heHSC product comprises at least about 2 x 106 cells. In some embodiments, the hematopoietic stem cells and/or progenitor cells are human or mouse cells.

Another aspect of the invention is directed to a method of treating a stem cell or progenitor cell disorder comprising: i) contacting hematopoietic stem cells and/or progenitor cells with at least one CXCR2 agonist and at least one CXCR4 antagonist, VLA-4 antagonist, α9β1 antagonist, α9β1 integrin/VLA-4 antagonist or combination thereof to produce a candidate product; ii) providing a target expression profile for an heHSC product; iii) determining whether the candidate product meets the target expression profile of an heHSC product; and iv) administering the candidate product to a subject in need thereof if the candidate product meets the target expression profile of an heHSC product.

In some embodiments, the target expression profile comprises Sca-1+, c-kit+ and Lin- (SKL) cells. In some embodiments, the target expression profile comprises CD48- cells. In some embodiments, the target expression profile comprises CD150+ cells. In some embodiments, the target expression profile comprises CD93+ cells. In some embodiments, the target expression profile comprises CD34- cells. In some embodiments, the target expression profile comprises OPN+ cells.

"The target expression profile" refers to a transcriptome and/or cell surface marker profile indicating the presence of heHSC cells or a certain percentage of heHSC cells in a cell population. In some embodiments, the target expression profile comprises at least 40%, 45%, 50%, 55%, 60%, 65%, 70%, 75%, 80%, 85%, 90%,

95%, or more of cells in the candidate product or enriched candidate product having one or more cell surface markers. In some embodiments, the target expression profile can be a transcriptome profile of the candidate product or enriched candidate product indicating an heHSC product. In some embodiments, the transcriptome profile can be similar or substantially similar to the profiles shown in FIG. 3 or FIG. 4.

In some embodiments, the contacting of the hematopoietic stem cells and/or progenitor cells with at least one CXCR2 agonist and at least one CXCR4 antagonist, VLA-4 antagonist, α9β1 antagonist, α9β1 integrin/VLA-4 antagonist or combination thereof is performed in vivo. In some embodiments, the contacting is performed in vitro.

In some embodiments, the at least one CXCR2 agonist comprises GROβ or an analog or derivative thereof. In some embodiments, the at least one CXCR2 agonist comprises GROβ-Δ4 or an analog or derivative thereof. In some embodiments, the at least one CXCR4 antagonist comprises plerixafor or an analog or derivative thereof. In some embodiments, the at least one CXCR2 agonist is GROβ or an analog or derivative thereof, and wherein the at least one CXCR4 antagonist is plerixafor or an analog or derivative thereof.

In some embodiments of the invention, the heHSC product, upon transplant into a subject, demonstrates increased engrafting ability relative to engraftment of the same quantity of hematopoietic stem cells contacted with granulocyte colony-stimulating factor (G-CSF), a chemotherapeutic agent, or a combination thereof. In some embodiments, the engrafting ability is increased by at least about two-fold. In certain embodiments, such engrafting ability is increased by at least about two-fold, three-fold, four-fold, five-fold, six-fold, or more.

In some embodiments of the invention, upon engraftment in a subject the heHSC product demonstrates increased donor chimerism relative to engraftment of the same quantity of hematopoietic stem cells contacted with G-CSF, a chemotherapeutic agent, or a combination thereof. In some embodiments, the donor chimerism is increased by at least about two fold. . In certain embodiments, such donor chimerism is increased by at least about two-fold, three-fold, four-fold, five-fold, six-fold, or more. In some embodiments, donor chimerism is increased by at least about 50%.

In some embodiments, the heHSC product is non-quiescent.

In some embodiments, the method of making an HSC product additionally comprises a step of enriching the candidate product for one or more cell surface markers and/or one or more gene expression profiles. Any suitable method of enrichment may be employed. In some embodiments, the method is FACS.

In some embodiments, the heHSC product comprises a unique transcriptome relative to hematopoietic stem cells contacted with granulocyte colony-stimulating factor (G-CSF), a chemotherapeutic agent, or a combination thereof. In some embodiments, the heHSC product differentially express one or more of genes selected from the group consisting of Fos, CD93, Fosb, Dusp1, Jun, Dusp6, Cdk1, Fignl1, Plk2, Rsad2, Sgk1, Sdc1, Serpine2, Spp1, Cdca8, Nrp1, Mcam, Pbk, Akr1cl and Cyp11a1, relative to one or more genes expressed by hematopoietic stem cells mobilized using G-CSF. In some embodiments, the heHSC product comprises at least a unique transcriptome or a unique phenotype as compared to a naturally occurring HSC.

In some aspects of the invention, the heHSC product is transformed to express a polynucleotide. In some embodiments, the heHSC product is transformed with an expression vector to express a polynucleotide. In some embodiments, the expression vector comprises a viral vector selected from the group consisting of a retrovirus, a herpes simplex, a lentivirus, an adenovirus, and an adeno-associated virus. In some embodiments, the heHSC product is transfected with an expression vector that comprises the polynucleotide. In some embodiments, polynucleotide comprises an exogenous polynucleotide.

In some embodiments, the heHSC product comprises at least 40% CD93+ cells. In some embodiments, the heHSC product comprises at least about 2 x 106 cells. In some embodiments, the hematopoietic stem cells and/or progenitor cells are human or mouse cells.

In some embodiments, the stem cell or progenitor cell disorder is a malignant hematologic disease. In some embodiments, the malignant hematologic disease is selected from the group consisting of acute lymphoid leukemia, acute myeloid leukemia, chronic lymphoid leukemia, chronic myeloid leukemia, diffuse large B-cell non-Hodgkin's lymphoma, mantle cell lymphoma, lymphoblastic lymphoma, Burkitt's lymphoma, follicular B-cell non-Hodgkin's lymphoma, lymphocyte predominant nodular Hodgkin's lymphoma, multiple myeloma, and juvenile myelomonocytic leukemia. In some embodiments, the stem cell or progenitor cell

disorder is a non-malignant disease. In some embodiments, the non-malignant disease is selected from the group consisting of myelofibrosis, myelodysplastic syndrome, amyloidosis, severe aplastic anemia, paroxysmal nocturnal hemoglobinuria, immune cytopenias, systemic sclerosis, rheumatoid arthritis, multiple sclerosis, systemic lupus erythematosus, Crohn's disorder, chronic inflammatory demyelinating polyradiculoneuropathy, human immunodeficiency virus (HIV), Fanconi anemia, sickle cell disorder, beta thalassemia major, Hurler's syndrome (MPS-IH), adrenoleukodystrophy, metachromatic leukodystrophy, familial erythrophagocytic lymphohistiocytosis and other histiocytic disorders, severe combined immunodeficiency (SCID), and Wiskott-Aldrich syndrome.

In certain aspects, the heHSCs described herein can be provided in the form of a kit. For example, the kit may comprise one or more isolated, non-native heHSCs and informational or instructional materials relating to the use or administration of such heHSCs to a subject in need. In some embodiments, such kits may comprise at least one CXCR2 agonist, at least one CXCR4 antagonist and instructions for their administration to a subject to mobilize and/or harvest the hematopoietic stem cells and/or progenitor cells, thereby preparing the isolated heHSCs disclosed herein.

It is to be understood that the invention is not limited in its application to the details set forth in the description or as exemplified. The invention encompasses other embodiments and is capable of being practiced or carried out in various ways. Also, it is to be understood that the phraseology and terminology employed herein is for the purpose of description and should not be regarded as limiting.

While certain agents, compounds, compositions and methods of the present invention have been described with specificity in accordance with certain embodiments, the following examples serve only to illustrate the methods and compositions of the invention and are not intended to limit the same.

The articles "a" and "an" as used herein in the specification and in the claims, unless clearly indicated to the contrary, should be understood to include the plural referents. Claims or descriptions that include "or" between one or more members of a group are considered satisfied if one, more than one, or all of the group members are present in, employed in, or otherwise relevant to a given product or process unless indicated to the contrary or otherwise evident from the context. The invention includes embodiments in which exactly one member of the group is present in, employed in, or otherwise relevant to a given product or process. The invention also

includes embodiments in which more than one, or the entire group members are present in, employed in, or otherwise relevant to a given product or process. Furthermore, it is to be understood that the invention encompasses all variations, combinations, and permutations in which one or more limitations, elements, clauses, descriptive terms, etc., from one or more of the listed claims is introduced into another claim dependent on the same base claim (or, as relevant, any other claim) unless otherwise indicated or unless it would be evident to one of ordinary skill in the art that a contradiction or inconsistency would arise. Where elements are presented as lists, (e.g., in Markush group or similar format) it is to be understood that each subgroup of the elements is also disclosed, and any element(s) can be removed from the group. It should be understood that, in general, where the invention, or aspects of the invention, is/are referred to as comprising particular elements, features, etc., certain embodiments of the invention or aspects of the invention consist, or consist essentially of, such elements, features, etc. For purposes of simplicity those embodiments have not in every case been specifically set forth in so many words herein. It should also be understood that any embodiment or aspect of the invention can be explicitly excluded from the claims, regardless of whether the specific exclusion is recited in the specification. The publications and other reference materials referenced herein to describe the background of the invention and to provide additional detail regarding its practice are hereby incorporated by reference.

EXAMPLES

Example 1 Rapid regimen

To address the still remaining deficiencies in hematopoietic mobilization, the present inventors believe an effective alternative method is the use of rapid mobilizing agents that do not require multiple injections, that are more predictable in their peak mobilization kinetics, and that result in an enhanced CD34+ number and hematopoietic function upon transplant. One agent with potential is the CXCR2 agonist, GROβ. GROβ and GROβ-Δ4 (collectively referred to herein as "GROβ") rapidly mobilize hematopoietic stem cells (HSC), including all classes of short-term progenitor cells as well as long-term repopulating cells. In mice, peak GROβ-induced mobilization occurs within 15-30 minutes of administration. Moreover, not only was the observed mobilization faster following GROβ administration, the present

inventors believe that the stem cell quality was also greater, at least in view of the improved engrafting ability of the mobilized stem cells (e.g., the two-fold greater engrafting ability of the stem cells mobilized from the bone marrow compartment, relative to stem cells mobilized using, for example, a mobilization regimen comprising C-GSF) and the donor chimerism observed following engraftment of such mobilized stem cells.

To assess this, the present inventors mobilized large cohorts of mice (15-20 per group) with either G-CSF (125ug/kg/day, five days) or with a combination of GROβ (2.5mg/kg) and plerixafor (AMD-3100) (5mg/kg), and then sorted the peripheral blood for highly purified SLAM SKL cells (CD150+, CD48-, Sca-1+, c-kit+, lineage negative)

In two separate experiments, the present inventors then competitively transplanted either (a) 190 SLAM SKL cells against 300,000 whole bone marrow competitors, or (b) 50 SLAM SKL cells against 300,000 whole bone marrow competitors. This experimental design allowed for a direct assessment of the engrafting ability of the mobilized SLAM SKL cells, independent of accessory cell populations (e.g., non- CD150+, CD48-, Sca-1+, c-kit+, lineage negative cells) that may have been mobilized, as well as normalized the HSC content so that the same number of HSCs from either the G-CSF-mobilized donors, or the GROβ plus plerixafor-mobilized donors, went into the irradiated recipients. As illustrated in **FIGS. 1** and **2** in both sets of experiments, the SLAM SKL cells that were mobilized by the combination of GROβ plus plerixafor demonstrated superior engrafting ability (2 fold greater) relative to the cells that were mobilized by G-CSF. This was evident even when the exact same numbers of phenotypically defined (SLAM SKL) HSCs were transplanted.

Example 2 Transcriptome signatures

Over the last decade, there has been increasing evidence that the hematopoietic stem cell (HSC) pool is heterogeneous in function, with identification of HSCs with differing lineage outputs, kinetics of repopulation, length of life-span, and perhaps differences amongst HSCs contributing to homeostatic blood production from those that are the engraftable units in transplantation. To date, however, there are no reliable methods for prospectively isolating differing HSC populations to study

heterogeneity. Rather, much of the available data has been acquired based on clonal tracking, single cell transplantation, etc.

Much like panning for gold, the present inventors can now use the differential mobilization properties of the mobilization regimen using GROβ and plerixafor and the regimen using G-CSF as a "biologic sieve" to isolate the heterogeneous HSC populations from the blood. These differential mobilization properties enabled the present inventors, and without destroying the cell, to prospectively isolate what is referred to herein as a highly engraftable HSC (heHSC) population for further functional analysis, and to prospectively isolate a differing HSC population with known, predictable function (the heHSCs) for further molecular characterization.

As a preliminary proof of concept and to demonstrate the feasibility of the approach described herein, SLAM SKL cells were sorted from large cohorts of mice that were treated or mobilized with either G-CSF, or with the combination of GROβ and plerixafor (AMD-3100), as described in Example 1.

In the present study, 200 cells were directly sorted into 5 uL TCL lysis buffer (Qiagen, #1031576). Library preparation was performed by the Smart-Seq2 protocol (Picelli et al., 2013) with subsequent RNA sequencing by Illumina NextSeq500. In addition to SLAM SKL cells from the G-CSF mobilized blood and the GROβ plus plerixafor mobilized blood, additional control samples were sequenced, including steady state bone marrow, bone marrow from the G-CSF-treated mice group, bone marrow from the GROβ plus plerixafor-treated mice, and a "drug spike" control, which consisted of G-CSF mobilized blood spiked with GROβ (350ng/ml) plus AMD-3100 (10ug/ml), concentrations based on prior PK data, for 15 minutes, with subsequent downstream processing for FACS sorting. This enabled the present inventors to directly compare the heHSCs from those that were isolated from G-CSF mobilized HSCs, HSCs from the bone marrow of treated and untreated mice, and a drug control to account for any direct effects the GROβ plus plerixafor may have had on the gene signatures that are not due to specific, differential mobilization effects. The RNASeq data was subsequently analyzed, as illustrated in **FIG. 3**.

Surprisingly, as illustrated in **FIG. 4**, the highly purified SLAM SKL cells from the GROβ plus plerixafor-mobilized peripheral blood demonstrated a unique transcriptomic signature, including, for example, the expression of CD93 a marker of early lineage stem cells, relative to those HSCs mobilized by G-CSF, as well as from the treated or untreated bone marrow and from the drug spike control. The present

inventors believe that the foregoing studies represent the first demonstration of predictable, differential HSC mobilization and provide a novel method to isolate the heHSC cells which have superior clinical utility.

Example 3 Generation of unique stem cell populations

Hematopoietic stem cells (HSCs) are at the apex of lifelong blood cell production. Recent clonal analysis studies suggest that HSCs are heterogeneous in function and those that contribute to homeostatic production may be distinct from those that engraft during transplant. The present inventors developed a rapid mobilization regimen utilizing a unique CXCR2 agonist (an N-terminal truncated MIP-2a) and the CXCR4 antagonist AMD-3100. A single subcutaneous injection of both agents together resulted in rapid mobilization in mice with a peak progenitor cell content in blood reached within 15 minutes.

The observed mobilization was equivalent to a 5-day regimen of G-CSF and is the result of synergistic signaling, and was blocked in CXCR4 or CXCR2 knockout mice, confirming receptor and mechanism specificity and is caused by synergistic release of MMP-9 from neutrophils that was blocked in MMP-9 knockout mice, mice treated with an anti-MMP-9 antibody, TIMP-1 transgenic mice, or mice where neutrophils were depleted in vivo using anti-GR-1 antibody. *In vivo* confocal imaging of mice demonstrated that the mobilization regimen caused a rapid and transient increase in bone marrow vascular permeability, "opening the doorway" for hematopoietic egress to the peripheral blood.

Transplantation of $2x10^6$ peripheral blood mononuclear cells (PBMCs) from the rapid regimen resulted in a 4 or 6 day quicker recovery of neutrophils and platelets, respectively, compared to a G-CSF mobilized graft (n=12 mice per group, $P<0.01$). In limiting dilution competitive transplants, the rapid regimen demonstrated a greater than 2-fold enhancement in competitiveness (n=30 mice/treatment group, 2 individual experiments, $P<0.001$). Additionally, in secondarily transplanted mice, competitiveness of the rapidly mobilized graft increased as measured by contribution to chimerism, while G-CSF mobilized grafts remained static (n=16 mice/group, $P<0.01$). Surprisingly, despite robust enhancement in both short and long-term engraftment by the rapidly mobilized graft, phenotypic analysis of the blood of mobilized mice for CD150+ CD48- Sca-1+ c-kit+ Lineage neg (SLAM SKL) cells, a

highly purified HSC population, showed lower numbers of phenotypically defined HSCs than in the G-CSF group.

The foregoing data suggest that a unique subset of "highly engraftable" HSCs (heHSCs) are mobilized by the rapid regimen comprising an N-terminal truncated MIP-2a and AMD-3100, compared to G-CSF. However, as our earlier studies were performed using grafts that contained the total PBMC fraction (similar to the clinical apheresis product) the present inventors could not rule out the potential contribution of accessory cells to the enhanced engrafting ability of the heHSCs.

Example 4 Long term effects

Following the conclusions set out in Example 3, in 3 independent experiments, the present inventors mobilized large cohorts of mice with the rapid regimen comprising an N-terminal truncated MIP-2a (2.5mg/kg) and AMD-3100 (5mg/kg), or G-CSF (125ug/kg/day, fice days) and sorted SLAM SKL cells from the PBMC fraction and competitively transplanted equal numbers of SLAM SKL cells (190, or 50) from either the rapid regimen or G-CSF and tracked contribution to chimerism over 36 weeks. Remarkably, the heHSCs from the rapid regimen demonstrated a 2-fold enhancement in competitiveness compared to SLAM SKL cells from the G-CSF group (n=11 mice/group, $P<0.0004$). See Figure 1.

Example 5 Molecular cell sorting and signature determination

While appreciation for HSC heterogeneity has grown, methods are lacking for prospectively isolating differing HSC populations with known biologic function, to study molecular heterogeneity. The present inventors sought to use the differential mobilization properties of our rapid regimen and G-CSF to isolate the heterogeneous HSC populations from the blood. The present inventors again flow sorted SLAM SKL cells from mice mobilized with the rapid regimen or G-CSF and performed RNASeq analysis of the purified populations. The heHSCs mobilized by the rapid regimen had a unique transcriptomic signature compared to G-CSF mobilized or random HSCs acquired from bone marrow ($P<0.000001$). Strikingly, gene set enrichment analysis (GSEA) demonstrated that the heHSCs had a gene signature highly significantly clustered to that of fetal liver HSCs, further demonstrating the selective harvesting of a subset of highly engraftable stem cells.

Our results mechanistically define a new mobilization strategy, that in a single day can mobilize a graft with superior engraftment properties compared to G-CSF, and

selectively mobilize a novel population of heHSCs with an immature molecular phenotype capable of robust long-term engraftment.

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<213> Homo sapiens

<220>
<221> MISC_FEATURE
<223> CDK1

<400> 10

Met Glu Asp Tyr Thr Lys Ile Glu Lys Ile Gly Glu Gly Thr Tyr Gly
1 5 10 15

Val Val Tyr Lys Gly Arg His Lys Thr Thr Gly Gln Val Val Ala Met
20 25 30

Lys Lys Ile Arg Leu Glu Ser Glu Glu Glu Gly Val Pro Ser Thr Ala
35 40 45

Ile Arg Glu Ile Ser Leu Leu Lys Glu Leu Arg His Pro Asn Ile Val
50 55 60

Ser Leu Gln Asp Val Leu Met Gln Asp Ser Arg Leu Tyr Leu Ile Phe
65 70 75 80

Glu Phe Leu Ser Met Asp Leu Lys Lys Tyr Leu Asp Ser Ile Pro Pro
85 90 95

Gly Gln Tyr Met Asp Ser Ser Leu Val Lys Ser Tyr Leu Tyr Gln Ile
100 105 110

Leu Gln Gly Ile Val Phe Cys His Ser Arg Arg Val Leu His Arg Asp
115 120 125

Leu Lys Pro Gln Asn Leu Leu Ile Asp Asp Lys Gly Thr Ile Lys Leu
130 135 140

Ala Asp Phe Gly Leu Ala Arg Ala Phe Gly Ile Pro Ile Arg Val Tyr
145 150 155 160

Thr His Glu Val Val Thr Leu Trp Tyr Arg Ser Pro Glu Val Leu Leu
165 170 175

Gly Ser Ala Arg Tyr Ser Thr Pro Val Asp Ile Trp Ser Ile Gly Thr
180 185 190

Ile Phe Ala Glu Leu Ala Thr Lys Lys Pro Leu Phe His Gly Asp Ser
195 200 205

Glu Ile Asp Gln Leu Phe Arg Ile Phe Arg Ala Leu Gly Thr Pro Asn
210 215 220

Asn Glu Val Trp Pro Glu Val Glu Ser Leu Gln Asp Tyr Lys Asn Thr
225 230 235 240

Phe Pro Lys Trp Lys Pro Gly Ser Leu Ala Ser His Val Lys Asn Leu
245 250 255

Asp Glu Asn Gly Leu Asp Leu Leu Ser Lys Met Leu Ile Tyr Asp Pro
260 265 270

Ala Lys Arg Ile Ser Gly Lys Met Ala Leu Asn His Pro Tyr Phe Asn
275 280 285

Asp Leu Asp Asn Gln Ile Lys Lys Met
290 295

<210> 11
<211> 674
<212> PRT
<213> Homo sapiens

<220>
<221> MISC_FEATURE
<223> Fignl1

<400> 11

Met Gln Thr Ser Ser Ser Arg Ser Val His Leu Ser Glu Trp Gln Lys
1 5 10 15

Asn Tyr Phe Ala Ile Thr Ser Gly Ile Cys Thr Gly Pro Lys Ala Asp
20 25 30

Ala Tyr Arg Ala Gln Ile Leu Arg Ile Gln Tyr Ala Trp Ala Asn Ser
35 40 45

Glu Ile Ser Gln Val Cys Ala Thr Lys Leu Phe Lys Lys Tyr Ala Glu
50 55 60

Lys Tyr Ser Ala Ile Ile Asp Ser Asp Asn Val Glu Ser Gly Leu Asn
65 70 75 80

Asn Tyr Ala Glu Asn Ile Leu Thr Leu Ala Gly Ser Gln Gln Thr Asp
85 90 95

Ser Asp Lys Trp Gln Ser Gly Leu Ser Ile Asn Asn Val Phe Lys Met
100 105 110

Ser Ser Val Gln Lys Met Met Gln Ala Gly Lys Lys Phe Lys Asp Ser
115 120 125

Leu Leu Glu Pro Ala Leu Ala Ser Val Val Ile His Lys Glu Ala Thr
130 135 140

Val Phe Asp Leu Pro Lys Phe Ser Val Cys Gly Ser Ser Gln Glu Ser
145 150 155 160

Asp Ser Leu Pro Asn Ser Ala His Asp Arg Asp Arg Thr Gln Asp Phe
165 170 175

Pro Glu Ser Asn Arg Leu Lys Leu Leu Gln Asn Ala Gln Pro Pro Met
180 185 190

Val Thr Asn Thr Ala Arg Thr Cys Pro Thr Phe Ser Ala Pro Val Gly
195 200 205

Glu Ser Ala Thr Ala Lys Phe His Val Thr Pro Leu Phe Gly Asn Val
210 215 220

Lys Lys Glu Asn His Ser Ser Ala Lys Glu Asn Ile Gly Leu Asn Val
225 230 235 240

Phe Leu Ser Asn Gln Ser Cys Phe Pro Ala Ala Cys Glu Asn Pro Gln
245 250 255

Arg Lys Ser Phe Tyr Gly Ser Gly Thr Ile Asp Ala Leu Ser Asn Pro
260 265 270

Ile Leu Asn Lys Ala Cys Ser Lys Thr Glu Asp Asn Gly Pro Lys Glu
275 280 285

Asp Ser Ser Leu Pro Thr Phe Lys Thr Ala Lys Glu Gln Leu Trp Val
290 295 300

Asp Gln Gln Lys Lys Tyr His Gln Pro Gln Arg Ala Ser Gly Ser Ser
305 310 315 320

Tyr Gly Gly Val Lys Lys Ser Leu Gly Ala Ser Arg Ser Arg Gly Ile
325 330 335

Leu Gly Lys Phe Val Pro Pro Ile Pro Lys Gln Asp Gly Gly Glu Gln
340 345 350

Asn Gly Gly Met Gln Cys Lys Pro Tyr Gly Ala Gly Pro Thr Glu Pro
355 360 365

Ala His Pro Val Asp Glu Arg Leu Lys Asn Leu Glu Pro Lys Met Ile
370 375 380

Glu Leu Ile Met Asn Glu Ile Met Asp His Gly Pro Pro Val Asn Trp
385 390 395 400

Glu Asp Ile Ala Gly Val Glu Phe Ala Lys Ala Thr Ile Lys Glu Ile
405 410 415

Val Val Trp Pro Met Leu Arg Pro Asp Ile Phe Thr Gly Leu Arg Gly
420 425 430

Pro Pro Lys Gly Ile Leu Leu Phe Gly Pro Pro Gly Thr Gly Lys Thr
435 440 445

Leu Ile Gly Lys Cys Ile Ala Ser Gln Ser Gly Ala Thr Phe Phe Ser
450 455 460

Ile Ser Ala Ser Ser Leu Thr Ser Lys Trp Val Gly Glu Gly Glu Lys
465 470 475 480

Met Val Arg Ala Leu Phe Ala Val Ala Arg Cys Gln Gln Pro Ala Val
485 490 495

Ile Phe Ile Asp Glu Ile Asp Ser Leu Leu Ser Gln Arg Gly Asp Gly
500 505 510

Glu His Glu Ser Ser Arg Arg Ile Lys Thr Glu Phe Leu Val Gln Leu
515 520 525

Asp Gly Ala Thr Thr Ser Ser Glu Asp Arg Ile Leu Val Val Gly Ala
530 535 540

Thr Asn Arg Pro Gln Glu Ile Asp Glu Ala Ala Arg Arg Arg Leu Val
545 550 555 560

Lys Arg Leu Tyr Ile Pro Leu Pro Glu Ala Ser Ala Arg Lys Gln Ile
565 570 575

Val Ile Asn Leu Met Ser Lys Glu Gln Cys Cys Leu Ser Glu Glu Glu
580 585 590

Ile Glu Gln Ile Val Gln Gln Ser Asp Ala Phe Ser Gly Ala Asp Met
595 600 605

Thr Gln Leu Cys Arg Glu Ala Ser Leu Gly Pro Ile Arg Ser Leu Gln
610 615 620

Thr Ala Asp Ile Ala Thr Ile Thr Pro Asp Gln Val Arg Pro Ile Ala
625 630 635 640

Tyr Ile Asp Phe Glu Asn Ala Phe Arg Thr Val Arg Pro Ser Val Ser
645 650 655

Pro Lys Asp Leu Glu Leu Tyr Glu Asn Trp Asn Lys Thr Phe Gly Cys
660 665 670

Gly Lys

<210> 12
<211> 685
<212> PRT
<213> Homo sapiens

<220>
<221> MISC_FEATURE
<223> Plk2

<400> 12

Met Glu Leu Leu Arg Thr Ile Thr Tyr Gln Pro Ala Ala Ser Thr Lys
1 5 10 15

Met Cys Glu Gln Ala Leu Gly Lys Gly Cys Gly Ala Asp Ser Lys Lys
20 25 30

Lys Arg Pro Pro Gln Pro Pro Glu Glu Ser Gln Pro Pro Gln Ser Gln
35 40 45

Ala Gln Val Pro Pro Ala Ala Pro His His His His His His Ser His
50 55 60

Ser Gly Pro Glu Ile Ser Arg Ile Ile Val Asp Pro Thr Thr Gly Lys
65 70 75 80

Arg Tyr Cys Arg Gly Lys Val Leu Gly Lys Gly Gly Phe Ala Lys Cys
85 90 95

Tyr Glu Met Thr Asp Leu Thr Asn Asn Lys Val Tyr Ala Ala Lys Ile
100 105 110

Ile Pro His Ser Arg Val Ala Lys Pro His Gln Arg Glu Lys Ile Asp
115 120 125

Lys Glu Ile Glu Leu His Arg Ile Leu His His Lys His Val Val Gln
130 135 140

Phe Tyr His Tyr Phe Glu Asp Lys Glu Asn Ile Tyr Ile Leu Leu Glu
145 150 155 160

Tyr Cys Ser Arg Arg Ser Met Ala His Ile Leu Lys Ala Arg Lys Val
165 170 175

Leu Thr Glu Pro Glu Val Arg Tyr Tyr Leu Arg Gln Ile Val Ser Gly
180 185 190

Leu Lys Tyr Leu His Glu Gln Glu Ile Leu His Arg Asp Leu Lys Leu
195 200 205

Gly Asn Phe Phe Ile Asn Glu Ala Met Glu Leu Lys Val Gly Asp Phe
210 215 220

Gly Leu Ala Ala Arg Leu Glu Pro Leu Glu His Arg Arg Arg Thr Ile
225 230 235 240

Cys Gly Thr Pro Asn Tyr Leu Ser Pro Glu Val Leu Asn Lys Gln Gly
245 250 255

His Gly Cys Glu Ser Asp Ile Trp Ala Leu Gly Cys Val Met Tyr Thr
260 265 270

Met Leu Leu Gly Arg Pro Pro Phe Glu Thr Thr Asn Leu Lys Glu Thr
275 280 285

Tyr Arg Cys Ile Arg Glu Ala Arg Tyr Thr Met Pro Ser Ser Leu Leu
290 295 300

Ala Pro Ala Lys His Leu Ile Ala Ser Met Leu Ser Lys Asn Pro Glu
305 310 315 320

Asp Arg Pro Ser Leu Asp Asp Ile Ile Arg His Asp Phe Phe Leu Gln
325 330 335

Gly Phe Thr Pro Asp Arg Leu Ser Ser Ser Cys Cys His Thr Val Pro
340 345 350

Asp Phe His Leu Ser Ser Pro Ala Lys Asn Phe Phe Lys Lys Ala Ala
355 360 365

Ala Ala Leu Phe Gly Gly Lys Lys Asp Lys Ala Arg Tyr Ile Asp Thr
370 375 380

His Asn Arg Val Ser Lys Glu Asp Glu Asp Ile Tyr Lys Leu Arg His
385 390 395 400

Asp Leu Lys Lys Thr Ser Ile Thr Gln Gln Pro Ser Lys His Arg Thr
405 410 415

Asp Glu Glu Leu Gln Pro Pro Thr Thr Thr Val Ala Arg Ser Gly Thr
420 425 430

Pro Ala Val Glu Asn Lys Gln Gln Ile Gly Asp Ala Ile Arg Met Ile
435 440 445

Val Arg Gly Thr Leu Gly Ser Cys Ser Ser Ser Ser Glu Cys Leu Glu
450 455 460

Asp Ser Thr Met Gly Ser Val Ala Asp Thr Val Ala Arg Val Leu Arg
465 470 475 480

Gly Cys Leu Glu Asn Met Pro Glu Ala Asp Cys Ile Pro Lys Glu Gln
485 490 495

Leu Ser Thr Ser Phe Gln Trp Val Thr Lys Trp Val Asp Tyr Ser Asn
500 505 510

Lys Tyr Gly Phe Gly Tyr Gln Leu Ser Asp His Thr Val Gly Val Leu
515 520 525

Phe Asn Asn Gly Ala His Met Ser Leu Leu Pro Asp Lys Lys Thr Val
530 535 540

His Tyr Tyr Ala Glu Leu Gly Gln Cys Ser Val Phe Pro Ala Thr Asp
545 550 555 560

Ala Pro Glu Gln Phe Ile Ser Gln Val Thr Val Leu Lys Tyr Phe Ser
565 570 575

His Tyr Met Glu Glu Asn Leu Met Asp Gly Gly Asp Leu Pro Ser Val
580 585 590

Thr Asp Ile Arg Arg Pro Arg Leu Tyr Leu Leu Gln Trp Leu Lys Ser
595 600 605

Asp Lys Ala Leu Met Met Leu Phe Asn Asp Gly Thr Phe Gln Val Asn
610 615 620

Phe Tyr His Asp His Thr Lys Ile Ile Ile Cys Ser Gln Asn Glu Glu
625 630 635 640

Tyr Leu Leu Thr Tyr Ile Asn Glu Asp Arg Ile Ser Thr Thr Phe Arg
645 650 655

Leu Thr Thr Leu Leu Met Ser Gly Cys Ser Ser Glu Leu Lys Asn Arg
660 665 670

Met Glu Tyr Ala Leu Asn Met Leu Leu Gln Arg Cys Asn
675 680 685

<210> 13
<211> 361
<212> PRT
<213> Homo sapiens

<220>
<221> MISC_FEATURE
<223> RSAD2

<400> 13

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

Phe Arg Gln Pro Leu Ser Ser Leu Trp Arg Ser Leu Val Pro Leu Phe
20 25 30

Cys Trp Leu Arg Ala Thr Phe Trp Leu Leu Ala Thr Lys Arg Arg Lys
35 40 45

Gln Gln Leu Val Leu Arg Gly Pro Asp Glu Thr Lys Glu Glu Glu Glu
50 55 60

Asp Pro Pro Leu Pro Thr Thr Pro Thr Ser Val Asn Tyr His Phe Thr
65 70 75 80

Arg Gln Cys Asn Tyr Lys Cys Gly Phe Cys Phe His Thr Ala Lys Thr
85 90 95

Ser Phe Val Leu Pro Leu Glu Glu Ala Lys Arg Gly Leu Leu Leu Leu
100 105 110

Lys Glu Ala Gly Met Glu Lys Ile Asn Phe Ser Gly Gly Glu Pro Phe
115 120 125

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

Val Glu Leu Arg Leu Pro Ser Val Ser Ile Val Ser Asn Gly Ser Leu
145 150 155 160

Ile Arg Glu Arg Trp Phe Gln Asn Tyr Gly Glu Tyr Leu Asp Ile Leu
165 170 175

Ala Ile Ser Cys Asp Ser Phe Asp Glu Glu Val Asn Val Leu Ile Gly
180 185 190

Arg Gly Gln Gly Lys Lys Asn His Val Glu Asn Leu Gln Lys Leu Arg
195 200 205

Arg Trp Cys Arg Asp Tyr Arg Val Ala Phe Lys Ile Asn Ser Val Ile
210 215 220

Asn Arg Phe Asn Val Glu Glu Asp Met Thr Glu Gln Ile Lys Ala Leu
225 230 235 240

Asn Pro Val Arg Trp Lys Val Phe Gln Cys Leu Leu Ile Glu Gly Glu
245 250 255

Asn Cys Gly Glu Asp Ala Leu Arg Glu Ala Glu Arg Phe Val Ile Gly
260 265 270

Asp Glu Glu Phe Glu Arg Phe Leu Glu Arg His Lys Glu Val Ser Cys
275 280 285

Leu Val Pro Glu Ser Asn Gln Lys Met Lys Asp Ser Tyr Leu Ile Leu
290 295 300

Asp Glu Tyr Met Arg Phe Leu Asn Cys Arg Lys Gly Arg Lys Asp Pro
305 310 315 320

Ser Lys Ser Ile Leu Asp Val Gly Val Glu Glu Ala Ile Lys Phe Ser
325 330 335

Gly Phe Asp Glu Lys Met Phe Leu Lys Arg Gly Gly Lys Tyr Ile Trp
340 345 350

Ser Lys Ala Asp Leu Lys Leu Asp Trp
355 360

<210> 14
<211> 431
<212> PRT
<213> Homo sapiens

<220>
<221> MISC_FEATURE
<223> SGK1

<400> 14

Met Thr Val Lys Thr Glu Ala Ala Lys Gly Thr Leu Thr Tyr Ser Arg
1 5 10 15

Met Arg Gly Met Val Ala Ile Leu Ile Ala Phe Met Lys Gln Arg Arg
20 25 30

Met Gly Leu Asn Asp Phe Ile Gln Lys Ile Ala Asn Asn Ser Tyr Ala
35 40 45

Cys Lys His Pro Glu Val Gln Ser Ile Leu Lys Ile Ser Gln Pro Gln
50 55 60

Glu Pro Glu Leu Met Asn Ala Asn Pro Ser Pro Pro Pro Ser Pro Ser
65 70 75 80

Gln Gln Ile Asn Leu Gly Pro Ser Ser Asn Pro His Ala Lys Pro Ser
85 90 95

Asp Phe His Phe Leu Lys Val Ile Gly Lys Gly Ser Phe Gly Lys Val
100 105 110

Leu Leu Ala Arg His Lys Ala Glu Glu Val Phe Tyr Ala Val Lys Val
115 120 125

Leu Gln Lys Lys Ala Ile Leu Lys Lys Lys Glu Glu Lys His Ile Met
130 135 140

Ser Glu Arg Asn Val Leu Leu Lys Asn Val Lys His Pro Phe Leu Val
145 150 155 160

Gly Leu His Phe Ser Phe Gln Thr Ala Asp Lys Leu Tyr Phe Val Leu
165 170 175

Asp Tyr Ile Asn Gly Gly Glu Leu Phe Tyr His Leu Gln Arg Glu Arg
180 185 190

Cys Phe Leu Glu Pro Arg Ala Arg Phe Tyr Ala Ala Glu Ile Ala Ser
195 200 205

Ala Leu Gly Tyr Leu His Ser Leu Asn Ile Val Tyr Arg Asp Leu Lys
210 215 220

Pro Glu Asn Ile Leu Leu Asp Ser Gln Gly His Ile Val Leu Thr Asp
225 230 235 240

Phe Gly Leu Cys Lys Glu Asn Ile Glu His Asn Ser Thr Thr Ser Thr
245 250 255

Phe Cys Gly Thr Pro Glu Tyr Leu Ala Pro Glu Val Leu His Lys Gln
260 265 270

Pro Tyr Asp Arg Thr Val Asp Trp Trp Cys Leu Gly Ala Val Leu Tyr
275 280 285

Glu Met Leu Tyr Gly Leu Pro Pro Phe Tyr Ser Arg Asn Thr Ala Glu
290 295 300

Met Tyr Asp Asn Ile Leu Asn Lys Pro Leu Gln Leu Lys Pro Asn Ile
305 310 315 320

Thr Asn Ser Ala Arg His Leu Leu Glu Gly Leu Leu Gln Lys Asp Arg
325 330 335

Thr Lys Arg Leu Gly Ala Lys Asp Asp Phe Met Glu Ile Lys Ser His
340 345 350

Val Phe Phe Ser Leu Ile Asn Trp Asp Asp Leu Ile Asn Lys Lys Ile
355 360 365

Thr Pro Pro Phe Asn Pro Asn Val Ser Gly Pro Asn Asp Leu Arg His
370 375 380

Phe Asp Pro Glu Phe Thr Glu Glu Pro Val Pro Asn Ser Ile Gly Lys
385 390 395 400

Ser Pro Asp Ser Val Leu Val Thr Ala Ser Val Lys Glu Ala Ala Glu
405 410 415

Ala Phe Leu Gly Phe Ser Tyr Ala Pro Pro Thr Asp Ser Phe Leu
420 425 430

<210> 15
<211> 310
<212> PRT
<213> Homo sapiens

<220>
<221> MISC_FEATURE
<223> Sdc1

<400> 15

Met Arg Arg Ala Ala Leu Trp Leu Trp Leu Cys Ala Leu Ala Leu Ser
1 5 10 15

Leu Gln Pro Ala Leu Pro Gln Ile Val Ala Thr Asn Leu Pro Pro Glu
20 25 30

Asp Gln Asp Gly Ser Gly Asp Asp Ser Asp Asn Phe Ser Gly Ser Gly
35 40 45

Ala Gly Ala Leu Gln Asp Ile Thr Leu Ser Gln Gln Thr Pro Ser Thr
50 55 60

Trp Lys Asp Thr Gln Leu Leu Thr Ala Ile Pro Thr Ser Pro Glu Pro
65 70 75 80

Thr Gly Leu Glu Ala Thr Ala Ala Ser Thr Ser Thr Leu Pro Ala Gly
85 90 95

Glu Gly Pro Lys Glu Gly Glu Ala Val Val Leu Pro Glu Val Glu Pro
100 105 110

Gly Leu Thr Ala Arg Glu Gln Glu Ala Thr Pro Arg Pro Arg Glu Thr
115 120 125

Thr Gln Leu Pro Thr Thr His Leu Ala Ser Thr Thr Thr Ala Thr Thr
130 135 140

Ala Gln Glu Pro Ala Thr Ser His Pro His Arg Asp Met Gln Pro Gly
145 150 155 160

His His Glu Thr Ser Thr Pro Ala Gly Pro Ser Gln Ala Asp Leu His
165 170 175

Thr Pro His Thr Glu Asp Gly Gly Pro Ser Ala Thr Glu Arg Ala Ala
180 185 190

Glu Asp Gly Ala Ser Ser Gln Leu Pro Ala Ala Glu Gly Ser Gly Glu
195 200 205

Gln Asp Phe Thr Phe Glu Thr Ser Gly Glu Asn Thr Ala Val Val Ala
210 215 220

Val Glu Pro Asp Arg Arg Asn Gln Ser Pro Val Asp Gln Gly Ala Thr
225 230 235 240

Gly Ala Ser Gln Gly Leu Leu Asp Arg Lys Glu Val Leu Gly Gly Val
245 250 255

Ile Ala Gly Gly Leu Val Gly Leu Ile Phe Ala Val Cys Leu Val Gly
260 265 270

Phe Met Leu Tyr Arg Met Lys Lys Lys Asp Glu Gly Ser Tyr Ser Leu
275 280 285

Glu Glu Pro Lys Gln Ala Asn Gly Gly Ala Tyr Gln Lys Pro Thr Lys
290 295 300

Gln Glu Glu Phe Tyr Ala
305 310

<210> 16
<211> 398
<212> PRT
<213> Homo sapiens

<220>
<221> MISC_FEATURE
<223> Serpine2

<400> 16

Met Asn Trp His Leu Pro Leu Phe Leu Leu Ala Ser Val Thr Leu Pro
1 5 10 15

Ser Ile Cys Ser His Phe Asn Pro Leu Ser Leu Glu Glu Leu Gly Ser
20 25 30

Asn Thr Gly Ile Gln Val Phe Asn Gln Ile Val Lys Ser Arg Pro His
35 40 45

Asp Asn Ile Val Ile Ser Pro His Gly Ile Ala Ser Val Leu Gly Met
50 55 60

Leu Gln Leu Gly Ala Asp Gly Arg Thr Lys Lys Gln Leu Ala Met Val
65 70 75 80

Met Arg Tyr Gly Val Asn Gly Val Gly Lys Ile Leu Lys Lys Ile Asn
85 90 95

Lys Ala Ile Val Ser Lys Lys Asn Lys Asp Ile Val Thr Val Ala Asn
100 105 110

Ala Val Phe Val Lys Asn Ala Ser Glu Ile Glu Val Pro Phe Val Thr
115 120 125

Arg Asn Lys Asp Val Phe Gln Cys Glu Val Arg Asn Val Asn Phe Glu
130 135 140

Asp Pro Ala Ser Ala Cys Asp Ser Ile Asn Ala Trp Val Lys Asn Glu
145 150 155 160

Thr Arg Asp Met Ile Asp Asn Leu Leu Ser Pro Asp Leu Ile Asp Gly
165 170 175

Val Leu Thr Arg Leu Val Leu Val Asn Ala Val Tyr Phe Lys Gly Leu
180 185 190

Trp Lys Ser Arg Phe Gln Pro Glu Asn Thr Lys Lys Arg Thr Phe Val
195 200 205

Ala Ala Asp Gly Lys Ser Tyr Gln Val Pro Met Leu Ala Gln Leu Ser
210 215 220

Val Phe Arg Cys Gly Ser Thr Ser Ala Pro Asn Asp Leu Trp Tyr Asn
225 230 235 240

Phe Ile Glu Leu Pro Tyr His Gly Glu Ser Ile Ser Met Leu Ile Ala
245 250 255

Leu Pro Thr Glu Ser Ser Thr Pro Leu Ser Ala Ile Ile Pro His Ile
260 265 270

Ser Thr Lys Thr Ile Asp Ser Trp Met Ser Ile Met Val Pro Lys Arg
275 280 285

Val Gln Val Ile Leu Pro Lys Phe Thr Ala Val Ala Gln Thr Asp Leu
290 295 300

Lys Glu Pro Leu Lys Val Leu Gly Ile Thr Asp Met Phe Asp Ser Ser
305 310 315 320

Lys Ala Asn Phe Ala Lys Ile Thr Thr Gly Ser Glu Asn Leu His Val
325 330 335

Ser His Ile Leu Gln Lys Ala Lys Ile Glu Val Ser Glu Asp Gly Thr
340 345 350

Lys Ala Ser Ala Ala Thr Thr Ala Ile Leu Ile Ala Arg Ser Ser Pro
355 360 365

Pro Trp Phe Ile Val Asp Arg Pro Phe Leu Phe Phe Ile Arg His Asn
370 375 380

Pro Thr Gly Ala Val Leu Phe Met Gly Gln Ile Asn Lys Pro
385 390 395

<210> 17
<211> 314
<212> PRT
<213> Homo sapiens

<220>
<221> MISC_FEATURE
<223> Spp1

<400> 17

Met Arg Ile Ala Val Ile Cys Phe Cys Leu Leu Gly Ile Thr Cys Ala
1 5 10 15

Ile Pro Val Lys Gln Ala Asp Ser Gly Ser Ser Glu Glu Lys Gln Leu
20 25 30

Tyr Asn Lys Tyr Pro Asp Ala Val Ala Thr Trp Leu Asn Pro Asp Pro
35 40 45

Ser Gln Lys Gln Asn Leu Leu Ala Pro Gln Asn Ala Val Ser Ser Glu
50 55 60

Glu Thr Asn Asp Phe Lys Gln Glu Thr Leu Pro Ser Lys Ser Asn Glu
65 70 75 80

Ser His Asp His Met Asp Asp Met Asp Asp Glu Asp Asp Asp Asp His
85 90 95

Val Asp Ser Gln Asp Ser Ile Asp Ser Asn Asp Ser Asp Asp Val Asp
100 105 110

Asp Thr Asp Asp Ser His Gln Ser Asp Glu Ser His His Ser Asp Glu
115 120 125

Ser Asp Glu Leu Val Thr Asp Phe Pro Thr Asp Leu Pro Ala Thr Glu
130 135 140

Val Phe Thr Pro Val Val Pro Thr Val Asp Thr Tyr Asp Gly Arg Gly
145 150 155 160

Asp Ser Val Val Tyr Gly Leu Arg Ser Lys Ser Lys Lys Phe Arg Arg
165 170 175

Pro Asp Ile Gln Tyr Pro Asp Ala Thr Asp Glu Asp Ile Thr Ser His
180 185 190

Met Glu Ser Glu Glu Leu Asn Gly Ala Tyr Lys Ala Ile Pro Val Ala
195 200 205

Gln Asp Leu Asn Ala Pro Ser Asp Trp Asp Ser Arg Gly Lys Asp Ser
210 215 220

Tyr Glu Thr Ser Gln Leu Asp Asp Gln Ser Ala Glu Thr His Ser His
225 230 235 240

Lys Gln Ser Arg Leu Tyr Lys Arg Lys Ala Asn Asp Glu Ser Asn Glu
245 250 255

His Ser Asp Val Ile Asp Ser Gln Glu Leu Ser Lys Val Ser Arg Glu
260 265 270

Phe His Ser His Glu Phe His Ser His Glu Asp Met Leu Val Val Asp
275 280 285

Pro Lys Ser Lys Glu Glu Asp Lys His Leu Lys Phe Arg Ile Ser His
290 295 300

Glu Leu Asp Ser Ala Ser Ser Glu Val Asn
305 310

<210> 18
<211> 280
<212> PRT
<213> Homo sapiens

<220>
<221> MISC_FEATURE
<223> Cdca8

<400> 18

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

Arg Arg Arg Lys Leu Ala Ser Phe Leu Lys Asp Phe Asp Arg Glu Val
20 25 30

Glu Ile Arg Ile Lys Gln Ile Glu Ser Asp Arg Gln Asn Leu Leu Lys
35 40 45

Glu Val Asp Asn Leu Tyr Asn Ile Glu Ile Leu Arg Leu Pro Lys Ala
50 55 60

Leu Arg Glu Met Asn Trp Leu Asp Tyr Phe Ala Leu Gly Gly Asn Lys
65 70 75 80

Gln Ala Leu Glu Glu Ala Ala Thr Ala Asp Leu Asp Ile Thr Glu Ile
85 90 95

Asn Lys Leu Thr Ala Glu Ala Ile Gln Thr Pro Leu Lys Ser Ala Lys
100 105 110

Thr Arg Lys Val Ile Gln Val Asp Glu Met Ile Val Glu Glu Glu Glu
115 120 125

Glu Glu Glu Asn Glu Arg Lys Asn Leu Gln Thr Ala Arg Val Lys Arg
130 135 140

Cys Pro Pro Ser Lys Lys Arg Thr Gln Ser Ile Gln Gly Lys Gly Lys
145 150 155 160

Gly Lys Arg Ser Ser Arg Ala Asn Thr Val Thr Pro Ala Val Gly Arg
165 170 175

Leu Glu Val Ser Met Val Lys Pro Thr Pro Gly Leu Thr Pro Arg Phe
180 185 190

Asp Ser Arg Val Phe Lys Thr Pro Gly Leu Arg Thr Pro Ala Ala Gly
195 200 205

Glu Arg Ile Tyr Asn Ile Ser Gly Asn Gly Ser Pro Leu Ala Asp Ser
210 215 220

Lys Glu Ile Phe Leu Thr Val Pro Val Gly Gly Gly Glu Ser Leu Arg
225 230 235 240

Leu Leu Ala Ser Asp Leu Gln Arg His Ser Ile Ala Gln Leu Asp Pro
245 250 255

Glu Ala Leu Gly Asn Ile Lys Lys Leu Ser Asn Arg Leu Ala Gln Ile
260 265 270

Cys Ser Ser Ile Arg Thr His Lys
275 280

<210> 19
<211> 923
<212> PRT
<213> Homo sapiens

<220>
<221> MISC_FEATURE
<223> Nrp1

<400> 19

Met Glu Arg Gly Leu Pro Leu Leu Cys Ala Val Leu Ala Leu Val Leu
1 5 10 15

Ala Pro Ala Gly Ala Phe Arg Asn Asp Lys Cys Gly Asp Thr Ile Lys
20 25 30

Ile Glu Ser Pro Gly Tyr Leu Thr Ser Pro Gly Tyr Pro His Ser Tyr
35 40 45

His Pro Ser Glu Lys Cys Glu Trp Leu Ile Gln Ala Pro Asp Pro Tyr
50 55 60

Gln Arg Ile Met Ile Asn Phe Asn Pro His Phe Asp Leu Glu Asp Arg
65 70 75 80

Asp Cys Lys Tyr Asp Tyr Val Glu Val Phe Asp Gly Glu Asn Glu Asn
85 90 95

Gly His Phe Arg Gly Lys Phe Cys Gly Lys Ile Ala Pro Pro Pro Val
100 105 110

Val Ser Ser Gly Pro Phe Leu Phe Ile Lys Phe Val Ser Asp Tyr Glu
115 120 125

Thr His Gly Ala Gly Phe Ser Ile Arg Tyr Glu Ile Phe Lys Arg Gly
130 135 140

Pro Glu Cys Ser Gln Asn Tyr Thr Thr Pro Ser Gly Val Ile Lys Ser
145 150 155 160

Pro Gly Phe Pro Glu Lys Tyr Pro Asn Ser Leu Glu Cys Thr Tyr Ile
165 170 175

Val Phe Val Pro Lys Met Ser Glu Ile Ile Leu Glu Phe Glu Ser Phe
180 185 190

Asp Leu Glu Pro Asp Ser Asn Pro Pro Gly Gly Met Phe Cys Arg Tyr
195 200 205

Asp Arg Leu Glu Ile Trp Asp Gly Phe Pro Asp Val Gly Pro His Ile
210 215 220

Gly Arg Tyr Cys Gly Gln Lys Thr Pro Gly Arg Ile Arg Ser Ser Ser
225 230 235 240

Gly Ile Leu Ser Met Val Phe Tyr Thr Asp Ser Ala Ile Ala Lys Glu
245 250 255

Gly Phe Ser Ala Asn Tyr Ser Val Leu Gln Ser Ser Val Ser Glu Asp
260 265 270

Phe Lys Cys Met Glu Ala Leu Gly Met Glu Ser Gly Glu Ile His Ser
275 280 285

Asp Gln Ile Thr Ala Ser Ser Gln Tyr Ser Thr Asn Trp Ser Ala Glu
290 295 300

Arg Ser Arg Leu Asn Tyr Pro Glu Asn Gly Trp Thr Pro Gly Glu Asp
305 310 315 320

Ser Tyr Arg Glu Trp Ile Gln Val Asp Leu Gly Leu Leu Arg Phe Val
325 330 335

Thr Ala Val Gly Thr Gln Gly Ala Ile Ser Lys Glu Thr Lys Lys Lys
340 345 350

Tyr Tyr Val Lys Thr Tyr Lys Ile Asp Val Ser Ser Asn Gly Glu Asp
355 360 365

Trp Ile Thr Ile Lys Glu Gly Asn Lys Pro Val Leu Phe Gln Gly Asn
370 375 380

Thr Asn Pro Thr Asp Val Val Val Ala Val Phe Pro Lys Pro Leu Ile
385 390 395 400

Thr Arg Phe Val Arg Ile Lys Pro Ala Thr Trp Glu Thr Gly Ile Ser
405 410 415

Met Arg Phe Glu Val Tyr Gly Cys Lys Ile Thr Asp Tyr Pro Cys Ser
420 425 430

Gly Met Leu Gly Met Val Ser Gly Leu Ile Ser Asp Ser Gln Ile Thr
435 440 445

Ser Ser Asn Gln Gly Asp Arg Asn Trp Met Pro Glu Asn Ile Arg Leu
450 455 460

Val Thr Ser Arg Ser Gly Trp Ala Leu Pro Pro Ala Pro His Ser Tyr
465 470 475 480

Ile Asn Glu Trp Leu Gln Ile Asp Leu Gly Glu Glu Lys Ile Val Arg
485 490 495

Gly Ile Ile Ile Gln Gly Gly Lys His Arg Glu Asn Lys Val Phe Met
500 505 510

Arg Lys Phe Lys Ile Gly Tyr Ser Asn Asn Gly Ser Asp Trp Lys Met
515 520 525

Ile Met Asp Asp Ser Lys Arg Lys Ala Lys Ser Phe Glu Gly Asn Asn
530 535 540

Asn Tyr Asp Thr Pro Glu Leu Arg Thr Phe Pro Ala Leu Ser Thr Arg
545 550 555 560

Phe Ile Arg Ile Tyr Pro Glu Arg Ala Thr His Gly Gly Leu Gly Leu
565 570 575

Arg Met Glu Leu Leu Gly Cys Glu Val Glu Ala Pro Thr Ala Gly Pro
580 585 590

Thr Thr Pro Asn Gly Asn Leu Val Asp Glu Cys Asp Asp Asp Gln Ala
595 600 605

Asn Cys His Ser Gly Thr Gly Asp Asp Phe Gln Leu Thr Gly Gly Thr
610 615 620

Thr Val Leu Ala Thr Glu Lys Pro Thr Val Ile Asp Ser Thr Ile Gln
625 630 635 640

Ser Glu Phe Pro Thr Tyr Gly Phe Asn Cys Glu Phe Gly Trp Gly Ser
645 650 655

His Lys Thr Phe Cys His Trp Glu His Asp Asn His Val Gln Leu Lys
660 665 670

Trp Ser Val Leu Thr Ser Lys Thr Gly Pro Ile Gln Asp His Thr Gly
675 680 685

Asp Gly Asn Phe Ile Tyr Ser Gln Ala Asp Glu Asn Gln Lys Gly Lys
690 695 700

Val Ala Arg Leu Val Ser Pro Val Val Tyr Ser Gln Asn Ser Ala His
705 710 715 720

Cys Met Thr Phe Trp Tyr His Met Ser Gly Ser His Val Gly Thr Leu
725 730 735

Arg Val Lys Leu Arg Tyr Gln Lys Pro Glu Glu Tyr Asp Gln Leu Val
740 745 750

Trp Met Ala Ile Gly His Gln Gly Asp His Trp Lys Glu Gly Arg Val
755 760 765

Leu Leu His Lys Ser Leu Lys Leu Tyr Gln Val Ile Phe Glu Gly Glu
770 775 780

Ile Gly Lys Gly Asn Leu Gly Gly Ile Ala Val Asp Asp Ile Ser Ile
785 790 795 800

Asn Asn His Ile Ser Gln Glu Asp Cys Ala Lys Pro Ala Asp Leu Asp
805 810 815

Lys Lys Asn Pro Glu Ile Lys Ile Asp Glu Thr Gly Ser Thr Pro Gly
820 825 830

Tyr Glu Gly Glu Gly Glu Gly Asp Lys Asn Ile Ser Arg Lys Pro Gly
835 840 845

Asn Val Leu Lys Thr Leu Asp Pro Ile Leu Ile Thr Ile Ile Ala Met
850 855 860

Ser Ala Leu Gly Val Leu Leu Gly Ala Val Cys Gly Val Val Leu Tyr
865 870 875 880

Cys Ala Cys Trp His Asn Gly Met Ser Glu Arg Asn Leu Ser Ala Leu
885 890 895

Glu Asn Tyr Asn Phe Glu Leu Val Asp Gly Val Lys Leu Lys Lys Asp
900 905 910

Lys Leu Asn Thr Gln Ser Thr Tyr Ser Glu Ala
915 920

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<223> Mcam

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Cys Cys Pro Arg Val Ala Gly Val Pro Gly Glu Ala Glu Gln Pro Ala
20 25 30

Pro Glu Leu Val Glu Val Glu Val Gly Ser Thr Ala Leu Leu Lys Cys
35 40 45

Gly Leu Ser Gln Ser Gln Gly Asn Leu Ser His Val Asp Trp Phe Ser
50 55 60

Val His Lys Glu Lys Arg Thr Leu Ile Phe Arg Val Arg Gln Gly Gln
65 70 75 80

Gly Gln Ser Glu Pro Gly Glu Tyr Glu Gln Arg Leu Ser Leu Gln Asp
85 90 95

Arg Gly Ala Thr Leu Ala Leu Thr Gln Val Thr Pro Gln Asp Glu Arg
100 105 110

Ile Phe Leu Cys Gln Gly Lys Arg Pro Arg Ser Gln Glu Tyr Arg Ile
115 120 125

Gln Leu Arg Val Tyr Lys Ala Pro Glu Glu Pro Asn Ile Gln Val Asn
130 135 140

Pro Leu Gly Ile Pro Val Asn Ser Lys Glu Pro Glu Glu Val Ala Thr
145 150 155 160

Cys Val Gly Arg Asn Gly Tyr Pro Ile Pro Gln Val Ile Trp Tyr Lys
165 170 175

Asn Gly Arg Pro Leu Lys Glu Glu Lys Asn Arg Val His Ile Gln Ser
180 185 190

Ser Gln Thr Val Glu Ser Ser Gly Leu Tyr Thr Leu Gln Ser Ile Leu
195 200 205

Lys Ala Gln Leu Val Lys Glu Asp Lys Asp Ala Gln Phe Tyr Cys Glu
210 215 220

Leu Asn Tyr Arg Leu Pro Ser Gly Asn His Met Lys Glu Ser Arg Glu
225 230 235 240

Val Thr Val Pro Val Phe Tyr Pro Thr Glu Lys Val Trp Leu Glu Val
245 250 255

Glu Pro Val Gly Met Leu Lys Glu Gly Asp Arg Val Glu Ile Arg Cys
260 265 270

Leu Ala Asp Gly Asn Pro Pro Pro His Phe Ser Ile Ser Lys Gln Asn
275 280 285

Pro Ser Thr Arg Glu Ala Glu Glu Glu Thr Thr Asn Asp Asn Gly Val
290 295 300

Leu Val Leu Glu Pro Ala Arg Lys Glu His Ser Gly Arg Tyr Glu Cys
305 310 315 320

Gln Gly Leu Asp Leu Asp Thr Met Ile Ser Leu Leu Ser Glu Pro Gln
325 330 335

Glu Leu Leu Val Asn Tyr Val Ser Asp Val Arg Val Ser Pro Ala Ala
340 345 350

Pro Glu Arg Gln Glu Gly Ser Ser Leu Thr Leu Thr Cys Glu Ala Glu
355 360 365

Ser Ser Gln Asp Leu Glu Phe Gln Trp Leu Arg Glu Glu Thr Gly Gln
370 375 380

Val Leu Glu Arg Gly Pro Val Leu Gln Leu His Asp Leu Lys Arg Glu
385 390 395 400

Ala Gly Gly Gly Tyr Arg Cys Val Ala Ser Val Pro Ser Ile Pro Gly
405 410 415

Leu Asn Arg Thr Gln Leu Val Asn Val Ala Ile Phe Gly Pro Pro Trp
420 425 430

Met Ala Phe Lys Glu Arg Lys Val Trp Val Lys Glu Asn Met Val Leu
435 440 445

Asn Leu Ser Cys Glu Ala Ser Gly His Pro Arg Pro Thr Ile Ser Trp
450 455 460

Asn Val Asn Gly Thr Ala Ser Glu Gln Asp Gln Asp Pro Gln Arg Val
465 470 475 480

Leu Ser Thr Leu Asn Val Leu Val Thr Pro Glu Leu Leu Glu Thr Gly
485 490 495

Val Glu Cys Thr Ala Ser Asn Asp Leu Gly Lys Asn Thr Ser Ile Leu
500 505 510

Phe Leu Glu Leu Val Asn Leu Thr Thr Leu Thr Pro Asp Ser Asn Thr
515 520 525

Thr Thr Gly Leu Ser Thr Ser Thr Ala Ser Pro His Thr Arg Ala Asn
530 535 540

Ser Thr Ser Thr Glu Arg Lys Leu Pro Glu Pro Glu Ser Arg Gly Val
545 550 555 560

Val Ile Val Ala Val Ile Val Cys Ile Leu Val Leu Ala Val Leu Gly
565 570 575

Ala Val Leu Tyr Phe Leu Tyr Lys Lys Gly Lys Leu Pro Cys Arg Arg
580 585 590

Ser Gly Lys Gln Glu Ile Thr Leu Pro Pro Ser Arg Lys Ser Glu Leu
595 600 605

Val Val Glu Val Lys Ser Asp Lys Leu Pro Glu Glu Met Gly Leu Leu
610 615 620

Gln Gly Ser Ser Gly Asp Lys Arg Ala Pro Gly Asp Gln Gly Glu Lys
625 630 635 640

Tyr Ile Asp Leu Arg His
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<213> Homo sapiens

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<221> MISC_FEATURE
<223> Pbk

<400> 21

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20 25 30

Pro Phe Met Gln Lys Leu Gly Phe Gly Thr Gly Val Asn Val Tyr Leu
35 40 45

Met Lys Arg Ser Pro Arg Gly Leu Ser His Ser Pro Trp Ala Val Lys
50 55 60

Lys Ile Asn Pro Ile Cys Asn Asp His Tyr Arg Ser Val Tyr Gln Lys
65 70 75 80

Arg Leu Met Asp Glu Ala Lys Ile Leu Lys Ser Leu His His Pro Asn
85 90 95

Ile Val Gly Tyr Arg Ala Phe Thr Glu Ala Asn Asp Gly Ser Leu Cys
100 105 110

Leu Ala Met Glu Tyr Gly Gly Glu Lys Ser Leu Asn Asp Leu Ile Glu
115 120 125

Glu Arg Tyr Lys Ala Ser Gln Asp Pro Phe Pro Ala Ala Ile Ile Leu
130 135 140

Lys Val Ala Leu Asn Met Ala Arg Gly Leu Lys Tyr Leu His Gln Glu
145 150 155 160

Lys Lys Leu Leu His Gly Asp Ile Lys Ser Ser Asn Val Val Ile Lys
165 170 175

Gly Asp Phe Glu Thr Ile Lys Ile Cys Asp Val Gly Val Ser Leu Pro
180 185 190

Leu Asp Glu Asn Met Thr Val Thr Asp Pro Glu Ala Cys Tyr Ile Gly
195 200 205

Thr Glu Pro Trp Lys Pro Lys Glu Ala Val Glu Glu Asn Gly Val Ile
210 215 220

Thr Asp Lys Ala Asp Ile Phe Ala Phe Gly Leu Thr Leu Trp Glu Met
225 230 235 240

Met Thr Leu Ser Ile Pro His Ile Asn Leu Ser Asn Asp Asp Asp Asp
245 250 255

Glu Asp Lys Thr Phe Asp Glu Ser Asp Phe Asp Asp Glu Ala Tyr Tyr
260 265 270

Ala Ala Leu Gly Thr Arg Pro Pro Ile Asn Met Glu Glu Leu Asp Glu
275 280 285

Ser Tyr Gln Lys Val Ile Glu Leu Phe Ser Val Cys Thr Asn Glu Asp
290 295 300

Pro Lys Asp Arg Pro Ser Ala Ala His Ile Val Glu Ala Leu Glu Thr
305 310 315 320

Asp Val

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<211> 262
<212> PRT
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<223> Akr1cl

<400> 22

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Asp Ile Phe Tyr Thr Ser Lys Leu Pro Cys Thr Cys His Arg Pro Glu
20 25 30

Leu Val Gln Pro Cys Leu Glu Gln Ser Leu Arg Lys Leu Gln Leu Asp
35 40 45

Tyr Val Asp Leu Tyr Leu Ile His Cys Pro Val Ser Met Lys Pro Gly
50 55 60

Asn Asp Leu Ile Pro Thr Asp Glu Asn Gly Lys Leu Leu Phe Asp Thr
65 70 75 80

Val Asp Leu Cys Asp Thr Trp Glu Ala Met Glu Lys Cys Lys Asp Ser
85 90 95

Gly Leu Ala Lys Ser Ile Gly Val Ser Asn Phe Asn Arg Arg Gln Leu
100 105 110

Glu Met Ile Leu Asn Lys Pro Gly Leu Arg Tyr Lys Pro Val Cys Asn
115 120 125

Gln Val Glu Cys His Pro Tyr Leu Asn Gln Ser Lys Leu Leu Asp Tyr
130 135 140

Cys Lys Ser Lys Asp Ile Val Leu Val Ala Tyr Gly Ala Leu Gly Ser
145 150 155 160

Gln Arg Cys Lys Asn Trp Ile Glu Glu Asn Ala Pro Tyr Leu Leu Glu
165 170 175

Asp Pro Thr Leu Cys Ala Met Ala Glu Lys His Lys Gln Thr Pro Ala
180 185 190

Leu Ile Ser Leu Arg Tyr Leu Leu Gln Arg Gly Ile Val Ile Val Thr
195 200 205

Lys Ser Phe Asn Glu Lys Arg Ile Lys Glu Asn Leu Lys Val Phe Glu
210 215 220

Phe His Leu Pro Ala Glu Asp Met Ala Val Ile Asp Arg Leu Asn Arg
225 230 235 240

Asn Tyr Arg Tyr Ala Thr Ala Arg Ile Ile Ser Ala His Pro Asn Tyr
245 250 255

Pro Phe Leu Asp Glu Tyr
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<400> 23

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20 25 30

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

Asn Glu Ile Pro Ser Pro Gly Asp Asn Gly Trp Leu Asn Leu Tyr His
50 55 60

Phe Trp Arg Glu Thr Gly Thr His Lys Val His Leu His His Val Gln
65 70 75 80

Asn Phe Gln Lys Tyr Gly Pro Ile Tyr Arg Glu Lys Leu Gly Asn Val
85 90 95

Glu Ser Val Tyr Val Ile Asp Pro Glu Asp Val Ala Leu Leu Phe Lys
100 105 110

Ser Glu Gly Pro Asn Pro Glu Arg Phe Leu Ile Pro Pro Trp Val Ala
115 120 125

Tyr His Gln Tyr Tyr Gln Arg Pro Ile Gly Val Leu Leu Lys Lys Ser
130 135 140

Ala Ala Trp Lys Lys Asp Arg Val Ala Leu Asn Gln Glu Val Met Ala
145 150 155 160

Pro Glu Ala Thr Lys Asn Phe Leu Pro Leu Leu Asp Ala Val Ser Arg
165 170 175

Asp Phe Val Ser Val Leu His Arg Arg Ile Lys Lys Ala Gly Ser Gly
180 185 190

Asn Tyr Ser Gly Asp Ile Ser Asp Asp Leu Phe Arg Phe Ala Phe Glu
195 200 205

Ser Ile Thr Asn Val Ile Phe Gly Glu Arg Gln Gly Met Leu Glu Glu
210 215 220

Val Val Asn Pro Glu Ala Gln Arg Phe Ile Asp Ala Ile Tyr Gln Met
225 230 235 240

Phe His Thr Ser Val Pro Met Leu Asn Leu Pro Pro Asp Leu Phe Arg
245 250 255

Leu Phe Arg Thr Lys Thr Trp Lys Asp His Val Ala Ala Trp Asp Val
260 265 270

Ile Phe Ser Lys Ala Asp Ile Tyr Thr Gln Asn Phe Tyr Trp Glu Leu
275 280 285

Arg Gln Lys Gly Ser Val His His Asp Tyr Arg Gly Ile Leu Tyr Arg
290 295 300

Leu Leu Gly Asp Ser Lys Met Ser Phe Glu Asp Ile Lys Ala Asn Val
305 310 315 320

Thr Glu Met Leu Ala Gly Gly Val Asp Thr Thr Ser Met Thr Leu Gln
325 330 335

Trp His Leu Tyr Glu Met Ala Arg Asn Leu Lys Val Gln Asp Met Leu
340 345 350

Arg Ala Glu Val Leu Ala Ala Arg His Gln Ala Gln Gly Asp Met Ala
355 360 365

Thr Met Leu Gln Leu Val Pro Leu Leu Lys Ala Ser Ile Lys Glu Thr
370 375 380

Leu Arg Leu His Pro Ile Ser Val Thr Leu Gln Arg Tyr Leu Val Asn
385 390 395 400

Asp Leu Val Leu Arg Asp Tyr Met Ile Pro Ala Lys Thr Leu Val Gln
405 410 415

Val Ala Ile Tyr Ala Leu Gly Arg Glu Pro Thr Phe Phe Phe Asp Pro
420 425 430

Glu Asn Phe Asp Pro Thr Arg Trp Leu Ser Lys Asp Lys Asn Ile Thr
435 440 445

Tyr Phe Arg Asn Leu Gly Phe Gly Trp Gly Val Arg Gln Cys Leu Gly
450 455 460

Arg Arg Ile Ala Glu Leu Glu Met Thr Ile Phe Leu Ile Asn Met Leu
465 470 475 480

Glu Asn Phe Arg Val Glu Ile Gln His Leu Ser Asp Val Gly Thr Thr
485 490 495

Phe Asn Leu Ile Leu Met Pro Glu Lys Pro Ile Ser Phe Thr Phe Trp
500 505 510

Pro Phe Asn Gln Glu Ala Thr Gln Gln
515 520

The following "DNA" are from mRNA

FOS Human DNA

AACCGCATCTGCAGCGAGCAACTGAGAAGCCAAGACTGAGCCGGCGGCCGCGGCGCAGCG
AACGAGCAGTGACCGTGCTCCTACCCAGCTCTGCTTCACAGCGCCCACCTGTCTCCGCCC
CTCGGCCCCTCGCCCGGCTTTGCCTAACCGCCACGATGATGTTCTCGGGCTTCAACGCAG
ACTACGAGGCGTCATCCTCCCGCTGCAGCAGCGCGTCCCCGGCCGGGGATAGCCTCTCTT
ACTACCACTCACCCTTTCGGAGTCCCCGCCCCCTCCGCTGGGGCTTACTCCAGGGCTGGC
GTTGTGAAGACCATGACAGGAGGCCGAGCGCAGAGCATTGGCAGGAGGGGCAAGGTGGAA
CAGTTATCTCCTGAAGAAGAAGAGAAAAGGAGAATCCGAAGGGAAAGGAATAAGATGGCT

GCAGCCAAATGCCGCAACCGGAGGAGGGAGCTGACTGATACACTCCAAGCGGAGACAGAC
CAACTAGAAGATGAGAAGTCTGCTTTGCAGACCGAGATTGCCAACCTGCTGAAGGAGAAG
GAAAAACTAGAGTTCATCCTGGCAGCTCACCGACCTGCCTGCAAGATCCCTGATGACCTG
GGCTTCCCAGAAGAGATGTCTGTGGCTTCCCTTGATCTGACTGGGGGCCTGCCAGAGGTT
GCCACCCCGGAGTCTGAGGAGGCCTTCACCCTGCCTCTCCTCAATGACCCTGAGCCCAAG
CCCTCAGTGGAACCTGTCAAGAGCATCAGCAGCATGGAGCTGAAGACCGAGCCCTTTGAT
GACTTCCTGTTCCCAGCATCATCCAGGCCCAGTGGCTCTGAGACAGCCCGCTCCGTGCCA
GACATGGACCTATCTGGGTCCTTCTATGCAGCAGACTGGGAGCCTCTGCACAGTGGCTCC
CTGGGGATGGGGCCCATGGCCACAGAGCTGGAGCCCCTGTGCACTCCGGTGGTCACCTGT
ACTCCCAGCTGCACTGCTTACACGTCTTCCTTCGTCTTCACCTACCCCGAGGCTGACTCC
TTCCCCAGCTGTGCAGCTGCCCACCGCAAGGGCAGCAGCAGCAATGAGCCTTCCTCTGAC
TCGCTCAGCTCACCCACGCTGCTGGCCCTGTGAGGGGGCAGGGAAGGGGAGGCAGCCGGC
ACCCACAAGTGCCACTGCCCGAGCTGGTGCATTACAGAGAGGAGAAACACATCTTCCCTA
GAGGGTTCCTGTAGACCTAGGGAGGACCTTATCTGTGCGTGAAACACACCAGGCTGTGGG
CCTCAAGGACTTGAAAGCATCCATGTGTGGACTCAAGTCCTTACCTCTTCCGGAGATGTA
GCAAAACGCATGGAGTGTGTATTGTTCCCAGTGACACTTCAGAGAGCTGGTAGTTAGTAG
CATGTTGAGCCAGGCCTGGGTCTGTGTCTCTTTTCTCTTTCTCCTTAGTCTTCTCATAGC
ATTAACTAATCTATTGGGTTCATTATTGGAATTAACCTGGTGCTGGATATTTTCAAATTG
TATCTAGTGCAGCTGATTTTAACAATAACTACTGTGTTCCTGGCAATAGTGTGTTCTGAT
TAGAAATGACCAATATTATACTAAGAAAAGATACGACTTTATTTTCTGGTAGATAGAAAT
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TTTTATTGTGTTTTTAATTTATTTATTAAGATGGATTCTCAGATATTTATATTTTTATTT
TATTTTTTTCTACCTTGAGGTCTTTTGACATGTGGAAAGTGAATTTGAATGAAAAATTTA
AGCATTGTTTGCTTATTGTTCCAAGACATTGTCAATAAAAGCATTTAAGTT
GAATGCG

FOS Mouse Protein

MMFSGFNADYEASSSRCSSASPAGDSLSYYHSPADSFSSMGSPVNTQDFCADLSVSSANF
IPTVTAISTSPDLQWLVQPTLVSSVAPSQTRAPHPYGLPTQSAGAYARAGMVKTVSGGRA
QSIGRRGKVEQLSPEEEEKRRIRRERNKMAAAKCRNRRRELTDTLQAETDQLEDEKSALQ
TEIANLLKEKEKLEFILAAHRPACKIPDDLGFPEEMSVASLDLTGGLPEASTPESEEAFT
LPLLNDPEPKPSLEPVKSISNVELKAEPFDDFLFPASSRPSGSETSRSVPDVDLSGSFYA
ADWEPLHSNSLGMGPMVTELEPLCTPVVTCTPGCTTYTSSFVFTYPEADSFPSCAAAHRK
GSSSNEPSSDSLSSPTLLAL

FOS Mouse DNA

CAGCGAGCAACTGAGAAGACTGGATAGAGCCGGCGGTTCCGCGAACGAGCAGTGACCGCG
CTCCCACCCAGCTCTGCTCTGCAGCTCCCACCAGTGTCTACCCCTGGACCCCTTGCCGGG
CTTTCCCCAAACTTCGACCATGATGTTCTCGGGTTTCAACGCCGACTACGAGGCGTCATC
CTCCCGCTGCAGTAGCGCCTCCCCGGCCGGGGACAGCCTTTCCTACTACCATTCCCCAGC
CGACTCCTTCTCCAGCATGGGCTCTCCTGTCAACACACAGGACTTTTGCGCAGATCTGTC
CGTCTCTAGTGCCAACTTTATCCCCACGGTGACAGCCATCTCCACCAGCCCAGACCTGCA
GTGGCTGGTGCAGCCCACTCTGGTCTCCTCCGTGGCCCCATCGCAGACCAGAGCGCCCCA
TCCTTACGGACTCCCCACCCAGTCTGCTGGGGCTTACGCCAGAGCGGGAATGGTGAAGAC
CGTGTCAGGAGGCAGAGCGCAGAGCATCGGCAGAAGGGGCAAAGTAGAGCAGCTATCTCC
TGAAGAGGAAGAGAAACGGAGAATCCGAAGGGAACGGAATAAGATGGCTGCAGCCAAGTG
CCGGAATCGGAGGAGGGAGCTGACAGATACACTCCAAGCGGAGACAGATCAACTTGAAGA
TGAGAAGTCTGCGTTGCAGACTGAGATTGCCAATCTGCTGAAAGAGAAGGAAAAACTGGA
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TCCGGCATCATCTAGGCCCAGTGGCTCAGAGACCTCCCGCTCTGTGCCAGATGTGGACCT
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ACCCACGCTGCTGGCCCTGTGAGCAGTCAGAGAAGGCAAGGCAGCCGGCATCCAGACGTG
CCACTGCCCGAGCTGGTGCATTACAGAGAGGAGAAACACGTCTTCCCTCGAAGGTTCCCG
TCGACCTAGGGAGGACCTTACCTGTTCGTGAAACACACCAGGCTGTGGGCCTCAAGGACT
TGCAAGCATCCACATCTGGCCTCCAGTCCTCACCTCTTCCAGAGATGTAGCAAAAACAAA

ACAAAACAAAACAAAAAACCGCATGGAGTGTGTTGTTCCTAGTGACACCTGAGAGCTGGT
AGTTAGTAGAGCATGTGAGTCAAGGCCTGGTCTGTGTCTCTTTTCTCTTTCTCCTTAGTT
TTCTCATAGCACTAACTAATCTGTTGGGTTCATTATTGGAATTAACCTGGTGCTGGATTG
TATCTAGTGCAGCTGATTTTAACAATACCTACTGTGTTCCTGGCAATAGCGTGTTCCAAT
TAGAAACGACCAATATTAAACTAAGAAAAGATAGGACTTTATTTTCCAGTAGATAGAAAT
CAATAGCTATATCCATGTACTGTAGTCCTTCAGCGTCAATGTTCATTGTCATGTTACTGA
TCATGCATTGTCGAGGTGGTCTGAATGTTCTGACATTAACAGTTTTCCATGAAAACGTTT
TTATTGTGTTTTCAATTTATTTATTAAGATGGATTCTCAGATATTTATATTTTTATTTTA
TTTTTTTCTACCCTGAGGTCTTTCGACATGTGGAAAGTGAATTTGAATGAAAAATTTTAA
GCATTGTTTGCTTATTGTTCCAAGACATTGTCAATAAAAGCATTTAAGTTGAAAAAAAAA
AAAAAAA

CD93 Human DNA

CTTCTCTGCGCCGGAGTGGCTGCAGCTCACCCCTCAGCTCCCCTTGGGGCCCAGCTGGGA
GCCGAGATAGAAGCTCCTGTCGCCGCTGGGCTTCTCGCCTCCCGCAGAGGGCCACACAGA
GACCGGGATGGCCACCTCCATGGGCCTGCTGCTGCTGCTGCTGCTGCTCCTGACCCAGCC
CGGGGCGGGGACGGGAGCTGACACGGAGGCGGTGGTCTGCGTGGGGACCGCCTGCTACAC
GGCCCACTCGGGCAAGCTGAGCGCTGCCGAGGCCCAGAACCACTGCAACCAGAACGGGGG
CAACCTGGCCACTGTGAAGAGCAAGGAGGAGGCCCAGCACGTCCAGCGAGTACTGGCCCA
GCTCCTGAGGCGGGAGGCAGCCCTGACGGCGAGGATGAGCAAGTTCTGGATTGGGCTCCA
GCGAGAGAAGGGCAAGTGCCTGGACCCTAGTCTGCCGCTGAAGGGCTTCAGCTGGGTGGG
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CAAGCGCTGTGTGTCTCTGCTGCTGGACCTGTCCCAGCCGCTCCTTCCCAGCCGCCTCCC
CAAGTGGTCTGAGGGCCCCTGTGGGAGCCCAGGCTCCCCCGGAAGTAACATTGAGGGCTT
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CCTGTGCAAGGAGAAGGCCCCCGATGTGTTCGACTGGGGCAGCTCGGGCCCCCTCTGTGT
CAGCCCCAAGTATGGCTGCAACTTCAACAATGGGGGCTGCCACCAGGACTGCTTTGAAGG
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GACCTGTGCCTCTCGAAACCCTTGCAGCTCCAGCCCATGTCGTGGGGGGGCCACGTGCGT
CCTGGGACCCCATGGGAAAAACTACACGTGCCGCTGCCCCCAAGGGTACCAGCTGGACTC
GAGTCAGCTGGACTGTGTGGACGTGGATGAATGCCAGGACTCCCCCTGTGCCCAGGAGTG
TGTCAACACCCCTGGGGGCTTCCGCTGCGAATGCTGGGTTGGCTATGAGCCGGGCGGTCC
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CGGGGAGGACGGGACTCAGTGCCAGGACGTGGATGAGTGTGTGGGCCCGGGGGGCCCCCT
CTGCGACAGCTTGTGCTTCAACACACAAGGGTCCTTCCACTGTGGCTGCCTGCCAGGCTG
GGTGCTGGCCCCAAATGGGGTCTCTTGCACCATGGGGCCTGTGTCTCTGGGACCACCATC
TGGGCCCCCCGATGAGGAGGACAAAGGAGAGAAAGAAGGGAGCACCGTGCCCCGTGCTGC
AACAGCCAGTCCCACAAGGGGCCCCGAGGGCACCCCCAAGGCTACACCCACCACAAGTAG
ACCTTCGCTGTCATCTGACGCCCCCATCACATCTGCCCCACTCAAGATGCTGGCCCCCAG
TGGGTCCCCAGGCGTCTGGAGGGAGCCCAGCATCCATCACGCCACAGCTGCCTCTGGCCC
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CCTGGCTCTGGGGCTACTGGTCTATCGCAAGCGGAGAGCGAAGAGGGAGGAGAAGAAGGA
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AAGCTGTGTGTTGGCGTGCCACGGTGGGGATTTCGTGACTCTATAATGATTGTTACTCCC
CCTCCCTTTTCAAATTCCAATGTGACCAATTCCGGATCAGGGTGTGAGGAGGCCGGGGCT
AAGGGGCTCCCCTGAATATCTTCTCTGCTCACTTCCACCATCTAAGAGGAAAAGGTGAGT
TGCTCATGCTGATTAGGATTGAAATGATTTGTTTCTCTTCCTAGGATGAAAACTAAATCA
ATTAATTATTCAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAA
AAAAAAAAA

CD93 Mouse Protein

MAISTGLFLLLGLLGQPWAGAAADSQAVVCEGTACYTAHWGKLSAAEAQHRCNENGGNLA
TVKSEEEARHVQQALTQLLKTKAPLEAKMGKFWIGLQREKGNCTYHDLPMRGFSWVGGGE
DTAYSNWYKASKSSCIFKRCVSLILDLSLTPHPSHLPKWHESPCGTPEAPGNSIEGFLCK

FNFKGMCRPLALGGPGRVTYTTPFQATTSSLEAVPFASVANVACGDEAKSETHYFLCNEK
TPGIFHWGSSGPLCVSPKFGCSFNNGGCQQDCFEGGDGSFRCGCRPGFRLLDDLVTCASR
NPCSSNPCTGGGMCHSVPLSENYTCRCPSGYQLDSSQVHCVDIDECQDSPCAQDCVNTLG
SFHCECWVGYQPSGPKEEACEDVDECAAANSPCAQGCINTDGSFYCSCKEGYIVSGEDST
QCEDIDECSDARGNPCDSLCFNTDGSFRCGCPPGWELAPNGVFCSRGTVFSELPARPPQK
EDNDDRKESTMPPTEMPSSPSGSKDVSNRAQTTGLFVQSDIPTASVPLEIEIPSEVSDVW
FELGTYLPTTSGHSKPTHEDSVSAHSDTDGQNLLLFYILGTVVAISLLLVLALGILIYHK
RRAKKEEIKEKKPQNAADSYSWVPERAESQAPENQYSPTPGTDC

CD93 Mouse DNA

GAAAGCAGCAGTGCGCCTCTGCTCCCTTCAGAGCACAGCCTGGTGTCAAGGTCCAGGTTC
CACCGGCTGCTGCTGTCACCGCAGGGGAGTCTAGCCCCTCCCAGAAGGAGACACAGAAGA
ATGGCCATCTCAACTGGTTTGTTCCTGCTGCTGGGGCTCCTTGGCCAGCCCTGGGCAGGG
GCTGCTGCTGATTCACAGGCTGTGGTGTGCGAGGGGACTGCCTGCTATACAGCCCATTGG
GGCAAGCTGAGTGCCGCTGAAGCCCAGCATCGCTGCAATGAGAATGGAGGCAATCTTGCC
ACCGTGAAGAGTGAGGAGGAGGCCCGGCATGTTCAGCAAGCCCTGACTCAGCTCCTGAAG
ACCAAGGCACCCTTGGAAGCAAAGATGGGCAAATTCTGGATCGGGCTCCAGCGAGAGAAG
GGCAACTGTACGTACCATGATTTGCCAATGAGGGGCTTCAGCTGGGTGGGTGGTGGAGAG
GACACAGCTTATTCAAACTGGTACAAAGCCAGCAAGAGCTCCTGTATCTTTAAACGCTGT
GTGTCCCTCATACTGGACCTGTCCTTGACACCTCACCCCAGCCATCTGCCCAAGTGGCAT
GAGAGTCCCTGTGGGACCCCCGAAGCTCCAGGTAACAGCATTGAAGGTTTCCTGTGCAAG
TTCAACTTCAAAGGCATGTGTAGGCCACTGGCGCTGGGTGGTCCAGGGCGGGTGACCTAT
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CTGAAAAAAT

FOSB Human DNA

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FOSB Mouse DNA

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AATTC

FOSB Mouse Protein

MFQAFPGDYDSGSRCSSSPSAESQYLSSVDSFGSPPTAAASQECAGLGEMPGSFVPTVTA
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Dusp1 Human DNA

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Dusp1 Mouse DNA

CGGCGGGAGGAAAGCGCGGTGAAGCCAGATTAGGAGCAGCGAGCACTTGGGGACTTAGGG

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Dusp1 Mouse Protein

MVMEVGILDAGGLRALLREGAAQCLLLDCRSFFAFNAGHIAGSVNVRFSTIVRRRAKGAM
GLEHIVPNAELRGRLLAGAYHAVVLLDERSASLDGAKRDGTLALAAGALCREARSTQVFF
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ITTSPSC

Jun Human DNA

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Jun Mouse DNA

GTGACGACTGGTCAGCACCGCCGGAGAGCCGCTGTTGCTGGGACTGGTCTGCGGGCTCCA

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Jun Mouse Protein

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LSSGGGAPSYGAAGLAFPSQPQQQQQPPQPPHHLPQQIPVQHPRLQALKEEPQTVPEMPG
ETPPLSPIDMESQERIKAERKRMRNRIAASKCRKRKLERIARLEEKVKTLKAQNSELAST
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Dusp6 Human DNA

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ACTTCTTAA

Dusp6 Mouse DNA

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Dusp6 Mouse Protein

MIDTLRPVPFASEMAICKTVSWLNEQLELGNERLLLMDCRPQELYESSHIESAINVAIPG
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KLKDEGCRAFYLEGGFSKFQAEFALHCETNLDGSCSSSSPPLPVLGLGGLRISSDSSSDI
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PNLPNLFENAGEFKYKQIPISDHWSQNLSQFFPEAISFIDEARGKNCGVLVHCLAGISRS
VTVTVAYLMQKLNLSMNDAYDIVKMKKSNISPNFNFMGQLLDFERTLGLSSPCDNRVPTP

QLYFTTPSNQNVYQVDSLQST

Cdk1 Human DNA

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CTAACTATGGAAGATTATACCAAAATAGAGAAAATTGGAGAAGGTACCTATGGAGTTGTG
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Cdk1 Mouse DNA

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TCG

Cdk1 Mouse Protein

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PNIVSLQDVLMQDSRLYLIFEFLSMDLKKYLDSIPPGQFMDSSLVKSYLHQILQGIVFCH
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NQIKKM

Fignl1 Human DNA

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Fignl1 Mouse DNA

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CC

Fignl1 Mouse Protein

METSSSMSVETTRSVQVDEWQKNYCVVTSSICTPKQKADAYRALLLHIQYAYANSEISQV
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RPTVSPKDLELYENWNETFGCGK

Plk2 Human DNA

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Plk2 Mouse DNA

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Plk2 Mouse Protein

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GCSLELKNRMEYALNMLLQRCN

Rsad2 Human DNA

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Rsad2 Mouse DNA

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Rsad2 Mouse Protein

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DW

Sgk1 Human DNA

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Sgk1 Mouse DNA

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Sgk1 Mouse Protein

MTVKAEAARSTLTYSRMRGMVAILIAFMKQRRMGLNDFIQKIASNTYACKHAEVQSILKM
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FSYAPPVDSFL

Sdc1 Human DNA

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ACAGCCACCACGGCCCAGGAGCCCGCCACCTCCCACCCCCACAGGGACATGCAGCCTGGC
CACCATGAGACCTCAACCCCTGCAGGACCCAGCCAAGCTGACCTTCACACTCCCCACACA
GAGGATGGAGGTCCTTCTGCCACCGAGAGGGCTGCTGAGGATGGAGCCTCCAGTCAGCTC
CCAGCAGCAGAGGGCTCTGGGGAGCAGGACTTCACCTTTGAAACCTCGGGGGAGAATACG
GCTGTAGTGGCCGTGGAGCCTGACCGCCGGAACCAGTCCCCAGTGGATCAGGGGGCCACG
GGGGCCTCACAGGGCCTCCTGGACAGGAAAGAGGTGCTGGGAGGGGTCATTGCCGGAGGC
CTCGTGGGGCTCATCTTTGCTGTGTGCCTGGTGGGTTTCATGCTGTACCGCATGAAGAAG
AAGGACGAAGGCAGCTACTCCTTGGAGGAGCCGAAACAAGCCAACGGCGGTGCCTACCAG
AAACCCACCAAGCAGGAGGAGTTCTACGCC

Sdc1 Mouse DNA

ACTCCGCGGGAGAGGTGCGGGCCAGAGGAGACAGAGCCTAACGCAGAGGAAGGGACCTGG
CAGTCGGGAGCTGACTCCAGCCGGCGAAACCTACAGCCCTCGCTCGAGAGAGCAGCGAGC
TGGGCAGGAGCCTGGGACAGCAAAGCGCAGAGCAATCAGCAGAGCCGGCCCGGAGCTCCG
TGCAACCGGCAACTCGGATCCACGAAGCCCACCGAGCTCCCGCCGCCGGTCTGGGCAGCA
TGAGACGCGCGGCGCTCTGGCTCTGGCTCTGCGCGCTGGCGCTGCGCCTGCAGCCTGCCC
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GCAGCAACACCGAGACTGCTTTTACCTCTGTCCTGCCAGCCGGAGAGAAGCCCGAGGAGG
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CAGCTGTGGCTGCCGTAGAGCCCGGCCTGCGGAATCAGCCCCCGGTGGACGAAGGAGCCA
CAGGTGCTTCTCAGAGCCTTTTGGACAGGAAGGAAGTGCTGGGAGGTGTCATTGCCGGAG
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AGAAGGACGAAGGCAGCTACTCCTTGGAGGAGCCCAAACAAGCCAATGGCGGTGCCTACC
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CTGACCAGCCATAGCACTTACCCATAGAGACCGCTAGGGTTGGCCGTGCTGTGGTGGGGG
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CATGCGTACAACAGGGTATGGACTATCTGTATGGTGCCCCATTTTTGGCGGCCCGTAAGT
AGGCTAGGCTAGTCCAGGATACTGTGGAATAGCCACCTCTTGACCAGTCATGCCTGTGTG
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TCCCGGAAGTTGACAAGACACATCTTGAGTATGGCTGGCACTGGTTCCTCCATCAAGAAC
CAAGTTCACCTTCAGCTCCTGTGGCCCCGCCCCCAGGCTGGAGTCAGAAATGTTTCCCAA
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TTTTGCAGATGTAATAAACTTTAATATAAAGG

Sdc1 Mouse Protein

MRRAALWLWLCALALRLQPALPQIVAVNVPPEDQDGSGDDSDNFSGSGTGALPDTLSRQT
PSTWKDVWLLTATPTAPEPTSSNTETAFTSVLPAGEKPEEGEPVLHVEAEPGFTARDKEK
EVTTRPRETVQLPITQRASTVRVTTAQAAVTSHPHGGMQPGLHETSAPTAPGQPDHQPPR
VEGGGTSVIKEVVEDGTANQLPAGEGSGEQDFTFETSGENTAVAAVEPGLRNQPPVDEGA
TGASQSLLDRKEVLGGVIAGGLVGLIFAVCLVAFMLYRMKKKDEGSYSLEEPKQANGGAY
QKPTKQEEFYA

Serpine2 Human DNA

ATGAACTGGCATCTCCCCCTCTTCCTCTTGGCCTCTGTGACGCTGCCTTCCATCTGCTCC
CACTTCAATCCTCTGTCTCTCGAGGAACTAGGCTCCAACACGGGGATCCAGGTTTTCAAT
CAGATTGTGAAGTCGAGGCCTCATGACAACATCGTGATCTCTCCCCATGGGATTGCGTCG
GTCCTGGGGATGCTTCAGCTGGGGGCGGACGGCAGGACCAAGAAGCAGCTCGCCATGGTG
ATGAGATACGGCGTAAATGGAGTTGGTAAAATATTAAAGAAGATCAACAAGGCCATCGTC
TCCAAGAAGAATAAAGACATTGTGACAGTGGCTAACGCCGTGTTTGTTAAGAATGCCTCT
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CTGGTCCTCGTCAACGCAGTGTATTTCAAGGGTCTGTGGAAATCACGGTTCCAACCCGAG
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CTCATTGCAAGATCATCGCCTCCCTGGTTTATAGTAGACAGACCTTTTCTGTTTTTCATC
CGACATAATCCTACAGGTGCTGTGTTATTCATGGGGCAGATAAACAAACC
C

Serpine2 Mouse DNA

AGTGCAGTGGTTGCACGGGAGTGCGGGCTGCACGCGTCACCGTCACCGCCGCCTGTCCCC
CACCGCCGCGCAGCGCCGATCTCCCTCCCGGTTTCGGCCGCCACCTGGGGATCCAAGCGA
GGACGGGCTGTCCTTGTTGGAAGGAACCATGAATTGGCATTTTCCTTTCTTCATCTTGAC
CACAGTGACTTTATACTCTGTGCACTCCCAGTTCAACTCTCTGTCACTGGAGGAACTAGG
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CAAGACAAAGAAGCAGCTCTCCACGGTGATGCGATATAATGTAAACGGAGTTGGTAAAGT
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CAGGACCCCGAATGGCTTATGGTACAACTTCATTGAGCTGCCCTACCATGGTGAGAGCAT
CAGCATGCTGATCGCCCTGCCAACAGAGAGCTCCACCCCACTGTCTGCCATCATCCCTCA
CATCACTACCAAGACCATTGATAGCTGGATGAACACCATGGTACCCAAGAGGATGCAGCT
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ATTTGCCTTTTTAATTCTTTTTCCTCTCACTTCCACCCAAAGGCTTGAGGGTGGCAAGGG
ATGGAGCTAGCAAAAGCCGTAGCCTCTTCGTGTGTTGTTTCTGTTGCTGTTGCTCTTGTT
GTTTTATATACTGCATGTGTTCACTAAAATAAAGTTGGAAAACT

Serpine2 Mouse Protein

MNWHFPFFILTTVTLYSVHSQFNSLSLEELGSNTGIQVFNQIIKSRPHENVVVSPHGIAS
ILGMLQLGADGKTKKQLSTVMRYNVNGVGKVLKKINKAIVSKKNKDIVTVANAVFLRNGF
KMEVPFAVRNKDVFQCEVQNVNFQDPASASESINFWVKNETRGMIDNLLSPNLIDGALTR
LVLVNAVYFKGLWKSRFQPESTKKRTFVAGDGKSYQVPMLAQLSVFRSGSTRTPNGLWYN
FIELPYHGESISMLIALPTESSTPLSAIIPHITTKTIDSWMNTMVPKRMQLVLPKFTAVA
QTDLKEPLKALGITEMFEPSKANFTKITRSESLHVSHILQKAKIEVSEDGTKASAATTAI
LIARSSPPWFIVDRPFLFSIRHNPTGAILFLGQVNKP

Spp1 Human DNA

GACCAGACTCGTCTCAGGCCAGTTGCAGCCTTCTCAGCCAAACGCCGACCAAGGAAAACT
CACTACCATGAGAATTGCAGTGATTTGCTTTTGCCTCCTAGGCATCACCTGTGCCATACC
AGTTAAACAGGCTGATTCTGGAAGTTCTGAGGAAAAGCAGCTTTACAACAAATACCCAGA
TGCTGTGGCCACATGGCTAAACCCTGACCCATCTCAGAAGCAGAATCTCCTAGCCCCACA
GAATGCTGTGTCCTCTGAAGAAACCAATGACTTTAAACAAGAGACCCTTCCAAGTAAGTC
CAACGAAAGCCATGACCACATGGATGATATGGATGATGAAGATGATGATGACCATGTGGA
CAGCCAGGACTCCATTGACTCGAACGACTCTGATGATGTAGATGACACTGATGATTCTCA
CCAGTCTGATGAGTCTCACCATTCTGATGAATCTGATGAACTGGTCACTGATTTTCCCAC
GGACCTGCCAGCAACCGAAGTTTTCACTCCAGTTGTCCCCACAGTAGACACATATGATGG
CCGAGGTGATAGTGTGGTTTATGGACTGAGGTCAAAATCTAAGAAGTTTCGCAGACCTGA
CATCCAGTACCCTGATGCTACAGACGAGGACATCACCTCACACATGGAAAGCGAGGAGTT
GAATGGTGCATACAAGGCCATCCCCGTTGCCCAGGACCTGAACGCGCCTTCTGATTGGGA
CAGCCGTGGGAAGGACAGTTATGAAACGAGTCAGCTGGATGACCAGAGTGCTGAAACCCA
CAGCCACAAGCAGTCCAGATTATATAAGCGGAAAGCCAATGATGAGAGCAATGAGCATTC
CGATGTGATTGATAGTCAGGAACTTTCCAAAGTCAGCCGTGAATTCCACAGCCATGAATT
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TATTTTAATATTTGTTATTCTCTCATGAATAGAAATTTATGTAGAAGCAAACAAAATACT
TTTACCCACTTAAAAAGAGAATATAACATTTTATGTCACTATAATCTTTTGTTTTTTAAG
TTAGTGTATATTTTGTTGTGATTATCTTTTTGTGGTGTGAATAA

Spp1 Mouse DNA

CTTGCTTGGGTTTGCAGTCTTCTGCGGCAGGCATTCTCGGAGGAAACCAGCCAAGGACTA
ACTACGACCATGAGATTGGCAGTGATTTGCTTTTGCCTGTTTGGCATTGCCTCCTCCCTC
CCGGTGAAAGTGACTGATTCTGGCAGCTCAGAGGAGAAGCTTTACAGCCTGCACCCAGAT
CCTATAGCCACATGGCTGGTGCCTGACCCATCTCAGAAGCAGAATCTCCTTGCGCCACAG
AATGCTGTGTCCTCTGAAGAAAAGGATGACTTTAAGCAAGAAACTCTTCCAAGCAATTCC
AATGAAAGCCATGACCACATGGACGACGATGATGACGATGATGATGACGATGGAGACCAT
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TCTGATGAGACCGTCACTGCTAGTACACAAGCAGACACTTTCACTCCAATCGTCCCTACA
GTCGATGTCCCCAACGGCCGAGGTGATAGCTTGGCTTATGGACTGAGGTCAAAGTCTAGG
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CAAAAGCTTCTGCACTTTGCTTCTGTTCTTCCTGTACAAGAAATGCAAACGGCCACTGCA
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AACAAGCAGAATTAAAAGAGAAACTGTAACAGTCTATATCACTATACCCTTTTAGTTTTA
TAATTAGCATATATTTTGTTGTGATTATTTTTTTTGTTGGTGTGAATAAATCTTGTAACG
AATGT

Spp1 Mouse Protein

MRLAVICFCLFGIASSLPVKVTDSGSSEEKLYSLHPDPIATWLVPDPSQKQNLLAPQNAV
SSEEKDDFKQETLPSNSNESHDHMDDDDDDDDDDGDHAESEDSVDSDESDESHHSDESDE
TVTASTQADTFTPIVPTVDVPNGRGDSLAYGLRSKSRSFQVSDEQYPDATDEDLTSHMKS
GESKESLDVIPVAQLLSMPSDQDNNGKGSHESSQLDEPSLETHRLEHSKESQESADQSDV
IDSQASSKASLEHQSHKFHSHKDKLVLDPKSKEDDRYLKFRISHELESSSSEVN

Cdca8 Human DNA

GGTTGACTGTAGAGCCGCTCTCTCTCACTGGCACAGCGAGGTTTTGCTCAGCCCTTGTCT
CGGGACCGCAGGTACGTGTCTGGCGACTTCTTCGGGTGGTCCCCGTCCGCCCTCCTCGTC
CCTACCCAGTTTCTTGCTTCCCTGCCCCATCTCCGCCGCTCCCCGCAGCCTCCGCCGAGC
GCCATGGCTCCTAGGAAGGGCAGTAGTCGGGTGGCCAAGACCAACTCCTTACGGAGGCGG
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TTCAATAAATTCTGGTTTTGTGTTTTCTTTTGT

Cdca8 Mouse DNA

GGAATTGAATTGGGTGGCGGTTAACCGAGGAGCCGCCCGTCCCTTAGTTGGAGCTGTGAG
GGTTCCTCAGACTGTGTTTTGGGACCTGCAGGTAGGTTTCGGCAGAGTTCTGGAAACCTA
GACTCCAACGACTGAACTTTCTCAGCTCTCCGACCGCTCACACCCTCTCCCCGTCTCAGT
CGCGGAGCCGGCTGCTTGGCCCCTCGCTCGACGCAGCCAGGCGCCATGGCTCCCAAGAAA
CGCAGCAGCCGCGGAACCAGGACCAACACGCTGCGGAGCCGGAAGCTCGCCTCCTTCCTG
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TTCAAGTTGGTTTTCTGTTGCTGAGGCTTTCATACACATCAGTTACCATCTCAGCTGATT
TGTCTACTGAAAGCTTGCTGTTTTCAATAAATCTTAGTTTGCCATGGTTTTA
AGTC

Cdca8 Mouse Protein

MAPKKRSSRGTRTNTLRSRKLASFLKDFDREVQVRTKQIESDRQTLLKEVENLYNIEILR
LPKALQGMKWLDYFALGGNKQALEEAAKADRDITEINNLTAEAIQTPLKSVKKRKVIEVE
ESIKEEEEEEEEGGGGGGRTKKSHKNLRSAKVKRCLPSKKRTQSIQGRGRSKRLSHDFVT
PAMSRLEPSLVKPTPGMTPRFDSRVFKTPGLRTPAAKEQVYNISINGSPLADSKEISLSV
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Nrp1 Human DNA

ATGGAGAGGGGGCTGCCGCTCCTCTGCGCCGTGCTCGCCCTCGTCCTCGCCCCGGCCGGC
GCTTTTCGCAACGATGAATGTGGCGATACTATAAAAATTGAAAGCCCCGGGTACCTTACA
TCTCCTGGTTATCCTCATTCTTATCACCCAAGTGAAAAATGCGAATGGCTGATTCAGGCT
CCGGACCCATACCAGAGAATTATGATCAACTTCAACCCTCACTTCGATTTGGAGGACAGA

GACTGCAAGTATGACTACGTGGAAGTCTTCGATGGAGAAAATGAAAATGGACATTTTAGG
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ATCAAATTTGTCTCTGACTACGAAACACATGGTGCAGGATTTTCCATACGTTATGAAATT
TTCAAGAGAGGTCCTGAATGTTCCCAGAACTACACAACACCTAGTGGAGTGATAAAGTCC
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Nrp1 Mouse DNA

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GG

Nrp1 Mouse Protein

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Mcam Human DNA

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Mcam Mouse DNA

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Mcam Mouse Protein

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Pbk Human DNA

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Pbk Mouse DNA

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Pbk Mouse Protein

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Akr1c1 Human DNA

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CCAGTCCTTTGTGCCTTGGCAAAAAAGCACAAGCGAACCCCAGCCCTGATTGCCCTGCGC
TACCAGCTACAGCGTGGGGTTGTGGTCCTGGCCAAGAGCTACAATGAGCAGCGCATCAGA
CAGAACGTGCAGGTGTTTGAATTCCAGTTGACTTCAGAGGAGATGAAAGCCATAGATGGC
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TTTTCTGATGAATATTAACATGGAGGGCATTGCATGAGGTCTGCCAGAAGGCCCTGCGTG
TGGATGGTGACACAGAGGATGGCTCTATGCTGGTGACTGGACACATCGCCTCTGGTTAAA
TCTCTCCTGCTTGGTGATTTCAGCAAGCTACAGCAAAGCCCATTGGCCAGAAAGGAAAGA
CAATAATTTTGTTTTTTCATTTTGAAAAAATTAAATGCTCTCTCCTAAAGATTCTTCACC
TAAAAAA

Akr1c1 Human Protein

MDSKYQCVKLNDGHFMPVLGFGTYAPAEVPKSKALEATKLAIEAGFRHIDSAHLYNNEEQ
VGLAIRSKIADGSVKREDIFYTSKLWCNSHRPELVRPALERSLKNLQLDYVDLYLIHFPV
SVKPGEEVIPKDENGKILFDTVDLCATWEAVEKCKDAGLAKSIGVSNFNRRQLEMILNKP
GLKYKPVCNQVECHPYFNQRKLLDFCKSKDIVLVAYSALGSHREEPWVDPNSPVLLEDPV
LCALAKKHKRTPALIALRYQLQRGVVVLAKSYNEQRIRQNVQVFEFQLTSEEMKAIDGLN
RNVRYLTLDIFAGPPNYPFSDEY

Akr1cl Mouse DNA

TTGTCCTGACTCTGTTCTGCAGCCCTGATTGATTAGTAGCAGCTTGGTTACAATACATTT
TTGTCATCTGCATTGACCTGGTCTTTAAGTTATATTGGATTTATGTTGGATTTAAGTGGA
CCCACAACACTTTGAGGAAGAAGAAGACACTCTTCTTACTTTGGAGTACCCAGTGATATC
AGGAAAGTCAGAGGCAGAGCCTGCAGATGAATCCCAAGCGCTACATGGAACTAAGTGATG
GCCACCACATTCCTGTGCTTGGCTTTGGAACCTTTGTCCCAGGAGAGGTTTCCAAGAGTA
TGGTTGCAAAAGCCACCAAAATAGCTATAGATGCTGGATTCCGCCATATTGACTCAGCTT
ATTTCTACCAAAATGAGGAGGAAGTAGGGCTGGCCATCCGAAGCAAGGTTGCTGATGGCA
CTGTGAGGAGAGAAGATATATTCTACACTTCAAAGCTTCCCTGCACATGTCATAGACCAG
AGCTGGTCCAGCCTTGCTTGGAACAATCCCTGAGAAAGCTTCAGCTGGATTATGTTGATC
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CTCACCCCAATTATCCATTTTTGGATGAATATTAACGCGGAAGCCTTTGTTGTGACATCG
CTCAGAGGGAGCAATGTGGGAGATGCTGTGGATGTTGATCAGCATCACCTCTGGTCGACG
TCGACATCACCGTCAACCCACACTGAACTGGATGGAGAGGGGTGGCCATGGTGTTTTGTG
ATACTTTGAAGACAATAAAGTTTTGGTCTATGAGGT

Akr1cl Mouse Protein

MNPKRYMELSDGHHIPVLGFGTFVPGEVSKSMVAKATKIAIDAGFRHIDSAYFYQNEEEV
GLAIRSKVADGTVRREDIFYTSKLPCTCHRPELVQPCLEQSLRKLQLDYVDLYLIHCPVS
MKPGNDLIPTDENGKLLFDTVDLCDTWEAMEKCKDSGLAKSIGVSNFNRRQLEMILNKPG
LRYKPVCNQVECHPYLNQSKLLDYCKSKDIVLVAYGALGSQRCKNWIEENAPYLLEDPTL
CAMAEKHKQTPALISLRYLLQRGIVIVTKSFNEKRIKENLKVFEFHLPAEDMAVIDRLNR
NYRYATARIISAHPNYPFLDEY

Cyp11a1 Human DNA

GGGCGCTGAAGTGGAGCAGGTACAGTCACAGCTGTGGGGACAGCATGCTGGCCAAGGGTC
TTCCCCCACGCTCAGTCCTGGTCAAAGGCTACCAGACCTTTCTGAGTGCCCCCAGGGAGG
GGCTGGGGCGTCTCAGGGTGCCCACTGGCGAGGGAGCTGGCATCTCCACCCGCAGTCCTC
GCCCCTTCAATGAGATCCCCTCTCCTGGTGACAATGGCTGGCTAAACCTGTACCATTTCT
GGAGGGAGACGGGCACACACAAAGTCCACCTTCACCATGTCCAGAATTTCCAGAAGTATG
GCCCGATTTACAGGGAGAAGCTCGGCAACGTGGAGTCGGTTTATGTCATCGACCCTGAAG
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GGGTCGCCTATCACCAGTATTACCAGAGACCCATAGGAGTCCTGTTGAAGAAGTCGGCAG
CCTGGAAGAAAGACCGGGTGGCCCTGAACCAGGAGGTGATGGCTCCAGAGGCCACCAAGA
ACTTTTTGCCCCTGTTGGATGCAGTGTCTCGGGACTTCGTCAGTGTCCTGCACAGGCGCA
TCAAGAAGGCGGGCTCCGGAAATTACTCGGGGGACATCAGTGATGACCTGTTCCGCTTTG
CCTTTGAGTCCATCACTAACGTCATTTTTGGGGAGCGCCAGGGGATGCTGGAGGAAGTAG
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ATGTGGCTGCATGGGACGTGATTTTCAGTAAAGCTGACATATACACCCAGAACTTCTACT
GGGAATTGAGACAGAAAGGAAGTGTTCACCACGATTACCGTGGCATGCTCTACAGACTCC
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ACATGGCCACGATGCTACAGCTGGTCCCCCTCCTCAAAGCCAGCATCAAGGAGACACTAA
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AAATCCAACACCTCAGCGATGTGGGCACCACATTCAACCTCATTCTGATGCCTGAAAAGC
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TGGCCTGCAGCCACATGGGAGGAAGGCCCAGGGGTGGGGCCCATGGGGTCTCTGCATCTT
CAGTCGTCTGTCCCAAGTCCTGCTCCTTTCTGCCCAGCCTGCTCAGCAGGTTGAATGGGT
TCTCAGTGGTCACCTTCCTCAGCTCAGCTGGGCCACTCCTCTTCACCCACCCCATGGAGA

CAATAAACAGCTGAACCATCG

Cyp11a1 Mouse DNA

AAGTGGCAGTCGTGGGGACAGTATGCTGGCTAAAGGACTTTCCCTGCGCTCAGTGCTGGT
CAAAGGCTGCCAACCTTTCCTGAGCCCTACGTGGCAGGGTCCAGTGCTGAGTACTGGAAA
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CAATGGTTGGCTAAACCTGTACCACTTCTGGAGGGAGAGTGGCACACAGAAAATCCATTA
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CAACCCGGAGCGGTTCCTTGTGCCCCCCTGGGTGGCCTATCACCAGTATTATCAGAGGCC
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GGACTTCATCAAAGTCTTACACAGACGCATCAAGCAGCAAAATTCTGGAAATTTCTCAGG
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GGAGCGCATGGGGATGCTGGAGGAGATCGTGGATCCCGAGGCCCAGCGGTTCATCAATGC
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ACTCCTCAGAACTAAGACCTGGAAGGACCATGCAGCTGCCTGGGATGTGATTTTCAATAA
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GTACCCTGGTGTCCTTTATAGCCTCCTGGGGGGCAACAAGCTGCCCTTCAAGAACATCCA
GGCCAACATTACCGAGATGCTGGCAGGAGGGGTGGACACGACCTCCATGACCCTGCAGTG
GAACCTTTATGAGATGGCACACAACTTGAAGGTACAGGAGATGCTGCGGGCTGAAGTCCT
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CAATCTGCTGGAGAACTTCAGAATTGAAGTTCAAAATCTCCGTGATGTGGGGACCAAGTT
CAGCCTCATCCTGATGCCTGAGAACCCCATCCTCTTCAACTTCCAGCCTCTCAAGCAGGA
CCTGGGCCCAGCCGTGACCAGAAAAGACAACACTGTGAACTGAAGGCTGGAGTCACATGG

GGAGGTGGCCCATGGGGCATTTGAGGGTGGTATCTCTGTATCTTCAGAAACAGCACTCTG
TGATTACCTGCCCAGGTTAGCTGGGCTCTCCTCTCCTTCATCCTCTTTCCCTCTTTCCCT
ACCCAGGGAGTTAATAAACACTTGAACACTGAGG

Cyp11a1 Mouse Protein

MLAKGLSLRSVLVKGCQPFLSPTWQGPVLSTGKGAGTSTSSPRSFNEIPSPGDNGWLNLY
HFWRESGTQKIHYHQMQSFQKYGPIYREKLGTLESVYIVDPKDASILFSCEGPNPERFLV
PPWVAYHQYYQRPIGVLFKSSDAWKKDRIVLNQEVMAPGAIKNFVPLLEGVAQDFIKVLH
RRIKQQNSGNFSGVISDDLFRFSFESISSVIFGERMGMLEEIVDPEAQRFINAVYQMFHT
SVPMLNLPPDFFRLLRTKTWKDHAAAWDVIFNKADEYTQNFYWDLRQKRDFSQYPGVLYS
LLGGNKLPFKNIQANITEMLAGGVDTTSMTLQWNLYEMAHNLKVQEMLRAEVLAARRQAQ
GDMAKMVQLVPLLKASIKETLRLHPISVTLQRYTVNDLVLRNYKIPAKTLVQVASFAMGR
DPGFFPNPNKFDPTRWLEKSQNTTHFRYLGFGWGVRQCLGRRIAELEMTILLINLLENFR
IEVQNLRDVGTKFSLILMPENPILFNFQPLKQDLGPAVTRKDNTVN

CLAIMS

What is claimed is:

1. An isolated, non-native highly engraftable hematopoietic stem cell (heHSC), wherein the heHSC is Sca-1+, c-kit+ and Lin- (SKL).

2. The isolated heHSC of claim 1, wherein the heHSC is CD48-.

3. The isolated heHSC of claims 1-2, wherein the heHSC is CD150+.

4. The isolated heHSC of claims 1-3, wherein the heHSC is CD93+.

5. The isolated heHSC of claims 1-4, wherein the heHSC is CD34-.

6. The isolated heHSC of claims 1-5, wherein the heHSC is OPN+.

7. The isolated heHSC of claims 1-6, wherein the heHSC does not express an immunophenotypic means of identifying human hematopoietic stem cells.

8. The isolated heHSC of claims 1-7, wherein the heHSC is prepared by contacting hematopoietic stem cells and/or progenitor cells with at least one CXCR2 agonist and at least one CXCR4 antagonist, VLA-4 antagonist, $\alpha_9\beta_1$ antagonist, $\alpha_9\beta_1$ integrin/VLA-4 antagonist or combination thereof.

9. The isolated heHSC of claim 8, wherein the heHSC is prepared by contacting hematopoietic stem cells and/or progenitor cells with at least one CXCR2 agonist and at least one CXCR4 antagonist.

10. The isolated heHSC of claims 1-9, wherein the contacting is performed *in vivo*.

11. The isolated heHSC of claims 1-9, wherein the contacting is performed *in vitro*.

12. The isolated heHSC of claims 1-11, wherein the at least one CXCR2 agonist comprises GROβ or an analog or derivative thereof.

13. The isolated heHSC of claims 1-11, wherein the at least one CXCR2 agonist comprises GROβ-Δ4 or an analog or derivative thereof.

14. The isolated heHSC of claims 1-13, wherein the at least one CXCR4 antagonist comprises plerixafor or an analog or derivative thereof.

15. The isolated heHSC of claims 1-14, wherein the at least one CXCR2 agonist is GROβ or an analog or derivative thereof, and wherein the at least one CXCR4 antagonist is plerixafor or an analog or derivative thereof.

16. The isolated heHSC of claims 1-15, wherein upon transplant of the heHSC in a subject the heHSC demonstrates increased engrafting ability relative to engraftment of the same quantity of hematopoietic stem cells contacted with granulocyte colony-stimulating factor (G-CSF), a chemotherapeutic agent, or a combination thereof.

17. The isolated heHSC of claim 16, wherein the engrafting ability is increased by at least about two-fold.

18. The isolated heHSC of claims 1-17, wherein upon engraftment in a subject the heHSC demonstrates increased donor chimerism relative to engraftment of the same quantity of hematopoietic stem cells contacted with G-CSF, a chemotherapeutic agent, or a combination thereof.

19. The isolated heHSC of claim 18, wherein the donor chimerism is increased by at least about two fold.

20. The isolated heHSC of claim 18, wherein the donor chimerism is at least about 50%.

21. The isolated heHSC of claims 1-20, wherein the heHSC is substantially pure.

22. The isolated heHSC of claims 1-21, wherein the heHSC is non-quiescent.

23. The isolated heHSC of claims 1-22, wherein the heHSC is OPN+.

24. The isolated heHSC of claims 1-23, wherein the heHSC comprises a unique transcriptome relative to hematopoietic stem cells contacted with granulocyte colony-stimulating factor (G-CSF), a chemotherapeutic agent, or a combination thereof.

25. The isolated heHSC of claims 1-24, wherein the heHSC differentially express one or more of the genes selected from the group consisting of Fos, CD93, Fosb, Dusp1, Jun, Dusp6, Cdk1, Fignl1, Plk2, Rsad2, Sgk1, Sdc1, Serpine2, Spp1, Cdca8, Nrp1, Mcam, Pbk, Akr1cl and Cyp11a1, relative to one or more genes expressed by hematopoietic stem cells mobilized using G-CSF.

26. The isolated heHSC of claims 1-25, wherein the heHSC comprises at least a unique transcriptome or a unique phenotype as compared to a naturally occurring HSC.

27. An isolated population of cells comprising a plurality of heHSC's of claims 1-26, wherein the isolated population has a unique cell surface marker expression profile as compared to a naturally occurring population of HSC.

28. An isolated population of cells comprising a plurality of heHSC's of claims 1-26, wherein the isolated population has a unique transcriptome profile as compared to a naturally occurring population of HSC.

29. The isolated heHSC of claims 1-26, wherein the heHSC is transformed to express a polynucleotide.

30. The isolated heHSC of claims 1-27, wherein the heHSC is transformed with an expression vector to express a polynucleotide.

31. The isolated heHSC of claim 28, wherein the expression vector comprises a viral vector selected from the group consisting of a retrovirus, a herpes simplex, a lentivirus, an adenovirus, and an adeno-associated virus.

32. The isolated heHSC of claims 26-29, wherein the heHSC is transfected with an expression vector that comprises the polynucleotide.

33. The isolated heHSC of claims 26-30, wherein the polynucleotide comprises an exogenous polynucleotide.

34. The use of the isolated heHSC of claims 1-27 to deliver an exogenous polynucleotide to a subject in need thereof.

35. A method of transforming the isolated heHSC of claims 1-31, wherein the method comprises contacting the heHSC with an expression vector under conditions sufficient for the vector to integrate into the heHSC genome.

36. The isolated heHSC of claims 1-33, wherein the heHSC is genetically modified to shut off expression of an endogenous polynucleotide.

37. A method of treating a stem cell or progenitor cell disorder comprising administering a cell population comprising the isolated heHSC of claims 1-34 to a subject in need thereof, wherein the administered heHSC population engrafts in the subject's bone marrow compartment, thereby treating the stem cell or progenitor cell disorder.

38. The method of claim 37, wherein the cell population comprises at least 40% heHSC cells.

39. The method of any one of claims 37-38, further comprising assaying the cell population to determine if the cell population is suitable for transplant into the subject.

40. The method of claim 39, wherein the assay comprises determining the relative percentage of CD93+ cells in the cell population.

41. The method of any one of claims 37-40, further comprising a step of enriching the cell population for heHSC.

42. The method of claim 41, wherein the step of enriching comprises enriching the cell population for CD93+ cells.

43. The method of any one of claims 37-42, wherein the stem cell or progenitor cell disorder is a malignant hematologic disease.

44. The method of any one of claims 37-42, wherein the malignant hematologic disease is selected from the group consisting of acute lymphoid leukemia, acute myeloid leukemia, chronic lymphoid leukemia, chronic myeloid leukemia, diffuse large B-cell non-Hodgkin's lymphoma, mantle cell lymphoma, lymphoblastic lymphoma, Burkitt's lymphoma, follicular B-cell non-Hodgkin's lymphoma, lymphocyte predominant nodular Hodgkin's lymphoma, multiple myeloma, and juvenile myelomonocytic leukemia.

45. The method of any one of claims 37-42, wherein the stem cell or progenitor cell disorder is a non-malignant disease.

46. The method of any one of claims 37-42, wherein the non-malignant disease is selected from the group consisting of myelofibrosis, myelodysplastic syndrome, amyloidosis, severe aplastic anemia, paroxysmal nocturnal hemoglobinuria, immune cytopenias, systemic sclerosis, rheumatoid arthritis, multiple sclerosis, systemic lupus erythematosus, Crohn's disorder, chronic inflammatory demyelinating polyradiculoneuropathy, human immunodeficiency virus (HIV), Fanconi anemia, sickle cell disorder, beta thalassemia major, Hurler's syndrome (MPS-IH), adrenoleukodystrophy, metachromatic leukodystrophy, familial erythrophagocytic lymphohistiocytosis and other histiocytic disorders, severe combined immunodeficiency (SCID), and Wiskott-Aldrich syndrome.

47. The method of any one of claims 37-46, wherein the subject is a human.

48. The method of any one of claims 37-47, wherein upon engraftment in a subject the engrafted heHSC demonstrates enhanced hematopoietic function relative to engraftment of the same quantity of hematopoietic stem cells contacted with G-CSF, a chemotherapeutic agent, or a combination thereof.

49. The method of any one of claims 37-48, wherein upon engraftment in a subject the engrafted heHSC demonstrates an enhanced CD34+ number relative to engraftment of the same quantity of hematopoietic stem cells contacted with G-CSF, a chemotherapeutic agent, or a combination thereof.

50. The method of any one of claims 37-49, wherein the subject is conditioned for engraftment prior to administering the isolated heHSC.

51. The method of any one of claims 37-50, wherein the subject exhibits poor mobilization in response to a conventional mobilization regimen consisting of G-CSF.

52. The method of any one of claims 37-50, wherein the subject exhibits poor mobilization in response to G-CSF.

53. The method of any one of claims 37-52, wherein the heHSC is substantially pure.

54. The method of any one of claims 37-53, wherein the heHSC is non-quiescent.

55. The method of any one of claims 37-54, wherein the heHSC is OPN+.

56. The method of any one of claims 37-55, wherein the heHSC is CD93+.

57. The method of any one of claims 37-56, wherein the heHSC is CD34-.

58. The method of any one of claims 37-57, wherein the heHSC comprises a unique transcriptome relative to hematopoietic stem cells contacted with granulocyte colony-stimulating factor (G-CSF), a chemotherapeutic agent, or a combination thereof.

59. The method of any one of claims 37-58, wherein the heHSC differentially express one or more of the genes selected from the group consisting of Fos, CD93, Fosb, Dusp1, Jun, Dusp6, Cdk1, Fignl1, Plk2, Rsad2, Sgk1, Sdc1, Serpine2, Spp1, Cdca8, Nrp1, Mcam, Pbk, Akr1cl and Cyp11a1, relative to

one or more genes expressed by hematopoietic stem cells (HSCs) mobilized using G-CSF.

60. A method of treating a stem cell or progenitor cell disorder in a subject, the method comprising: (a) depleting an endogenous hematopoietic stem cell or progenitor cell population in a bone marrow compartment of the subject; and (b) administering an isolated, non-native highly engraftable hematopoietic stem cell (heHSC) to the subject, wherein the heHSC is Sca-1+, c-kit+ and Lin- (SKL), and wherein the administered heHSC engrafts in the bone marrow compartment of the subject.

61. The method of claim 60, wherein the stem cell or progenitor cell disorder is a malignant hematologic disease.

62. The method of claim 61, wherein the malignant hematologic disease is selected from the group consisting of acute lymphoid leukemia, acute myeloid leukemia, chronic lymphoid leukemia, chronic myeloid leukemia, diffuse large B-cell non-Hodgkin's lymphoma, mantle cell lymphoma, lymphoblastic lymphoma, Burkitt's lymphoma, follicular B-cell non-Hodgkin's lymphoma, lymphocyte predominant nodular Hodgkin's lymphoma, multiple myeloma, and juvenile myelomonocytic leukemia.

63. The method of claim 60, wherein the stem cell or progenitor cell disorder is a non-malignant disease.

64. The method of claim 63, wherein the non-malignant disease is selected from the group consisting of myelofibrosis, myelodysplastic syndrome, amyloidosis, severe aplastic anemia, paroxysmal nocturnal hemoglobinuria, immune cytopenias, systemic sclerosis, rheumatoid arthritis, multiple sclerosis, systemic lupus erythematosus, Crohn's disorder, chronic inflammatory demyelinating polyradiculoneuropathy, human immunodeficiency virus (HIV), Fanconi anemia, sickle cell disorder, beta thalassemia major, Hurler's syndrome (MPS-IH), adrenoleukodystrophy, metachromatic leukodystrophy, familial erythrophagocytic

lymphohistiocytosis and other histiocytic disorders, severe combined immunodeficiency (SCID), and Wiskott-Aldrich syndrome.

65. The method of claims 60-64, wherein the subject is a human.

66. The method of claims 60-65, wherein upon engraftment in a subject the engrafted heHSC demonstrates enhanced hematopoietic function relative to engraftment of the same quantity of hematopoietic stem cells contacted with granulocyte colony-stimulating factor (G-CSF), a chemotherapeutic agent, or a combination thereof.

67. The method of claims 60-66, wherein the heHSC is substantially pure.

68. The method of claims 60-67, wherein the heHSC is non-quiescent.

69. The method of claims 60-68, wherein the heHSC is OPN+.

70. The method of claims 60-69, wherein the heHSC is CD93+.

71. The method of claims 60-70, wherein the heHSC is CD34-.

72. The method of claims 60-71, wherein the heHSC comprises a unique transcriptome relative to hematopoietic stem cells contacted with granulocyte colony-stimulating factor (G-CSF), a chemotherapeutic agent, or a combination thereof.

73. The methods of claims 60-72, wherein the heHSC differentially express one or more of the genes selected from the group consisting of Fos, CD93, Fosb, Dusp1, Jun, Dusp6, Cdk1, Fignl1, Plk2, Rsad2, Sgk1, Sdc1, Serpine2, Spp1, Cdca8, Nrp1, Mcam, Pbk, Akr1cl and Cyp11a1, relative to one or more genes expressed by hematopoietic stem cells (HSCs) mobilized using G-CSF.

74. An isolated, non-native highly engraftable hematopoietic stem cell (heHSC), wherein the heHSC is Sca-1+, c-kit+ and Lin- (SKL); wherein the heHSC is prepared by mobilizing hematopoietic stem cells and/or progenitor cells from

a bone marrow compartment of a subject to a peripheral compartment of the subject by administering at least one CXCR2 agonist and at least one CXCR4 antagonist, VLA-4 antagonist, $\alpha_9\beta_1$ antagonist, $\alpha_9\beta_1$ integrin/VLA-4 antagonist or combination thereof to the subject, and isolating the mobilized hematopoietic stem cells and/or progenitor cells from the peripheral compartment of the subject.

75. The isolated heHSC of claim 74, wherein the heHSC is prepared by mobilizing hematopoietic stem cells and/or progenitor cells from a bone marrow compartment of a subject to a peripheral compartment of the subject by administering at least one CXCR2 agonist and at least one CXCR4 antagonist, and isolating the mobilized hematopoietic stem cells and/or progenitor cells from the peripheral compartment of the subject.

76. The isolated heHSC of claims 74-75, wherein the heHSC is CD48-.

77. The isolated heHSC of claims 74-76, wherein the heHSC is CD150+.

78. The isolated heHSC of claims 74-77, wherein the heHSC is CD93+.

79. The isolated heHSC of claims 74-78, wherein the heHSC is CD34-.

80. The isolated heHSC of claims 74-79, wherein the at least one CXCR2 agonist comprises GROβ or an analog or derivative thereof.

81. The isolated heHSC of claims 74-79, wherein the at least one CXCR2 agonist comprises GROβ-Δ4 or an analog or derivative thereof.

82. The isolated heHSC of claims 74-81, wherein the at least one CXCR4 antagonist comprises plerixafor or an analog or derivative thereof.

83. The isolated heHSC of claims 74-79, wherein the at least one CXCR2 agonist is GROβ or an analog or derivative thereof, and wherein the CXCR4 antagonist is plerixafor or an analog or derivative thereof.

84. The isolated heHSC of claims 74-83, wherein upon transplant in a subject the heHSC demonstrates increased engrafting ability relative to engraftment of the same quantity of hematopoietic stem cells mobilized using granulocyte colony-stimulating factor (G-CSF), a chemotherapeutic agent, or a combination thereof.

85. The isolated heHSC of claim 84, wherein the engrafting ability is increased by at least about two-fold.

86. The isolated heHSC of claims 74-85, wherein upon engraftment in a subject the heHSC demonstrates increased donor chimerism relative to engraftment of the same quantity of hematopoietic stem cells mobilized using G-CSF, a chemotherapeutic agent, or a combination thereof.

87. The isolated heHSC of claim 86, wherein the donor chimerism is increased by at least about two fold.

88. The isolated heHSC of claim 86, wherein the donor chimerism is at least about 50%.

89. The isolated heHSC of claims 74-88, wherein the heHSC is substantially pure.

90. The isolated heHSC of claims 74-89, wherein the heHSC is non-quiescent.

91. The isolated heHSC of claims 74-90, wherein the heHSC is OPN+.

92. The isolated heHSC of claims 74-91, wherein the heHSC comprises a unique transcriptome relative to hematopoietic stem cells contacted with granulocyte colony-stimulating factor (G-CSF), a chemotherapeutic agent, or a combination thereof.

93. The isolated heHSC of claims 74-92, wherein the heHSC differentially express one or more of the genes selected from the group consisting of Fos, CD93, Fosb, Dusp1, Jun, Dusp6, Cdk1, Fignl1, Plk2, Rsad2, Sgk1, Sdc1, Serpine2, Spp1, Cdca8, Nrp1, Mcam, Pbk, Akr1cl and Cyp11a1, relative to

one or more genes expressed in hematopoietic stem cells (HSCs) mobilized using G-CSF.

94. The isolated heHSC of claims 74-93, wherein the heHSC is transformed to express a polynucleotide.

95. The isolated heHSC of claims 74-93, wherein the heHSC is transformed with an expression vector to express a polynucleotide.

96. The isolated heHSC of claim 95, wherein the expression vector comprises a viral vector selected from the group consisting of a retrovirus, a herpes simplex, a lentivirus, an adenovirus, and an adeno-associated virus.

97. The isolated heHSC of claim 95, wherein the heHSC is transfected with an expression vector that comprises the polynucleotide.

98. The isolated heHSC of claim 97, wherein the polynucleotide comprises an exogenous polynucleotide.

99. The use of the isolated heHSC of claims 94-98 to deliver an exogenous polynucleotide to a subject in need thereof.

100. A method of transforming the isolated heHSC of claims 74-93, wherein the method comprises contacting the heHSC with an expression vector under conditions sufficient for the vector to integrate into the heHSC genome.

101. The isolated heHSC of claims 74-100, wherein the heHSC is genetically modified to shut off expression of an endogenous polynucleotide.

102. A method of identifying an heHSC cell population comprising

a. mobilizing hematopoietic stem cells and/or progenitor cells from a bone marrow compartment of a subject to a peripheral compartment of the subject by administering at least one CXCR2 agonist and at least one CXCR4 antagonist, VLA-4 antagonist, $\alpha_9\beta_1$ antagonist, $\alpha_9\beta_1$

integrin/VLA-4 antagonist or combination thereof to the subject, and isolating the mobilized hematopoietic stem cells and/or progenitor cells from the peripheral compartment of the subject;

b. mobilizing hematopoietic stem cells and/or progenitor cells from a bone marrow compartment of a subject to a peripheral compartment of the subject by a mobilization regimen not comprising a CXCR2 agonist, and isolating the mobilized hematopoietic stem cells and/or progenitor cells from the peripheral compartment of the subject;

c. comparing one or more immunophenotypical and/or functional properties of the isolated cell population of step (a) to the isolated cell population of step (b); and

d. identifying a subpopulation of the mobilized cell population of step (a) with one or more immunophenotypical and/or functional properties different than the isolated cell population of step (b).

103. The method of claim 94, wherein step (a) comprises administering at least one CXCR2 agonist and at least one CXCR4 antagonist.

104. The method of claims 94-95, wherein the mobilization regimen not comprising a CXCR2 agonist consists of G-CSF.

105. The method of claims 94-96, wherein the compared one or more immunophenotypical and/or functional properties comprises at least one of engraftment ability, degree of donor chimerism, and cell surface markers.

106. A method of preparing a HSC population, comprising contacting hematopoietic stem cells and/or progenitor cells with at least one CXCR2 agonist and at least one VLA-4 antagonist, $\alpha_9\beta_1$ antagonist, $\alpha_9\beta_1$ integrin/VLA-4 antagonist or combination thereof.

107. The method of claim 98, wherein the CXCR2 agonist is GROβ, GROβ-Δ4, or an analog or derivative thereof.

108. A method of making an HSC product comprising: i) contacting hematopoietic stem cells and/or progenitor cells with at least one CXCR2 agonist and at least

one CXCR4 antagonist, VLA-4 antagonist, α9β1 antagonist, α9β1 integrin/VLA-4 antagonist or combination thereof to produce a candidate product; ii) providing a target expression profile for an heHSC product; iii) determining whether the candidate product meets the target expression profile of an heHSC product; and iv) releasing the candidate product as an heHSC product if the candidate product meets the target expression profile of an heHSC product.

109. The method of claims 108, wherein the target expression profile comprises Sca-1+, c-kit+ and Lin- (SKL) cells.

110. The method of claim 108-109, wherein the target expression profile comprises CD48- cells.

111. The method of claims 108-110, wherein the target expression profile comprises CD150+ cells.

112. The method of claims 108-111, wherein the target expression profile comprises CD93+ cells.

113. The method of claims 108-112, wherein the target expression profile comprises CD34- cells.

114. The method of claims 108-113, wherein the target expression profile comprises OPN+ cells.

115. The method of claims 108-114, wherein the contacting is performed *in vivo*.

116. The method of claims 108-114, wherein the contacting is performed *in vitro*.

117. The method of claims 108-116, wherein the at least one CXCR2 agonist comprises GROβ or an analog or derivative thereof.

118. The method of claims 108-116, wherein the at least one CXCR2 agonist comprises GROβ-Δ4 or an analog or derivative thereof.

119. The method of claims 108-118, wherein the at least one CXCR4 antagonist comprises plerixafor or an analog or derivative thereof.

120. The method of claims 108-118, wherein the at least one CXCR2 agonist is GROβ or an analog or derivative thereof, and wherein the at least one CXCR4 antagonist is plerixafor or an analog or derivative thereof.

121. The method of claims 108-120, wherein the heHSC product, upon transplant into a subject demonstrates increased engrafting ability relative to engraftment of the same quantity of hematopoietic stem cells contacted with granulocyte colony-stimulating factor (G-CSF), a chemotherapeutic agent, or a combination thereof.

122. The method of claim 121, wherein the engrafting ability is increased by at least about two-fold.

123. The method of claims 108-122, wherein upon engraftment in a subject the heHSC product demonstrates increased donor chimerism relative to engraftment of the same quantity of hematopoietic stem cells contacted with G-CSF, a chemotherapeutic agent, or a combination thereof.

124. The method of claim 123, wherein the donor chimerism is increased by at least about two fold.

125. The method of claim 123, wherein the donor chimerism is increased by at least about 50%.

126. The method of claims 108-125, wherein the heHSC product is non-quiescent.

127. The method of claims 108-126, wherein the method additionally comprises a step of enriching the candidate product for one or more cell surface markers and/or one or more gene expression profiles.

128. The method of claims 108-127, wherein the heHSC product comprises a unique transcriptome relative to hematopoietic stem cells contacted with granulocyte colony-stimulating factor (G-CSF), a chemotherapeutic agent, or a combination thereof.

129. The method of claims 108-128, wherein the heHSC product differentially express one or more of the genes selected from the group consisting of Fos, CD93, Fosb, Dusp1, Jun, Dusp6, Cdk1, Fignl1, Plk2, Rsad2, Sgk1, Sdc1, Serpine2, Spp1, Cdca8, Nrp1, Mcam, Pbk, Akr1cl and Cyp11a1, relative to one or more genes expressed by hematopoietic stem cells mobilized using G-CSF.

130. The method of claims 108-129, wherein the heHSC product comprises at least a unique transcriptome or a unique phenotype as compared to a naturally occurring HSC.

131. The method of claims 108-130, wherein the heHSC product is transformed to express a polynucleotide.

132. The method of claims 108-131, wherein the heHSC product is transformed with an expression vector to express a polynucleotide.

133. The method of claims 132, wherein the expression vector comprises a viral vector selected from the group consisting of a retrovirus, a herpes simplex, a lentivirus, an adenovirus, and an adeno-associated virus.

134. The method of claims 131-133, wherein the heHSC product is transfected with an expression vector that comprises the polynucleotide.

135. The method of claims 131-134, wherein the polynucleotide comprises an exogenous polynucleotide.

136. The method of claims 108-135, wherein the heHSC product comprises at least 40% CD93+ cells.

137. The method of claims 108-136, wherein the heHSC product comprises at least about 2 x 10^6 cells.

138. The method of claims 108-137, wherein the hematopoietic stem cells and/or progenitor cells are human or mouse cells.

139. A method of treating a stem cell or progenitor cell disorder comprising: i) contacting hematopoietic stem cells and/or progenitor cells with at least one CXCR2 agonist and at least one CXCR4 antagonist, VLA-4 antagonist, α9β1 antagonist, α9β1 integrin/VLA-4 antagonist or combination thereof to produce a candidate product; ii) providing a target expression profile for an heHSC product; iii) determining whether the candidate product meets the target expression profile of an heHSC product; and iv) administering the candidate product to a subject in need thereof if the candidate product meets the target expression profile of an heHSC product.

140. The method of claims 139, wherein the target expression profile comprises Sca-1+, c-kit+ and Lin- (SKL) cells.

141. The method of claim 139-140, wherein the target expression profile comprises CD48- cells.

142. The method of claims 139-141, wherein the target expression profile comprises CD150+ cells.

143. The method of claims 139-142, wherein the target expression profile comprises CD93+ cells.

144. The method of claims 139-143, wherein the target expression profile comprises CD34- cells.

145. The method of claims 139-144, wherein the target expression profile comprises OPN+ cells.

146. The method of claims 139-145, wherein the contacting is performed *in vivo*.

147. The method of claims 139-145, wherein the contacting is performed *in vitro*.

148. The method of claims 139-147, wherein the at least one CXCR2 agonist comprises GROβ or an analog or derivative thereof.

149. The method of claims 139-147, wherein the at least one CXCR2 agonist comprises GROβ-Δ4 or an analog or derivative thereof.

150. The method of claims 139-149, wherein the at least one CXCR4 antagonist comprises plerixafor or an analog or derivative thereof.

151. The method of claims 139-149, wherein the at least one CXCR2 agonist is GROβ or an analog or derivative thereof, and wherein the at least one CXCR4 antagonist is plerixafor or an analog or derivative thereof.

152. The method of claims 139-151, wherein the heHSC product, upon transplant into a subject demonstrates increased engrafting ability relative to engraftment of the same quantity of hematopoietic stem cells contacted with granulocyte colony-stimulating factor (G-CSF), a chemotherapeutic agent, or a combination thereof.

153. The method of claim 152, wherein the engrafting ability is increased by at least about two-fold.

154. The method of claims 139-153, wherein upon engraftment in a subject the heHSC product demonstrates increased donor chimerism relative to engraftment of the same quantity of hematopoietic stem cells contacted with G-CSF, a chemotherapeutic agent, or a combination thereof.

155. The method of claim 154, wherein the donor chimerism is increased by at least about two fold.

156. The method of claim 154, wherein the donor chimerism is increased by at least about 50%.

157. The method of claims 139-156, wherein the heHSC product is non-quiescent.

158. The method of claims 139-157, wherein the method additionally comprises a step of enriching the candidate product for one or more cell surface markers and/or one or more gene expression profiles.

159. The method of claims 139-158, wherein the heHSC product comprises a unique transcriptome relative to hematopoietic stem cells contacted with granulocyte colony-stimulating factor (G-CSF), a chemotherapeutic agent, or a combination thereof.

160. The method of claims 139-159, wherein the heHSC product differentially express one or more of the genes selected from the group consisting of Fos, CD93, Fosb, Dusp1, Jun, Dusp6, Cdk1, Fignl1, Plk2, Rsad2, Sgk1, Sdc1, Serpine2, Spp1, Cdca8, Nrp1, Mcam, Pbk, Akr1cl and Cyp11a1, relative to one or more genes expressed by hematopoietic stem cells mobilized using G-CSF.

161. The method of claims 139-160, wherein the heHSC product comprises at least a unique transcriptome or a unique phenotype as compared to a naturally occurring HSC.

162. The method of claims 139-161, wherein the heHSC product is transformed to express a polynucleotide.

163. The method of claims 139-162, wherein the heHSC product is transformed with an expression vector to express a polynucleotide.

164. The method of claims 163, wherein the expression vector comprises a viral vector selected from the group consisting of a retrovirus, a herpes simplex, a lentivirus, an adenovirus, and an adeno-associated virus.

165. The method of claims 163-164, wherein the heHSC product is transfected with an expression vector that comprises the polynucleotide.

166. The method of claims 163-165, wherein the polynucleotide comprises an exogenous polynucleotide.

167. The method of claims 139-166, wherein the heHSC product comprises at least 40% CD93+ cells.

168. The method of claims 139-167, wherein the heHSC product comprises at least about 2 x 10^6 cells.

169. The method of claims 139-168, wherein the hematopoietic stem cells and/or progenitor cells are human or mouse cells.

170. The method of claims 139-169, wherein the stem cell or progenitor cell disorder is a malignant hematologic disease.

171. The method of claim 170, wherein the malignant hematologic disease is selected from the group consisting of acute lymphoid leukemia, acute myeloid leukemia, chronic lymphoid leukemia, chronic myeloid leukemia, diffuse large B-cell non-Hodgkin's lymphoma, mantle cell lymphoma, lymphoblastic lymphoma, Burkitt's lymphoma, follicular B-cell non-Hodgkin's lymphoma, lymphocyte predominant nodular Hodgkin's lymphoma, multiple myeloma, and juvenile myelomonocytic leukemia.

172. The method of claim 170, wherein the stem cell or progenitor cell disorder is a non-malignant disease.

173. The method of claim 172, wherein the non-malignant disease is selected from the group consisting of myelofibrosis, myelodysplastic syndrome, amyloidosis, severe aplastic anemia, paroxysmal nocturnal hemoglobinuria, immune cytopenias, systemic sclerosis, rheumatoid arthritis, multiple sclerosis, systemic lupus erythematosus, Crohn's disorder, chronic inflammatory demyelinating polyradiculoneuropathy, human immunodeficiency virus (HIV), Fanconi anemia, sickle cell disorder, beta thalassemia major, Hurler's syndrome (MPS-IH), adrenoleukodystrophy, metachromatic leukodystrophy, familial erythrophagocytic lymphohistiocytosis and other histiocytic disorders, severe combined immunodeficiency (SCID), and Wiskott-Aldrich syndrome.

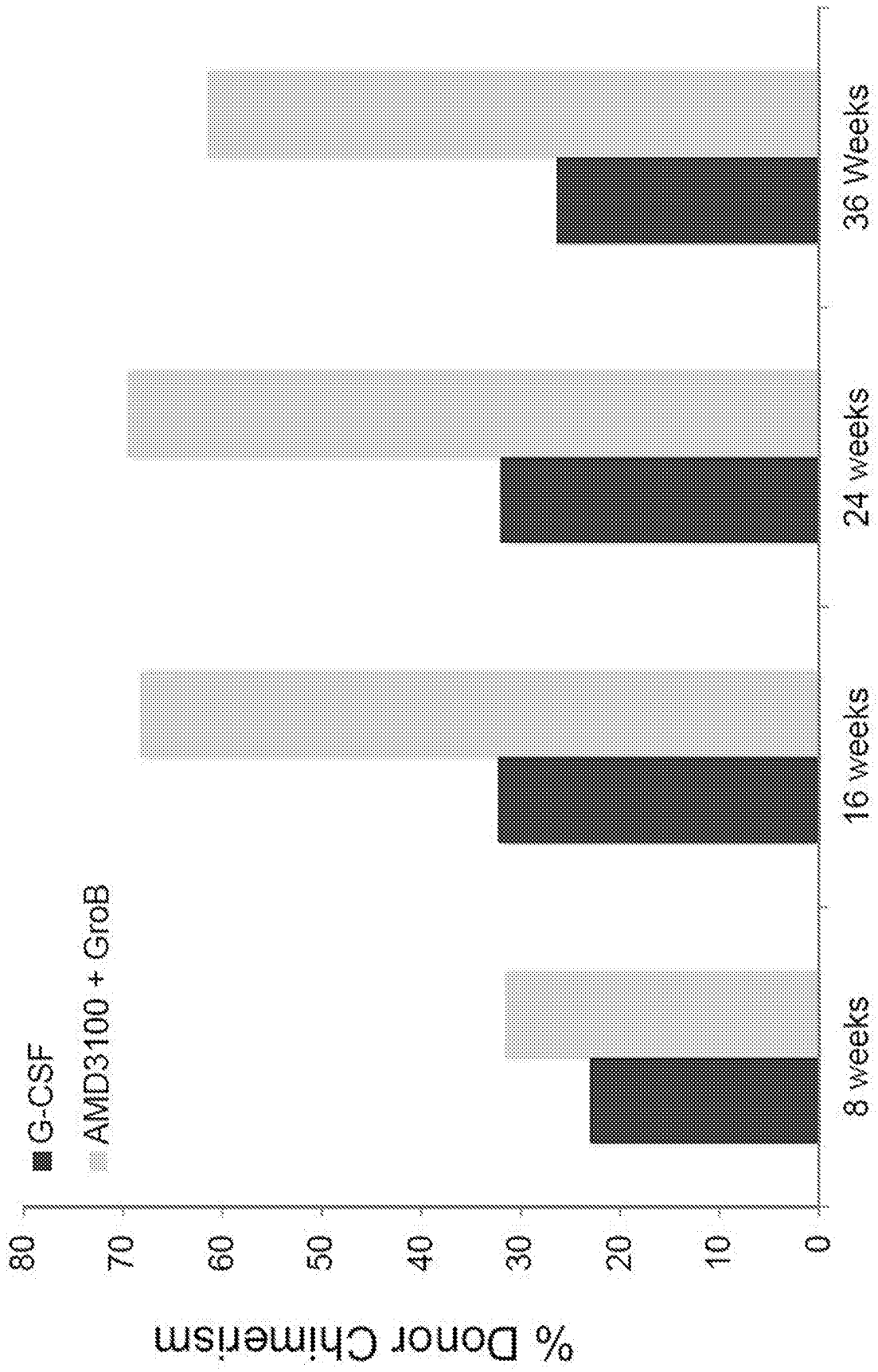
% Donor Chimerism
80
70
60
50
40
30
20
10
0
G-CSF
AMD3100 + GroB
8 weeks
16 weeks
24 weeks
36 Weeks

FIG. 1

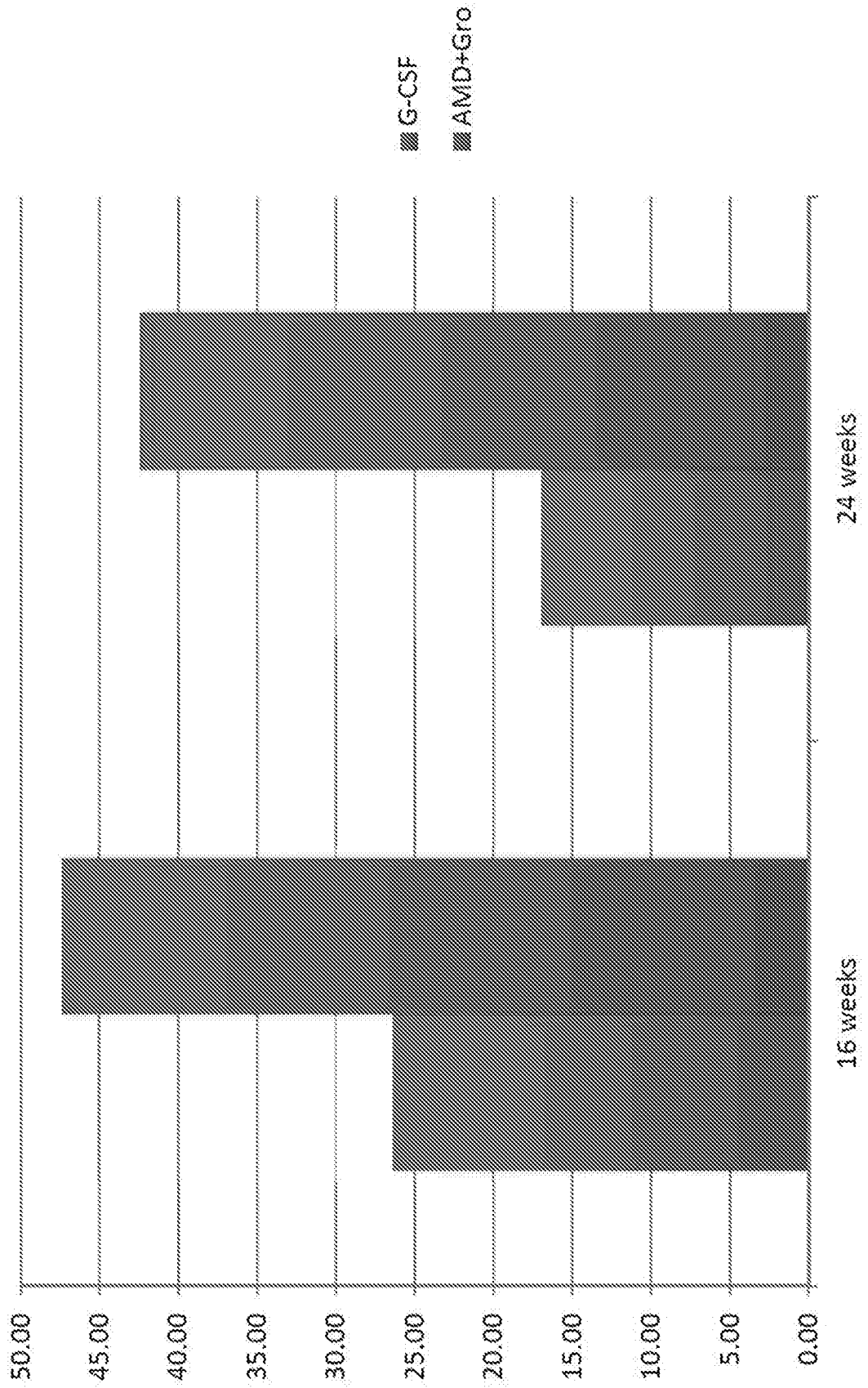
G-CSF
AMD+Gro
50.00
45.00
40.00
35.00
30.00
25.00
20.00
15.00
10.00
5.00
0.00
16 weeks
24 weeks

FIG. 2

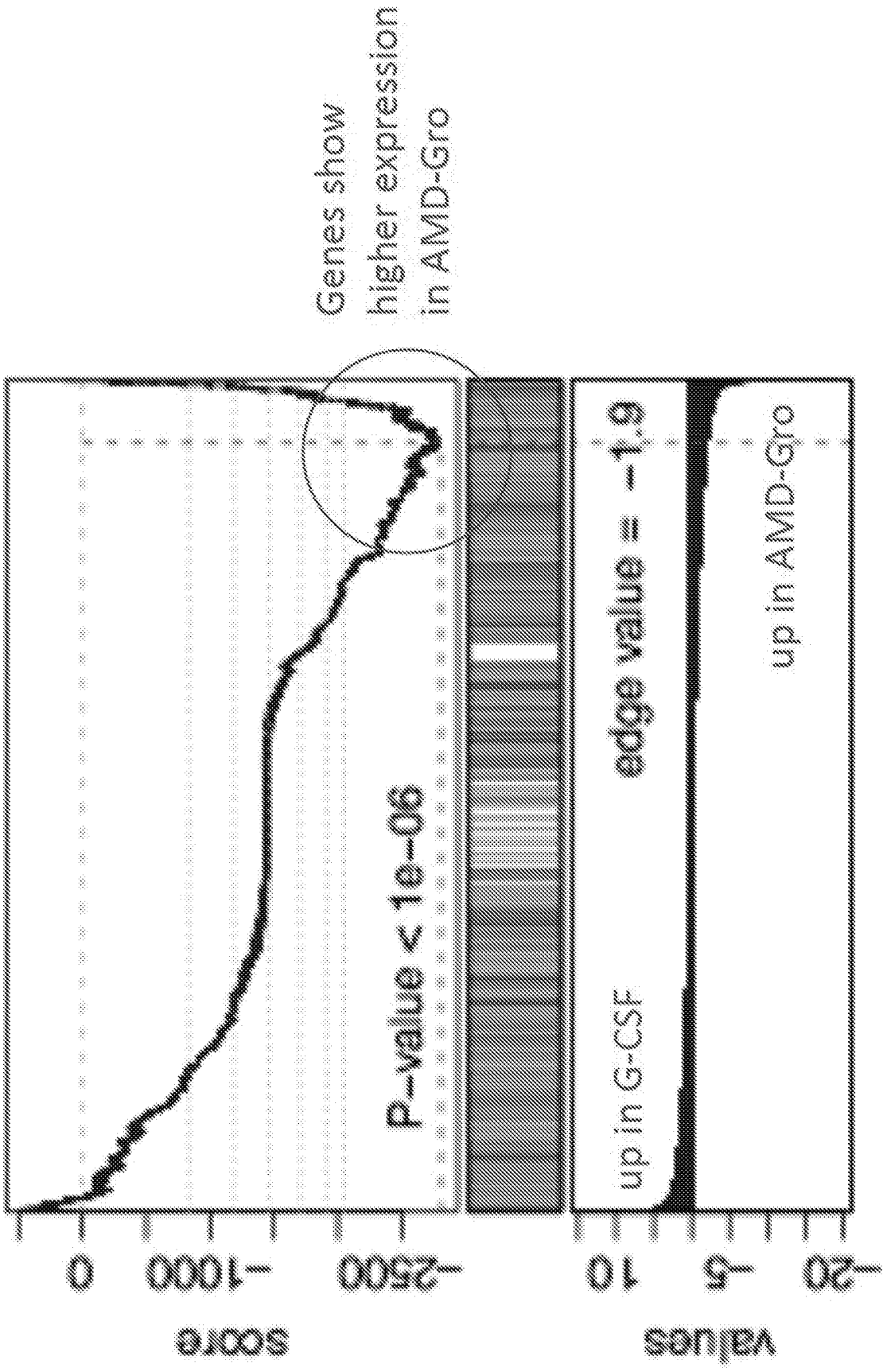
Genes show
higher expression
in AMD-Gro
P-value < 1e-06
edge value = -1.9
up in G-CSF
up in AMD-Gro
score
values
0
-1000
-2500
10
5
-20

FIG. 3

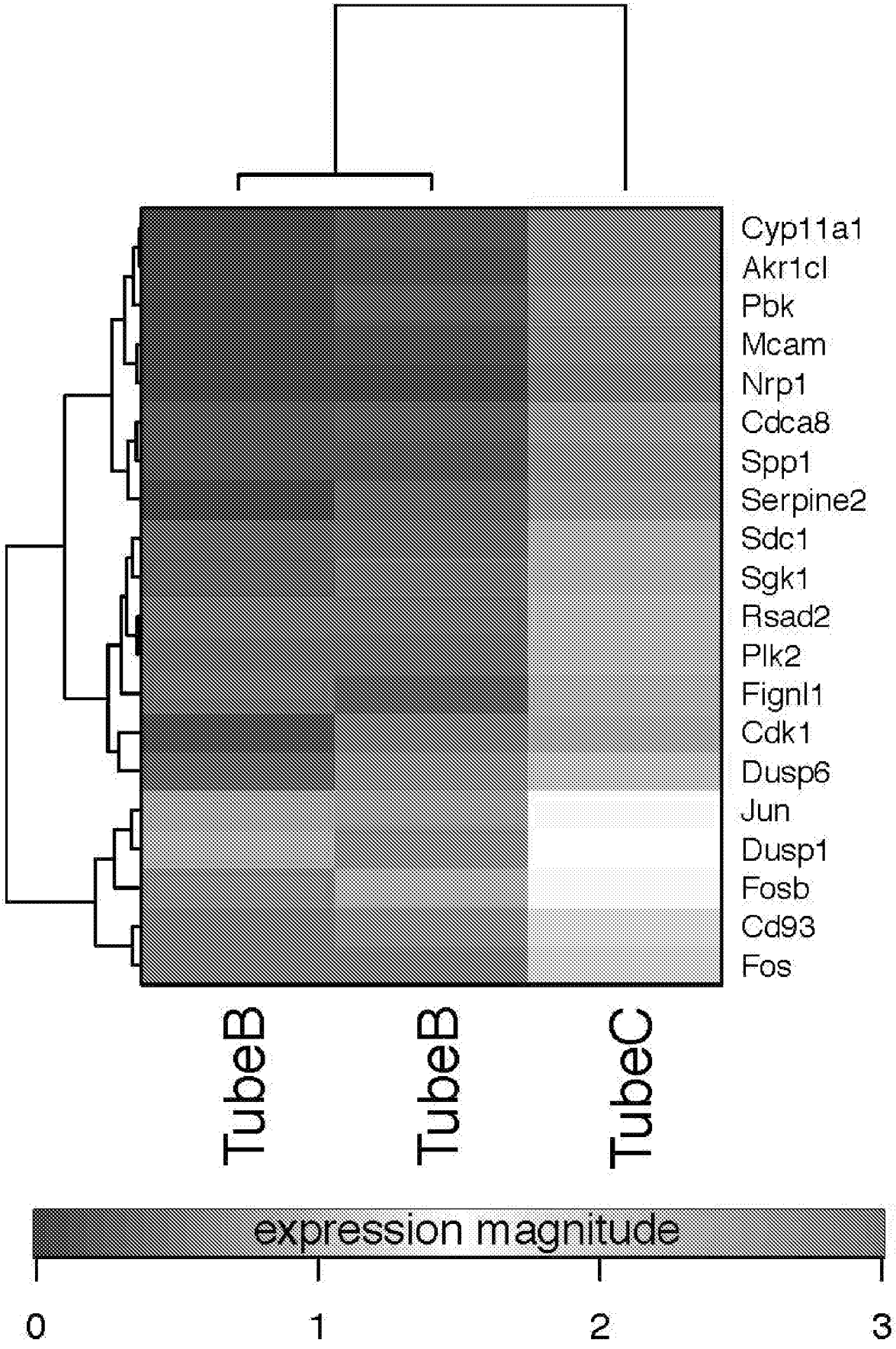
Cyp11a1
Akr1cl
Pbk
Mcam
Nrp1
Cdca8
Spp1
Serpine2
Sdc1
Sgk1
Rsad2
Plk2
Fignl1
Cdk1
Dusp6
Jun
Dusp1
Fosb
Cd93
Fos
TubeB
TubeB
TubeC
expression magnitude
0
1
2
3

FIG. 4

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US 17/19778

A. CLASSIFICATION OF SUBJECT MATTER
IPC(8) - A61K 31/395, A61K 35/28, A61K 38/19 (2017.01)
CPC - G01N 33/5073, A61K 38/1703, A61K 35/28, A61K 45/06, A61K 38/195, A61K 31/395, A61K 38/202

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
See Search History Document

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched
See Search History Document

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
See Search History Document

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 2014/134539 A1 (PRESIDENT AND FELLOWS OF HARVARD COLLEGE et al.) 04 September 2014 (04.09.2014) para [0008]; [0018]; [0124]-[0131]; [0326]-[0327].	1, 2, 74, 75
A	KARPONI et al. "Plerixafor+ G-CSF-mobilized CD34+ cells represent an optimal graft source for thalassemia gene therapy." Blood 126.5 (2015): 616-619. entire document, especially abstract, pg 618, col 1	1

☐ Further documents are listed in the continuation of Box C. ☐ See patent family annex.

* Special categories of cited documents:
"A" document defining the general state of the art which is not considered to be of particular relevance
"E" earlier application or patent but published on or after the international filing date
"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
"O" document referring to an oral disclosure, use, exhibition or other means
"P" document published prior to the international filing date but later than the priority date claimed
"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
07 July 2017	31 JUL 2017
Name and mailing address of the ISA/US Mail Stop PCT, Attn: ISA/US, Commissioner for Patents P.O. Box 1450, Alexandria, Virginia 22313-1450 Facsimile No. 571-273-8300	Authorized officer: Lee W. Young PCT Helpdesk: 571-272-4300 PCT OSP: 571-272-7774

Form PCT/ISA/210 (second sheet) (January 2015)

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US 17/19778

Box No. II Observations where certain claims were found unsearchable (Continuation of item 2 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

2. ☐ Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

3. ☒ Claims Nos.: 3-59, 65-73, 76-101, 104, 105, 110-138, 141-173
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box No. III Observations where unity of invention is lacking (Continuation of item 3 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:
This application contains the following inventions or groups of inventions which are not so linked as to form a single general inventive concept under PCT Rule 13.1. In order for all inventions to be examined, the appropriate additional examination fees must be paid.

Group I, claims 1-2 and 74-75, directed to an isolated, non-native highly engraftable hematopoietic stem cell (heHSC).

Group II, claims 60-64 and 139-140, directed to a method of treating a stem cell or progenitor cell disorder in a subject.

Group III, claims 102-103 and 106-109, directed to a method of identifying or preparing an heHSC cell population.

The inventions listed as Groups I-III do not relate to a single special technical feature under PCT Rule 13.1 because, under PCT Rule 13.2, they lack the same or corresponding special technical features for the following reasons:

--continued on first extra sheet attached hereto--

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.

2. ☐ As all searchable claims could be searched without effort justifying additional fees, this Authority did not invite payment of additional fees.

3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:

4. ☒ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:
1-2, 74-75

Remark on Protest

☐ The additional search fees were accompanied by the applicant's protest and, where applicable, the payment of a protest fee.

☐ The additional search fees were accompanied by the applicant's protest but the applicable protest fee was not paid within the time limit specified in the invitation.

☐ No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US 17/19778

--continuation of Box No III: Observations where unity of invention is lacking--

Special technical features:

Group I has the special technical feature of an isolated, non-native heHSC, that is not required by any other Groups.

Group II has the special technical feature of a method of treating a stem cell or progenitor cell disorder in a subject by administering a product that meets the target expression profile of an heHSC product, that is not required by any other Groups.

Group III has the special technical feature of identifying an heHSC cell population by mobilizing hematopoietic stem cells and/or progenitor cells by different mobilization regimens, and comparing one or more immunophenotypical and/or functional properties of the isolated cell populations, and identifying a subpopulation of the mobilized cell population, that is not required by any other Groups.

Common technical features:

Groups I-III share the common technical feature of preparing/producing a heHSC product comprising mobilizing hematopoietic stem cells and/or progenitor cells from a bone marrow compartment of a subject to a peripheral compartment of a subject by administering at least one CXCR2 agonist and at least one CXCR4 antagonist, VLA-4 antagonist, an alpha9beta1 antagonist, alpha9beta1 integrin/VLA-4 antagonist or combination thereof.
Groups I-II further share the common technical feature of wherein the heHSC is Sea-I+, c-kit+ and Lin- (SKL).
Groups II and III further share the common technical feature of ii) providing a target expression profile for an heHSC product; and iii) determining whether the candidate product meets the target expression profile of an heHSC product.

However, these shared technical features do not represent a contribution over prior art, because these shared technical feature are made obvious by WO 2014/134539 A1 to President and Fellows of Harvard College et al., (hereinafter Harvard).

Harvard teaches a method of preparing/producing a HSC product comprising mobilizing hematopoietic stem cells and/or progenitor cells from a bone marrow compartment of a subject to a peripheral compartment of the subject by administering at least one CXCR2 agonist and at least one CXCR4 antagonist to the subject (para [0127] "The disclosure relates to mobilization of stem cells and/or progenitor cells (e.g., hematopoietic stem cells and/or progenitor cells) for use in connection with stem cell transplantations. Briefly, the stem cell transplantation process may include any or all of injection of mobilization agents into a subject (e.g., a donor), mobilization of the subject's stem cells into the subject's blood from the bone marrow space"; [0130] "mobilizing hematopoietic stem cells and/or progenitor cells" are used interchangeably to refer to the act of inducing the migration of hematopoietic stem sells and/or progenitor cells from a first location (e.g., stem cell niche, e.g., bone marrow) into a second location (e.g., tissue (e.g., peripheral blood) or organ (e.g., spleen"; [0131] "methods and compositions relating to mobilizing hematopoietic stem cells and/or progenitor cells using at least one CXCR2 agonist (e.g., Gro-beta) and at least one CXCR4 antagonist (e.g., Plerixafor)"), and isolating the mobilized hematopoietic stem cells and/or progenitor cells from the peripheral compartment of the subject (para [0127] "collection of the mobilized stem cells from the blood (e.g., via apheresis), preparation of the collected stem cells").

Harvard further teaches providing a target expression profile for an heHSC product; and determining whether the candidate product meets the target expression profile of an heHSC product, wherein the heHSC is Sea-I+, c-kit+ and Lin- (SKL) (para [0124] "FIGS. 9D-9F illustrate clustering of genes differentially expressed in FACS sorted HSPCs (Lin-, cKit+, Sca1+) from PB upon GCSF (n=1) or G-CSF plus heparin (n=2) induced mobilization showing changes in cell adhesion genes (FIG. 9D)"; [0151] "the hematopoietic progenitor cells comprise Lin-SCA-1.sup.-c-Kit+CD34+CD16/32.sup.mid cells. In some embodiments, the hematopoietic progenitor cells comprise lin-SCA-1-c-kit+CD34-CD16/32.sup.low cells").

As the technical features were known in the art at the time of the invention, they cannot be considered special technical features that would otherwise unify the groups.

Therefore, Group I-III inventions lack unity under PCT Rule 13 because they do not share the same or corresponding special technical feature.