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(54) **Title:** RETROGRADE DELIVERY OF CELLS AND NUCLEIC ACIDS FOR TREATMENT OF CARDIOVASCULAR DISEASES

(57) **Abstract:** Methods, compositions of matter, medical devices, and kits useful for the treatment of cardiovascular conditions are disclosed comprising of administering cells and/or nucleic acids into the cardiac venous system in a retrograde manner so as to obtain tissue perfusion of said cells and/or nucleic acids. In one embodiment, administration of endometrial regenerative cells in a retrograde manner is disclosed. Additionally, nucleic acids capable of suppressing inflammation and/or inhibition of pathological remodeling may be administered alone or in combination with said cells.



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RETROGRADE DELIVERY OF CELLS AND NUCLEIC ACIDS FOR TREATMENT OF CARDIOVASCULAR DISEASES

CROSS-REFERENCE TO RELATED APPLICATIONS

[001] This application claims priority to U.S. Provisional Application No. 61/732,439, titled “Retrograde Delivery of Cells and Nucleic Acids for Treatment of Cardiovascular Diseases”, filed December 3, 2012, which is hereby expressly incorporated by reference in its entirety.

FIELD OF THE INVENTION

[002] The invention pertains to the field of cardiovascular diseases, more particularly, the invention pertains to treatment of cardiovascular diseases by inhibition myocardial degeneration through administration of agents, and/or nucleic acids, and/or cells using the technique of retrograde administration into the coronary venous system. More specifically, the invention relates to the administration of agents, and/or nucleic acids, and/or cells into the coronary sinus of a patient using a catheter-based system, wherein said catheter is associated with a balloon and said balloon is used to temporarily obstruct the flow of blood.

BACKGROUND

[003] Stem cell therapeutics are considered by many the next revolution in cardiovascular therapy. Unfortunately, this promise has not yet come to realization. Stem cell-based approaches to heart failure are grounded in the concept that regeneration is mediated by the administered cells and/or that the cells act as producers of trophic factors which stimulate cardiac reparative processes such as angiogenesis and expansion of endogenous cardiac specific stem cells [1, 2]. Heart failure due to congestive heart failure (CHF) has emerged as a major chronic disease among patients in the United States and internationally. About 400,000 new patients develop CHF each year. Morbidity and mortality rates are high; annually, approximately 900,000 patients require hospitalization for CHF, and up to 200,000 patients die from this condition. The average annual mortality rate is 40-50% in patients with severe (New York Heart Association [NYHA] class IV) heart failure.

CHF accounts for over 10 million office visits, 6 million hospital days and \$30 billion in direct costs each year. The initial stages of heart failure are managed with medical therapy and the end-stage heart failure is managed with surgical procedures in addition to medical therapy. Some of the proven surgical procedures include myocardial revascularization, ventricular assist devices, and heart transplantation. Although surgical and catheter based revascularization of ischemic myocardium can treat angina, reduce the risk of myocardial infarction, and improve function of viable myocardium, these treatments cannot restore the viability of severely ischemic and/or necrotic myocardium. Many patients with reversible ischemia in regions of the myocardium are not amenable to Coronary Artery Bypass Graft (CABG) or Percutaneous Transluminal Coronary Angioplasty (PTCA). These patients have severely compromised perfusion of the myocardium leading to angina, which significantly limits their daily activities and interferes with their rest at night. A major advance in treatment would be to reverse this condition and to restore perfusion within the affected area of the myocardium. Thus, the aim of cellular transplantation is to repopulate the myocardium with cells that may restore blood supply and thereby improve the patient's quality of life. Additionally, a major cause of heart failure is heart attack. The advent of revascularization procedures, while saving many lives, still causes patients to have pathological remodeling, with many patients having heart attacks in the first year after initial heart attack. The pathological remodeling leaves scar tissue formation that not only increases the possibility of a subsequent heart attack, but also predisposition of eventual heart failure.

[004] In 2001, clinical use of cell therapy was reported by three independent groups using autologous myoblast [3], and bone marrow[4] cells transepically implanted as an adjunct to coronary artery bypass grafting (CABG), in patients with refractory ischemic angina in order to stimulate angiogenesis, as well as bone marrow administration via the intracoronary route post-infarct into the infarct-related artery [5]. The promising results of these "clinical experiments" led to formal trials which demonstrated statistically significant, albeit small, improvements. For example, a meta-analysis of 4 randomized controlled studies [6-9] and 2 cohort studies [10, 11] evaluating autologous bone marrow cells administered transepically during CABG revealed a 5.4% increase in LVEF in a total of 179 patients [12]. Bone marrow cells administered via the intracoronary route were

analyzed in 8 clinical trials in post-infarct patients [13-22]. A meta-analysis of the cumulative 725 patients revealed increased LVEF by 4.37% and reduction in left ventricular end-diastolic volume (LVEDV) by 5.71 mL, left ventricular end-systolic volume (LVESV) by 8.94 mL, and infarct size by 2.42%, which were all statistically significant [23]. While autologous myoblast implantation resulted in arrhythmias and eventual loss of favor of this approach [24], other cell therapies such as mesenchymal stem cells (MSC) have been attracting attention. Since MSC possess can be transplanted from allogeneic sources, optimized “universal donor” cells may be used that do not have the potential disadvantage of senescence associated with age or loss of function associated with underlying disease [25-27]. MSC administration has demonstrated therapeutic effects subsequent to intravenous administration. In a 53 patient trial, the global symptom score in all MSC treated patients and ejection fraction was significantly improved as compared to placebo. Additionally in a MRI substudy MSC treatment, but not placebo, increased left ventricular ejection fraction and led to reverse remodeling [28]. Thus there appears to be some clinical benefit, however these are not substantial enough to obtain regulatory approval. Additionally, these approaches are invasive and expensive.

[005] The possibility of using MSC-based therapies for heart failure is enticing. On the one hand, MSC have the ability to not only differentiate into cardiomyocytes [29, 30], but also potently secrete angiogenic and trophic factors [31-33], which assist in regeneration and possibly activation of endogenous cardiac stem cells [34]. On the other hand, MSC are attractive because of the possibility to utilize them in a “universal donor” fashion. That is, MSC appear to be immune privileged and immune modulatory. Specifically, they are poor stimulators of allogeneic immunity and in many cases have been shown to actively inhibit ongoing immune responses [35, 36]. Besides practical applications of MSC being capable of storage and delivery to the site of care in the same manner that a drug would be, MSC may be standardized and optimized for specific cytokine/regenerative activities. This is useful in that autologous cells from patients with underlying conditions appear to function sub-optimally as compared to age-matched control cells. For example, Dimmeler’s group demonstrated that angiogenic potency of bone marrow from patients with coronary artery disease is extremely impaired, in part due to deficiencies in the CXCR4 migration activity [25].

[006] Unfortunately there exist still two major problems associated with stem cell therapeutics of heart failure. On the one hand, the issue of delivery is still a major hurdle. Endovascular delivery using machines such as the NOGA system require extensive operator training and only a handful of clinical sites have these set ups in the USA. The other hurdle is overcoming the fibrotic/damaged cardiac environment when placing the cells in the heart.

[007] The current invention provides several means of overcoming these obstacles by disclosing a new cell population, a new administration means, and a novel method of modulating the cardiac microenvironment. Additionally, the same principles of the invention may be useful for treatment of other cardiovascular diseases such as stroke or critical limb ischemia.

SUMMARY OF THE INVENTION

[008] The current invention discloses methods of administering stem cells for patients with cardiovascular disorders. One particular administration technique that is disclosed in the current invention is the use of retrograde administration into the coronary sinus. This means of administration has previously been used for decades in delivery of oxygen to the heart, but to our knowledge, has not been applied within the specific means thought in the invention. Additionally, the invention provides means of modulating the cardiac microenvironment in order to increase the efficacy of an implanted stem cell. These means include silencing of genes associated with inflammation/fibrosis/apoptosis through induction of the process of RNA interference (RNAi), and/or transfection of the cardiac microenvironment with genes expressing stem cell specific chemokines, stem cell growth factors, angiogenic factors and anti-apoptotic factors. The invention provides a new stem cell derived from the endometrium that possesses a significantly higher angiogenic profile as compared to previously described bone marrow derived mesenchymal stem cells.

[009] In one aspect of the invention, a solution useful for the treatment of cardiovascular disorders comprising: a) a nucleic acid capable of inducing the process of RNA interference (RNAi); and/or b) a cellular population is disclosed. Said solution can be administered intravenously, epicardially, endocardially,

intracoronarily or via retrograde into the coronary sinus. Said solution may be administered in other areas of the body, including through retrograde means. In one aspect of the invention, said solution contains nucleic acids capable of inducing RNAi, which may be selected from a group of nucleic acids comprising a short hairpin RNA, alone or on a plasmid, or other type of vector, a short interfering RNA or virally expressed RNA. It is within the purpose of the current invention to selectively use the process of RNAi, stimulated by various means known to one of skill in the art, to cause the reduction of inflammatory mediators, including ABCF1, BCL6, C3, C4A, CEBPB, CRP, ICEBERG, IL1R1, IL1RN, IL8RB, LTB4R, TOLLIP, IFNA2, IL10RA, IL10RB, IL13, IL13RA1, IL5RA, IL9, IL9R, CD40LG (TNFSF5), IFNA2, IL10, IL13, IL17C, IL1A, IL1B, IL1F10, IL1F5, IL1F6, IL1F7, IL1F8, IL1F9, IL22, IL5, IL-6, IL8, IL9, IL-18, IL-33, LTA, LTB, MIF, SCYE1, SPP1, TNF, CCL13 (mcp-4), CCR1, CCR2, CCR3, CCR4, CCR5, CCR6, CCR7, CCR8, CCR9, CX3CR1, IL8RA, XCR1 (CCXCR1), C5, CCL1 (I-309), CCL11 (eotaxin), CCL13 (mcp-4), CCL15 (MIP-1d), CCL16 (HCC-4), CCL17 (TARC), CCL18 (PARC), CCL19, CCL2 (mcp-1), CCL20 (MIP-3a), CCL21 (MIP-2), CCL23 (MPIF-1), CCL24 (MPIF-2 / eotaxin-2), CCL25 (TECK) , CCL26, CCL3 (MIP-1a), CCL4 (MIP-1b), CCL5 (RANTES), CCL7 (mcp-3), CCL8 (mcp-2), CXCL1, CXCL10 (IP-10), CXCL11 (I-TAC / IP-9), CXCL12 (SDF1), CXCL13, CXCL14, CXCL2, CXCL3, CXCL5 (ENA-78 / LIX), CXCL6 (GCP-2), CXCL9, IL13, and IL8, to cause reduction in mediators of fibrosis, including ACTA2 (a-SMA), AGT, CTGF, CCL11 (Eotaxin), CCL2 (MCP-1), CCL3 (MIP-1a), GREM1, IL13, IL13RA2, IL4, IL5, SNAI1 (Snail), COL1A2, COL3A1, LOX, MMP1, MMP13, MMP14, MMP2 (Gelatinase A), MMP3, MMP8, MMP9, PLA1 (uPA), PLG, SERPINA1 (a1-antitrypsin), SERPINE1 (PAI-1), SERPINH1, TIMP1, TIMP2, TIMP3, TIMP4, ITGA1, ITGA2, ITGA3, ITGAV, ITGB1, ITGB3, ITGB5, ITGB6, ITGB8, BMP7, CAV1, DCN, ENG (EVI-1), GREM1, INHBE, LTBP1, SMAD2, SMAD3, SMAD4, SMAD6, SMAD7, TGFB1, TGFB2, TGFB3, TGFB1 (ALK5), TGFB2, TGIF1, THBS1, and THBS2 and to reduce expression of pro-apoptotic molecules, including CASP1 (ICE), CASP10 (MCH4), CASP14, CASP2, CASP3, CASP4, CASP5, CASP6, CASP7, CASP8, CASP9, CFLAR (CASPER), CRADD, PYCARD (TMS1/ASC), ABL1, AKT1, BAD, BAK1, BAX, BCL2L11, BCLAF1, BID, BIK, BNIP3, BNIP3L, CASP1 (ICE), CASP10 (MCH4), CASP14, CASP2, CASP4, CASP6, CASP8, CD70 (TNFSF7), CIDEA, CRADD, FADD, FASLG (TNFSF6),

HRK, LTA (TNFB), NOD1 (CARD4), PYCARD (TMS1/ASC), RIPK2, TNF, TNFRSF10A, TNFRSF10B (DR5), TNFRSF25 (DR3), TNFRSF9, TNFSF10 (TRAIL), TNFSF8, TP53, TP53BP2, TRADD, TRAF2, TRAF3, and TRAF4.

[0010] In one aspect of the invention, nucleic acids are administered via a deliver vector, said vectors may be viral, or may be plasmid-based, or may be nanoparticle based. Means of delivery of nucleic acids include naked DNA/RNA administration, liposomal DNA/RNA administration, viral administration, ultrasound based administration, microbubble based administration; and targeted nanoparticle based administration.

[0011] In one aspect of the invention, genes stimulatory of angiogenesis are administered as part of the therapeutic solution, alone, in combination with the cells, or in various combination with other genes and/or nucleic acids. Numerous pro-angiogenic genes are known in the art, these include FGF, VEGF, SDF-1, VEGFR, NRP-1, Ang1, Ang2, PDGF (BB-homodimer), PDGFR, TGF- β , endoglin, TGF- β receptors, MCP-1, integrins α V β 3, α V β 5, α 5 β 1, VE-cadherin, CD31, ephrin, ANGPTL3, BAI1, COL4A3, IL8, LAMA5, NRP1, NRP2, STAB1, plasminogen activators, ANGPTL4, PECAM1, PF4, PROK2, SERPINF1, TNFAIP2, HAND2, SPHK1, CCL11, CCL2, CXCL1, CXCL10, CXCL3, CXCL5, CXCL6, CXCL9, IFNA1, IFNB1, IFNG, IL1B, IL6, MDK, TNF, plasminogen activator inhibitor-1, eNOS, COX-2, AC133, Id1/Id3, ANGPT1, ANGPT2, ANPEP, TYMP, EREG, FGF1, FGF2, FIGF, FLT1, JAG1, KDR, S1PR1, EFNA1, EFNA3, EFNB2, EGF, EPHB4, FGFR3, HGF, IGF1, ITGB3, PDGFA, TEK, TGFA, TGFB1, TGFB2, TGFB1, LAMA5, CCL11, CCL2, CDH5, COL18A1, S1PR1, ENG, ITGAV, ITGB3, THBS1, LECT1, LEP, MMP2, MMP9, PLAUG, PLG, TIMP1, TIMP2, AKT1, HIF1A, HPSE, ID1, ID3, NOTCH4, PTGS1, TIMP3, THBS2, NRP1, NRP2, PGF, PLXDC1, STAB1, VEGFA, VEGFC. In an aspect of the invention, the cardiac microenvironment is transfected with genes that prevent apoptosis, these may include, obestatin, XIAP, survivin, BCL-2, BCL-XL, GATA-4, IGF-1, EGF, heme-oxygenase-1, NF-kB, akt, pi3-k, and epha-2.

[0012] In one aspect of the invention, the cell administered is a monocytic cell. In another aspect, the cell type administered may be autologous, allogeneic, or

xenogeneic to the recipient. In another aspect, the cell administered may be a progenitor cell, a pluripotent stem cell, an induced pluripotent stem cell, a hematopoietic stem cell, a very small embryonic like stem cell, a mesenchymal stem cell, an endometrial regenerative cell that was selected on the basis of a marker, an unselected endometrial regenerative cell, a cardiac progenitor cell and a cell programmed to be a cardiogenic cell. Stem cell types useful for the invention include embryonic stem cells, cord blood stem cells, placental stem cells, bone marrow stem cells, amniotic fluid stem cells, neuronal stem cells, circulating peripheral blood stem cells, mesenchymal stem cells, germinal stem cells, adipose tissue derived stem cells, exfoliated teeth derived stem cells, hair follicle stem cells, dermal stem cells, parthenogenically derived stem cells, reprogrammed stem cells and side population stem cells.

[0013] In one aspect of the invention, the therapeutic solution contains an agent or plurality of agents capable of epigenetically modifying stem cell activity. Said agents include a DNA methyltransferase inhibitor, an inhibitor of GSK-3, and/or a histone deacetylase inhibitor. DNA methyltransferase inhibitors include 5-azacytidine, histone deacetylase inhibitors include valproic acid, phenylbutyrate, trichostatin A, and AR42. Inhibitors of GSK-3 include lithium.

[0014] In one aspect of the invention, cells used in the generation of the therapeutic solution include cells that have been optimized in vitro for possessing specific biological activity. Biological activity of relevance include cardiac differentiation ability, muscle differentiation activity, cytokine production activity, immune modulatory activity, angiogenic activity and endothelial differentiation activity.

[0015] In another aspect of the invention, cells are used as part of a therapeutic solution, said cells being transfected with nucleic acids capable of modulating biological activities of said cells, specific nucleic acids capable of stimulating angiogenesis, inhibiting apoptosis, inhibiting fibrosis, inhibiting inflammation. Genes capable of stimulating angiogenesis are well known and can be transfected to enhance this activity. Specific examples of genes useful for this purpose include: FGF, VEGF, SDF-1, VEGFR, NRP-1, Ang1, Ang2, PDGF (BB-homodimer), PDGFR, TGF- β , endoglin, TGF- β receptors, MCP-1, integrins α V β 3,

$\alpha V\beta 5$, $\alpha 5\beta 1$, VE-cadherin, CD31, ephrin, ANGPTL3, BAI1, COL4A3, IL8, LAMA5, NRP1, NRP2, STAB1, plasminogen activators, ANGPTL4, PECAM1, PF4, PROK2, SERPINF1, TNFAIP2, HAND2, SPHK1, CCL11, CCL2, CXCL1, CXCL10, CXCL3, CXCL5, CXCL6, CXCL9, IFNA1, IFNB1, IFNG, IL1B, IL6, MDK, TNF, plasminogen activator inhibitor-1, eNOS, COX-2, AC133, Id1/Id3, ANGPT1, ANGPT2, ANPEP, TYMP, EREG, FGF1, FGF2, FIGF, FLT1, JAG1, KDR, S1PR1, EFNA1, EFNA3, EFNB2, EGF, EPHB4, FGFR3, HGF, IGF1, ITGB3, PDGFA, TEK, TGFA, TGFB1, TGFB2, TGFB1, LAMA5, CCL11, CCL2, CDH5, COL18A1, S1PR1, ENG, ITGAV, ITGB3, THBS1, LECT1, LEP, MMP2, MMP9, PLA1, PLG, TIMP1, TIMP2, AKT1, HIF1A, HPSE, ID1, ID3, NOTCH4, PTGS1, TIMP3, THBS2, NRP1, NRP2, PGF, PLXDC1, STAB1, VEGFA, VEGFC. In another aspect, cells are increased in resistance to apoptosis by transfecting with a nucleic acid capable of inducing RNAi to genes associated with apoptosis comprised of complementary sequences of nucleic acids, said nucleic acids capable of stimulating RNAi, said sequences having homology to genes selected from a group comprising of: CASP1 (ICE), CASP10 (MCH4), CASP14, CASP2, CASP3, CASP4, CASP5, CASP6, CASP7, CASP8, CASP9, CFLAR (CASPER), CRADD, PYCARD (TMS1/ASC), ABL1, AKT1, BAD, BAK1, BAX, BCL2L11, BCLAF1, BID, BIK, BNIP3, BNIP3L, CASP1 (ICE), CASP10 (MCH4), CASP14, CASP2, CASP4, CASP6, CASP8, CD70 (TNFSF7), CIDEB, CRADD, FADD, FASLG (TNFSF6), HRK, LTA (TNFB), NOD1 (CARD4), PYCARD (TMS1/ASC), RIPK2, TNF, TNFRSF10A, TNFRSF10B (DR5), TNFRSF25 (DR3), TNFRSF9, TNFSF10 (TRAIL), TNFSF8, TP53, TP53BP2, TRADD, TRAF2, TRAF3, and TRAF4. In another aspect, the cells to be injected as part of the therapeutic solution are transfected with anti-apoptotic genes, said genes selected from a group of genes comprising of: obestatin, XIAP, survivin, BCL-2, BCL-XL, GATA-4, IGF-1, EGF, heme-oxygenase-1, NF-kB, akt, pi3-k, and epha-2. In another aspect, cells to be injected are made resistant to fibrosis by transfection with genes selected from a group comprising of: ACTA2 (α -SMA), AGT, CTGF, CCL11 (Eotaxin), CCL2 (MCP-1), CCL3 (MIP-1a), GREM1, IL13, IL13RA2, IL4, IL5, SNAI1 (Snail), COL1A2, COL3A1, LOX, MMP1, MMP13, MMP14, MMP2 (Gelatinase A), MMP3, MMP8, MMP9, PLA1 (uPA), PLG, SERPINA1 (α 1-antitrypsin), SERPINE1 (PAI-1), SERPINH1, TIMP1, TIMP2, TIMP3, TIMP4, ITGA1, ITGA2, ITGA3, ITGAV, ITGB1, ITGB3, ITGB5, ITGB6, ITGB8, BMP7, CAV1, DCN, ENG (EVI-1),

GREM1, INHBE, LTBP1, SMAD2, SMAD3, SMAD4, SMAD6, SMAD7, TGFB1, TGFB2, TGFB3, TGFB1 (ALK5), TGFB2, TGIF1, THBS1, and THBS2. In another aspect cells to be injected are enhanced in resistance to inflammation by transfection with nucleic acids capable of inducing RNAi to genes associated with inflammation, said genes selected from a group comprising of: ABCF1, BCL6, C3, C4A, CEBPB, CRP, ICEBERG, IL1R1, IL1RN, IL8RB, LTB4R, TOLLIP, IFNA2, IL10RA, IL10RB, IL13, IL13RA1, IL5RA, IL9, IL9R, CD40LG (TNFSF5), IFNA2, IL10, IL13, IL17C, IL1A, IL1B, IL1F10, IL1F5, IL1F6, IL1F7, IL1F8, IL1F9, IL22, IL5, IL-6, IL8, IL9, IL-18, IL-33, LTA, LTB, MIF, SCYE1, SPP1, TNF, CCL13 (mcp-4), CCR1, CCR2, CCR3, CCR4, CCR5, CCR6, CCR7, CCR8, CCR9, CX3CR1, IL8RA, XCR1 (CCXCR1), C5, CCL1 (I-309), CCL11 (eotaxin), CCL13 (mcp-4), CCL15 (MIP-1d), CCL16 (HCC-4), CCL17 (TARC), CCL18 (PARC), CCL19, CCL2 (mcp-1), CCL20 (MIP-3a), CCL21 (MIP-2), CCL23 (MPIF-1), CCL24 (MPIF-2 / eotaxin-2), CCL25 (TECK) , CCL26, CCL3 (MIP-1a), CCL4 (MIP-1b), CCL5 (RANTES), CCL7 (mcp-3), CCL8 (mcp-2), CXCL1, CXCL10 (IP-10), CXCL11 (I-TAC / IP-9), CXCL12 (SDF1), CXCL13, CXCL14, CXCL2, CXCL3, CXCL5 (ENA-78 / LIX), CXCL6 (GCP-2), CXCL9, IL13, and IL8.

[0016] In another aspect, antibodies, aptamers, soluble proteins, or peptide inhibitors are added as part of the therapeutic solution. It is the purpose of adding these inhibitory agents in order to reduce expression, transcription, translation or activity of genes or gene products of inflammatory agents. Said inflammatory agents are selected from a group comprising of: TLR-2, TLR3, TLR-4, TLR-5, TLR-7, TLR8, TLR9, C3, C4A, CEBPB, CRP, ICEBERG, IL1R1, IL1RN, IL8RB, LTB4R, TOLLIP, IFNA2, IL10RA, IL10RB, IL13, IL13RA1, IL5RA, IL9, IL9R, CD40LG (TNFSF5), IFNA2, IL10, IL13, IL17C, IL1A, IL1B, IL1F10, IL1F5, IL1F6, IL1F7, IL1F8, IL1F9, IL22, IL5, IL-6, IL8, IL9, IL-18, IL-33, LTA, LTB, MIF, SCYE1, SPP1, TNF, CCL13 (mcp-4), CCR1, CCR2, CCR3, CCR4, CCR5, CCR6, CCR7, CCR8, CCR9, CX3CR1, IL8RA, XCR1 (CCXCR1), C5, CCL1 (I-309), CCL11 (eotaxin), CCL13 (mcp-4), CCL15 (MIP-1d), CCL16 (HCC-4), CCL17 (TARC), CCL18 (PARC), CCL19, CCL2 (mcp-1), CCL20 (MIP-3a), CCL21 (MIP-2), CCL23 (MPIF-1), CCL24 (MPIF-2 / eotaxin-2), CCL25 (TECK) , CCL26, CCL3 (MIP-1a), CCL4 (MIP-1b), CCL5 (RANTES), CCL7 (mcp-3), CCL8 (mcp-2), CXCL1,

CXCL10 (IP-10), CXCL11 (I-TAC / IP-9), CXCL12 (SDF1), CXCL13, CXCL14, CXCL2, CXCL3, CXCL5 (ENA-78 / LIX), CXCL6 (GCP-2), CXCL9, IL13, and IL8.

[0017] In another aspect of the invention, the therapeutic solution is administered by the steps of: a) inserting a balloon catheter into the coronary sinus, said catheter containing a guide wire; b) inflating said balloon in the mid portion of the coronary sinus to create a stagnation of blood flow; and c) administering said therapeutic solution in a retrograde manner across the balloon against the coronary venous circulation. Specifically, said catheter is inserted by cannulation of the femoral vein with a sheath of approximately 7 French, a catheter of approximately 6 French is placed into the coronary sinus, a hydrophilic guide wire of approximately 0.035 mm is placed in the interventricular or lateral vein, and said balloon is inflated at a pressure approximately 1 to 2 atm in order to allow for stagnation of coronary circulation for a time period of approximately 10 minutes, with said therapeutic solution being injected at a rate of approximately 10 ml per minute.

[0018] In another aspect, the therapeutic solution is used to prevent rejection of a transplanted heart, said solution optimized to contain immune modulatory biologics, nucleic acids and cells. Cells useful for the practice of the invention include mesenchymal stem cells, endometrial regenerative cells, and dendritic cells. In one aspect, endometrial cells are derived from the endometrium by endometrial biopsy, curettage, or isolated by hysterectomy.

DETAILED DESCRIPTION OF THE ILLUSTRATED EMBODIMENTS

[0019] The current invention teaches methods of treating cardiovascular disease through the combination of a retrograde administration technique, the use of a new stem cell type, and the use of microenvironment modifiers. The invention may be practiced with each of these components as stand-alone procedures, with combinations of these components, or with substitution of various cells for the cell types described.

[0020] In one embodiment, the invention teaches the use of an endometrially-derived cell generated to express a unique gene transcription pattern.

Specifically, endometrial regenerative cells (ERC) may be purified, isolated, expanded, or extracted using protocols already disclosed, or protocols described here, and purified for higher activity based on markers disclosed in the current invention such as CD73, somatostatin receptor 1, spondin 2, aldehyde dehydrogenase, or anoctamin 4. The selection of these cells may be performed using means known in the art such as flow cytometry sorting, magnetic activated cell sorting, panning, or other affinity-based purification means.

[0021] The endometrium is chosen as starting material for cells useful in the practice of the invention given that it is a unique tissue in that it undergoes approximately 500 cycles of highly vascularized tissue growth and regression within a tightly controlled manner in the lifetime of the average female. This has triggered the concept that a self-renewing cell capable of differentiating into various tissues may be present in the endometrium.

[0022] One of the first series of data describing stem cells in the endometrium came from Prianishnikov in 1978 who reported that three types of stem cells exist: estradiol-sensitive cells, estradiol- and progesterone-sensitive cells and progesterone-sensitive cells [37]. Methods used by Prianshnikov et al are incorporated by reference to guide one of skill in the art to sources of endometrial cells for the practice of the invention in one embodiment. A study in 1982 demonstrated that cells in the endometrium destined to generate the decidua portion of the placenta are bone marrow derived [38], which prompted the speculation of a stem cell like cell in the endometrium. Further hinting at the possibility of stem cells in the endometrium were studies demonstrating expression of telomerase in endometrial tissue collected during the proliferative phase [39, 40]. One study demonstrated that telomerase expression was upregulated by estradiol and FGF-2, however this was restricted to epithelial cells of the endometrium [41]. Expression of stem cell markers such as c-kit and the pluripotency marker Oct-4 was reported in proliferating “label retaining” cells of the endometrium, thus further supporting the concept that stem cells exist in this compartment [42]. These references are incorporated to guide one of skill in the art to practical techniques that are useful in the isolation of cells that are useful for the practice of the invention.

[0023] One of the first reports of cloned stem cells from the endometrium was by Gargett's group who identified clonogenic cells capable of generating stromal and epithelial cell colonies, however no differentiation into other tissues was reported [43, 44]. The phenotype of these cells was found to be CD90 positive and CD146 positive [45]. The cells isolated by this group appear to be related to maintaining structural aspects of the endometrium but to date have not demonstrated therapeutic potential. Identification of stem cells capable of muscle differentiation from endometrial origin was first performed by Cui et al. [46], who used menstrual blood as a starting source for cell culture. They grew out adherent cells from a mononuclear preparation of screened menstrual blood that possessed a mesenchymal stem cell (MSC)-like morphology. The cells were positive for CD13, CD29, CD44, CD54, CD55, CD59, CD73, CD90, CD105 and STRO-1, and lacked CD14, CD34, CD45, CD133, and c-kit. The investigators demonstrated in vitro myocyte generation and myotubule formation, as well as in vivo ability to differentiate into dystrophin expressing muscle tissue in MDX-SCID mice. While these cells have unique differences to the stem cells described in the invention, the literature provides data that regenerative cells exist in the endometrium, which may be useful for stimulation of angiogenesis as part of a solution as described in one embodiment of the invention.

[0024] The first demonstration of pluripotent stem cells derived from the endometrium occurred almost simultaneously by two independent groups. Meng et al [47], used the process of cloning rapidly proliferating adherence cells derived from menstrual blood and generated a homogenous cell population expressing CD9, CD29, CD41a, CD44, CD59, CD73, CD90, and CD105 and lacking CD14, CD34, CD45 and STRO-1 expression. In contrast to Cui et al, the authors demonstrated the cells had substantially faster replicative potential as compared to bone marrow MSC, a unique cytokine and MMP profile, as well as ability to differentiate into cardiomyocytic, respiratory epithelial, neurocytic, myocytic, endothelial, pancreatic, hepatic, adipocytic, and osteogenic lineages. Interestingly, the cells identified expressed telomerase and OCT-4 but lacked expression of NANOG-1. Given the pluripotent nature of these cells, the authors named them "Endometrial Regenerative Cells" (ERC). Shortly after, Patel et al [48] reported a population of cells isolated using c-kit selection of menstrual blood mononuclear cells. The cells had a similar phenotype, proliferative capacity, and ability to be expanded for over 68 doublings without

induction of karyotypic abnormalities. Interestingly both groups found expression of the pluripotency gene OCT-4 but not NANOG. More recent investigations have confirmed these initial findings. For example, Park et al demonstrated that endometrial cells are significantly more potent originating sources for dedifferentiation into inducible pluripotent cells as compared to other cell populations [49]. Specifically, human endometrial cells displayed accelerated expression of endogenous NANOG and OCT4 during reprogramming compared with neonatal skin fibroblasts. Additionally, the reprogramming resulted in an average colony-forming iPS efficiency of $0.49 \pm 0.10\%$, with a range from 0.31-0.66%, compared with the neonatal skin fibroblasts, resulting in an average efficiency of $0.03 \pm 0.00\%$ per transduction, with a range from 0.02-0.03%. Suggesting pluripotency within the endometrium compartment, another study demonstrated that purification of side population (eg rhodamine effluxing) cells from the endometrium results in a population of cells expressing transdifferentiation potential with a genetic signature similar to other types of somatic stem cells [50].

[0025] In another aspect of the invention, cells are generated using a series of systems and standard operating procedures that allow for creation of a purified, clinical grade cell population. Specifically, female donors aged 12-50, more preferably, 18-30, are recruited under to collect menstrual blood samples for cell isolation and expansion. To be selected, donors are required to maintain a general health status, for example, in one embodiment, donors are required to be non-smokers, non-diabetic with no history of syphilis, hepatitis B or C, HIV or Chlamydia infection and no history or drug or alcohol abuse. Subjects are supplied with the menstrual blood collection kit (DivaCup®) and instructions (verbal and written). Donors are screened according to federal regulation 21 CFR1271 regarding allogeneic cell product. Also at this visit, the subjects complete: a Medical History Questionnaire; a Demographic Questionnaire; and a blood draw and urine specimen for Communicable Disease Screening (donors are required to test negative for: gonorrhea, Chlamydia, Hepatitis B, Hepatitis C, HIV, HTLV, CMV, and Syphilis). In one embodiment of the invention, collection of menstrual blood occurs on day 2 of the subject's cycle. Specifically, the menstrual blood collection device is inserted and worn for 12 hours. Each subject's collection schedule is coordinated with the study coordinator who arranges for courier pick up of the sample from the clinic to

the laboratory. The subject returns to the site for self-removal of the menstrual blood collection device. The subject then verifies that the label on the container matches the name on the form and then places the sealed container into the bag provided. The subject records the date and time when the sample was collected, and signs the collection form. The sample is then taken via courier to the laboratory. Subjects are instructed to immediately remove the menstrual blood collection cup at any sign of irritation. The menstrual blood collection cup (DivaCup®) is made of silicone – it is latex-free, plastic-free and BPA-free. Subjects are instructed to wear a sanitary pad while wearing the menstrual collection cup. Subjects are instructed that the menstrual collection cup should not be in place for longer than 12 hours. People who have a history of Toxic Shock Syndrome are excluded from enrollment. Subjects are also instructed that the menstrual collection cup is not a contraceptive device and is not to be worn during intercourse. Subjects are instructed that the menstrual collection cup will not protect against sexually transmitted disease. Subjects are instructed that the menstrual collection cup should not be flushed down the toilet. The subjects are required to dispose of the menstrual collection cup at the clinic. Identifiers associated with the health history of the subject are kept hard copy in locked file cabinets and only the PI, Co-I's and Sponsor director/manager have access to this information. Risks related to blood draw are minimized by using staff experienced with blood drawing. The menstrual blood sample is transferred at the clinic into ACD-A anticoagulant with 1% Pen/Strep and 0.1% Amphotericin B. At the laboratory (General BioTechnology, LLC), the collection tube containing the menstrual blood is transferred to a 50 ml conical tube and filled to the top with GMP manufactured Phosphate Buffered Saline (PBS) and centrifuged at 500 x g for 10 minutes. All supernatant is removed and the tube is filled to the top with PBS and centrifuged again at 500 x g for 10 minutes. Once the supernatant is removed, the pellet is re-suspended in 15mL DME/F-12 with 10% FBS. The cells are plated in a T75 flask and placed in the 37°C incubator. In one embodiment, the cells are cultured for a period of 1-30 days, more specifically, the cells may be cultured for 16 days in DMEF-12 with approximately 10%FBS (the culture is 70% confluent and passage 0). Cells are detached using TrypZean and 3 vials of 1M cells per vial are frozen. For ERC expansion, one vial of the passage 0 cells is thawed and plated into a T225 tissue culture treated flask. The cells are cultured for 3-4 days between each splitting, and one vial is frozen at each P1, P2, and P3. For cryopreservation, cells are collected and

equilibrated in a 10% GMP manufactured dimethyl sulfoxide (DMSO) solution, added step wise over 10 minutes. Cells are then packaged into cryovials and cooled at a controlled rate of $-1^{\circ}\text{C}/\text{minute}$ to -80°C and then placed into vapor phase LN2 for storage. One passage 3 vial is thawed and cultured until passage 6, splitting every 3-4 days between each passage. At passage 6, vials (24 total) are cryopreserved and one T225 flask (1M cells or ~ 4500 cells per cm^2) is plated for passage 7 in antibiotic free media. Once 70% confluent, four passage 7 vials are frozen down, and passage 6 and 7 vials are stored for the next expansion for the mice trials (MCB). The four passage 7 vials are used for each of the four days the mice will be transplanted. The passage 7 vials are thawed over 4 consecutive days, thawing one vial each day. Once plated, each culture is split every 3 days through passage 9. Once passage 9 is on the third day of culture, cells are harvested and split among 3 vials. One vial contains 5M cells, one vial contains 1M cells and one vial contains 0.15M cells, all re-suspended in 125 μl Isolyte S injectable saline solution (the transplant vehicle). Cells are then couriered to Indiana University for murine injection over 4 consecutive days (each day they receive the same 3 doses). The second round of mouse trials is performed in an identical fashion, thawing 1 x 1M cell vial of passage 6 cells, culturing 3 days and freezing 4 vials of passage 7 cells. Once the mouse trial is ready, each of the 4 x passage 7 vials are thawed over 4 consecutive days, cultured 3 days between each splitting and harvested at passage 9. Cell aliquots from each donor batch meet the following release criteria: (i) negative for bacterial and mycoplasma contamination; (ii) endotoxin levels < 1.65 EU/ml; (iii) morphology consistent with adherent, fibroblastic-like shape; (iv) CD90 and CD105 positive ($> 90\%$) and CD45 and CD34 negative ($< 5\%$) by flow cytometry; (v) Cell viability $> 70\%$ by 7-AAD staining. Mycoplasma, endotoxin and sterility are tested using validated contract laboratories. Cells are observed directly for morphology over the course of the expansion. All cultures are required to exhibit CFU-F morphology with robust growth (estimated doubling rate of 26 hours). Remaining passage 9 cells are centrifuged and re-suspended in 1X PBS, and counted on a hemocytometer. Cells are incubated with CD45, CD34, CD90, CD105, and 7-AAD. All antibodies are directly conjugated. After incubation, cells are centrifuged and re-suspended in 1X PBS and ran immediately on the Epics XL-MCL (Beckman Coulter). Channel settings for the flow cytometer consist of: CD90 FITC: 455V; CD45 FITC: 455V; CD105 PE: 730V; CD34 PE: 730V; and 7AAD: 876V. Emission Wavelengths consist of: FITC

wavelength 488nm; PE wavelength 570nm; and 7AAD wavelength 647nm. Flow cytometry is run on every murine dose. On all injections, cells mark >90% positive for CD105 and CD90, and <5% for CD45 and CD34. Additionally, cells are >90% viable based on 7-AAD. For clinical development, the use of a master cell bank is contemplated. The Master Cell Bank (MCB) may be generated from Passage 3 cells that are frozen down in CellSeal vials, containing 1 million cells per vial, with approximately 200 vials according to MS-CM-010. The MCB is stored at -180°C in liquid nitrogen temperature monitored containers. A flow cytometry test is done on a sample of the MCB cells (10% of product). Cells should mark >90% positive for CD90, CD105 and <5% positive for CD34, CD45. Sample cells along with expended media from the culture plates are sent to LABS, Inc for a sterility test. Two SPS tubes containing 1mL of expended media are labeled for aerobic and anaerobic testing and shipped to LABS, Inc. A mycoplasma test is done at LABS, Inc to look for the presence of agar cultivable and non-agar cultivable mycoplasma. The sterility testing and mycoplasma testing should both yield negative results. An in vivo viral assay will be performed on cells by BioReliance (“In Vivo: Suckling and Adult Mice, Guinea Pigs, Embry. Hen Eggs” and has protocol number 005002). This assay is used routinely to check for unapparent viruses in cell banks and is run in compliance with the U.S. FDA Good Laboratory Practice regulations (21 CFR Part 58). Lytic and/or haemadsorbing viruses will be detected after inoculation using 3 sensitive indicator cell lines (specifically MRC-5, Vero and NBL-6 lines) with the MCB test article. This will be performed by a contract provider (BioReliance Corporation, Rockville, MD; protocol 003000 Indicator cells will be examined regularly for signs of a cytopathic effect (CPE) over a period of 14 or 28 days (with a passage after a period of 14 days) with two haemadsorption assays carried out with each of the three erythrocyte species. The 28-day period will be used for detection of cytomegalovirus (CMV). Isoenzyme electrophoresis will be performed for the MCB testing, WCB testing and final product lot release by BioReliance according to GMP Code: 380801. Karyology may be evaluated by a contract laboratory (BioReliance; GMP Code: 378001). After the testing panel from the master cell bank (MCB test panel) is received, one vial from the master cell bank is thawed (SOP MS-CM-009) using the same protocol as the passage 0 cells, and placed into one T225 flask using cDME/F-12 with 10% FBS (passage 4). After culturing for 4-5 days, cells are split to five T225s flasks and cultured for 4-5 days (passage 5). Cells are then split again to 30

T225 flasks and cultured for 4-5 days (passage 6). When cells are 70% confluent, they are frozen down in approximately 140 vials of 1 million cells per vial generating the working cell bank

[0026] For production of cells, reagent qualification may be necessary. The qualification process begins with the vendor of the reagent. The vendor is qualified through our standard operating procedure. A corresponding form is completed and approval gained before a vendor can be used. The Criteria identified as important in qualifying a supplier include quality of product, services offered, competitive pricing, communication, availability, how complaints are handled and the overall fit to our systems. This list is not all inclusive. Quality Systems reviews each qualification form and will approve based on the criteria stated above. Once the vendor is approved, they are added to the Supplies and Services List. Associates ordering supplies including reagents use the list. Only approved vendors on the list are used by associates ordering supplies involving reagents. Once the reagent arrives, it is logged on the Supplies Receipt, Inspection and Inventory Log. The form instructs the associate to complete certain information for the incoming reagent. These fields are date received, initials of receiver, name of the item, manufacturer, lot number, expiration date, package passed visual inspection, product passed visual inspection, date available for use and quantity. The COA is examined for reagents and placed in the applicable COA binder under that reagent name. These binders are retained per the record retention procedure. Once this is completed the reagent is released from quarantine and placed in the applicable area. If the reagent needs refrigerated or is to remain frozen, it is placed in the applicable storage environment. FDA or other national regulatory body-approved reagents are used if available. In one embodiment, an excipient used in the cryopreservation of the cells is Dimethyl Sulfoxide (DMSO). Each dose of ERC is cryopreserved using 10% DMSO, or 2 mL of DMSO in a total volume of 10 mL of final product. Infusion of this amount of DMSO is well within the safety parameters for a 30 kg child; Pediatric Stem Cell Transplant SOP states that the maximum dose of DMSO is 15 mg/kg/dose.

[0027] During the process of manufacturing, it is ideal for the production to occur in a class 10,000 clean production suite. Each technician properly gowns when entering in the GMP room. Before entry into the clean lab area, the technician obtains

a bunny suit in the ante room. After the hood of the bunny suit is placed on, a mouth covering is put on, making sure that all hair is fully covered under the hood and mouth covering. The technician puts on a pair of sterile powder free gloves, and enters the clean lab space with the sample. Environmental monitoring is performed in the Class 10,000 clean room. The clean room uses Biological Safety Cabinets (BSC) which maintains a Class 5 environment. BSC are certified annually by an outside qualified vendor. Settling plates are performed every time the BSC is in use for processing and evaluated for acceptable criteria based on USP. One settling plate is placed in the BSC during processing for a minimum of 30 minutes. Once per package, as a negative control, one covered settling plate is placed inside the BSC at the same time. After the settling plate is in the BSC, evaluate the plate for presence of bacterial colonies, Colony Forming Units (cfu), by allowing the plate to incubate for 48 hours at 37°C. Levels requiring alert are more than 1 colony per plate. Incubator temperature should be 36-38°C. TSA plates are used to evaluate the wide spectrum of possible bacteria present. Prepared plates are in their original wrapping at 2 – 8°C and are warmed to room temperature prior to use. The product is validated from the time of manufacture to be stable at room temperature (25°C) for 192 h (8 days). Additionally the clean room is monitored for room temperature and particle counts. Acceptable room temperature is between 15 and 30 degrees Celsius. A MetOne Aerocet 531 particle counter, or alternative, may be used to evaluate the particles in the air. The particle counter is used to detect and count the number of particles found in the air of the clean room. It is used to confirm that the number of loose particles in the air is less than 10,000 0.5 micron particles per ft³. The particle counter is run on a weekly basis in the three major areas of the clean room space. It is run for 30 minutes each in the gowning area, on the counter inside the clean room space and inside the hood. A settle plate is placed each time the particle counter is in use, next to the counter for the 30 minutes it is being run. After each use of the clean room, the BSC is wiped down with 5.25% bleach then followed by a 70% isopropyl alcohol. Countertops inside the clean room space are wiped down with 70% isopropyl alcohol each day. Once a week all surfaces inside the clean room, including floor, are wiped down with enzymatic cleaner LpH using a dry disposable cloth. Yearly, all walls and ceiling are cleaned with a lint roller, and all soft walls are cleaned with 70% isopropyl alcohol. Before laboratory technicians are allowed into the clean room, a gowning competency must be passed. RODAC plates are utilized to assess the competency of

the technician. The acceptable limits of CFU/ plate are determined according to local regulations. In one example, the following limits are used: Finger tips 10, CFU/plate, Gown Zipper 5 CFU/plate, Gown Lower Sleeve Area 5 CFU/plate, Hood Corner 5 CFU/Plate, Floor Surface 10 CFU/plate.

[0028] In another example, Menstrual Blood Mononuclear Cell Isolation begins with the delivery of the sample to the processing lab. Washing Tube containing the menstrual blood sample is topped up to 50 ml with PBS in the Biological Safety Cabinet and cells are washed by centrifugation at 500 g for 10 minutes at room temperature, which produces a cell pellet at the bottom of the conical tube. Under sterile conditions supernatant is decanted and the cell pellet is gently dissociated by tapping until the pellet appeared liquid. The pellet is re-suspended in 50 ml of PBS and gently mixed so as to produce a uniform mixture of cells in PBS. The cells are washed again by centrifugation at 500g for 10 minutes at room temperature. Under sterile conditions, the supernatant is decanted and the cell pellet is re-suspended in 15mL complete DME/F-12 media (Hyclone) supplemented with 10% Fetal Bovine Serum (Atlas Biologicals specified to have Endotoxin level: ≤ 100 EU/ml (levels routinely ≤ 10 EU/ml) and hemoglobin level: ≤ 30 mg/dl (levels routinely ≤ 25 mg/dl). The serum lot used is sequestered and one lot is used for all experiments. Additionally, the media is supplemented with 1% penicillin/streptomycin and 0.1% amphotericin B. The sample is plated in a T75 flask and placed in a 37°C incubator. Media is changed after 24 hours, and then every 2-3 days at the discretion of the laboratory staff. Once cells reach 70-80% confluent, they are frozen down for quarantine (minimum 2 vials) and a culture screen is completed. The expended media from the culture is sent for sterility and mycoplasma testing. For sterility testing, the media is placed in 2 SPS tubes (1mL media per tube) and sent to the testing facility. Cells from the sample are aliquotted into 2 vials which are frozen in 2 CellSeal 2.0 ml cryovials containing approximately 1 million cells per vial. Freezing is performed as follows: Freezing media is prepared by adding 1 ml of DMSO to 4 ml of complete DME/F-12 for a final product of 20% DMSO.

[0029] Cells are frozen as follows: a) Two 2mL CellSeal vials are labeled to include processing date, passage number, donor identifier code, and cell count. Labeled cryovials are placed in a cryovial rack; b) Cells are pelleted by centrifugation

at 500g for 5 minutes at room temperature. Centrifugation is performed in 15 ml conical tubes; c) After the supernatant is removed, cells are re-suspended in 1mL complete DME/F-12; d) Then, 1 ml of the 20% DMSO is added the cells at a rate of 10 drops per 30 seconds using an 18 gauge needle. This is based on the cell concentration to yield approximately 1 million cells per ml in a volume of approximately 2 ml of 10% DMSO; e) Using a syringe and 18 gauge needle, 1mL of the cell mixture is drawn into the syringe. The sample is injected into the vial through puncturing the top septum of the vial. F) Using a heat sealer, seal both tubing segments. G) Place the vials into a box in box freezer and place in a -85 validated freezer. H) Vials are transferred to LN2 after 24 hours into a designated LN2 tank for ERC vials only. In a sterile class II biologic safety within a class 10,000 clean production suite, cells from the two vials frozen at passage 0 are thawed under controlled conditions and each is washed in a 50 ml conical tube with 45mL complete DME/F-12 (cDME/F-12) media (Hyclone) supplemented with 10% Fetal Bovine Serum from qualified dairy cattle herds with known negative pathogen pedigree (Atlas Biologicals) specified to have Endotoxin level: ≤ 100 EU/ml (levels routinely ≤ 10 EU/ml) and hemoglobin level: ≤ 30 mg/dl (levels routinely ≤ 25 mg/dl). The serum lot used is sequestered and one lot is used for all experiments. Cells are subsequently placed in two T-225 flasks containing 45 ml of cDME/F-12 and cultured for 24 hours at 37 °C at 5% CO₂ in a fully humidified atmosphere. This allows the ERC precursors to adhere. Non-adherent cells are washed off using cDME/F-12 by gentle rinsing of the flask. The flask is then cultured for 4 days after which approximately 6.5M cells will be present per flask (passage 1). The cells from the flasks are split into ten T225s and cultured for 4 days (passage 2), after which it is split again to 50 T225 flasks (passage 3). This yields approximately 200 million cells. These cells are frozen down in vials containing ~1M cells generating the master cell bank (on average 200 vials). After the testing panel from the master cell bank (MCB test panel) is received (see table 3), one vial from the master cell bank is thawed using the same protocol as the passage 0 cells, and placed into one T225 flask using cDME/F-12 with 10% FBS (passage 4). After culturing for 4-5 days, cells are split to five T225s and cultured for 4-5 days (passage 5). Cells are split again to 30 T225 and cultured for 4-5 days (passage 6). When cells are 70% confluent, they are frozen down in approximately 140 vials of 1 million cells per vial generating the working cell bank. When a patient dose is needed, one vial from the working cell bank is

thawed and placed in one T225 flask (passage 7). After 4-5 days of culturing, cells are split to 5 T225 flasks (passage 8). After another 4-5 days of culturing, cells are split to 30 T225 flasks (passage 9). When the plates reach 70% confluence, cells are harvested for the clinical dose. The flasks yield approximately 120 million cells. Only 100 million cells are needed per clinical dose, and any extra cells will be used for release testing panel or are discarded. Cells are re-suspended in 10mL of Isolyte S Multi-Electrolyte Solution. Then, ten milliliters of a 10% DMSO made with Isolyte S is added at a controlled rate over 5 minutes to the cells for a total of 20mL of final product. The cell dose is packaged in a Charter CF-50 freezing bag, placed in a box in box freezing case and put in a validated -85°C freezer. All processes in the generation, expansion, and product production are performed under conditions and testing that is compliant with current Good Manufacturing Processes and appropriate controls. Guidance issued by the FDA in 1998 Guidance for Industry: Guidance for Human Somatic Cell Therapy and Gene Therapy, the 2008 Guidance for FDA Reviewers and Sponsors Content and Review of Chemistry, Manufacturing, and Control (CMC) Information for Human Somatic Cell Therapy Investigational New Drug Applications (INDs), and the 1993 FDA points-to-consider document for master cell banks are all followed for the generation of the cell products described. The time elapsed from cell collection to storage is variable. A typical sample will take 2 weeks from time of collection until freezing for quarantine. Time cannot be calculated through final harvest because storage time is unknown. Storage time is based on need for the cells. ERC are stored as frozen cells according to the validated instructions for use for the Charter CF-50 bags. Some data concerning ERC freezing and recovery are presented in the validation procedure for cell products. This is in agreement with other industry standards for storage of cell therapy products. Stability during cryopreservation is monitored using a comparison of pre-freeze and post-thaw data. The criterion tested is flow cytometry including viability and time to confluence. Prior to patient administration, doses will be sent to the administering facility frozen. The dose(s) will be sent in a dry shipper that will continuously monitor the temperature in route. Temperature data from shipment will be downloaded upon return of the dry shipper. Data will be shared with administering facility upon request. The facility will be responsible for the thawing of the cells. Once the cells are thawed a time limit of 6 hours has been established by which the cells must be administered. The temperature of 4 degrees Celsius must be maintained during

storage of the thawed cells prior to administration. This is found in Appendix II under ERC Validations. Charter CF-50 bags are filled with cellular product from cell bank that has been generated and tested according to the tests described in sections 1 and 2. Filling of Cryocyte bags will be performed by General Biotechnology with cells previously expanded from the working cell bank at passage 9. Cells are resuspended in 20mL of Isolyte S Multi-Electrolyte Solution (B. Braun Medical) containing 10% DMSO. Each Charter CF-50 bag will contain 25, 50, or 100 million cells in a volume of 10 ml. Depending on indication, various doses may be used. For example, it may be possible to administer up to 400 million cells without observation of cell-mediated adverse events.

[0030] In order to test cell sterility, a variety of assays are known to one of skill in the art. Specifically, in one embodiment, a 2mL aliquot of expended media from the culture is collected and placed into 2 SPS collection tubes (each tube containing 1mL of the expended media). One tube is labeled for “Aerobic” and one tube is labeled for “Anaerobic” with a unique identifier for the sample. Samples are shipped to LABS, Inc for sterility testing. The USP/CFR 610.12 GMP (BASIC STERILITY) testing method is used for sterility. Bacteriostatic/Fungistatic activity uses the direct inoculation method. Cultures are incubated at LABS, Inc for two weeks for sterility screening. General BioTechnology received results within 3 weeks of shipment. For mycoplasma contamination testing, in process testing can be completed using expended media from the MSC cultures can be tested for mycoplasma using the Lonza Lucetta™ Luminometer with MycoAlert® Mycoplasma Detection Assay at General BioTechnology. MCB and final release testing is completed at Labs, Inc. Testing at Labs, Inc will test for the presence of agar cultivable and non-agar cultivable mycoplasma. The donors from which the ERC are generated are extensively tested for infectious agents. The ERC are cultured in a Class 10,000 clean room restricted to production of human cell products. At the MCB and WCB level, lytic and/or haemadsorbing viruses will be detected after inoculation using 3 sensitive indicator cell lines (specifically MRC-5, Vero and NBL-6 lines) with the MCB test article. This will be performed by a contract provider (BioReliance Corporation, Rockville, MD; protocol 003000 Indicator cells will be examined regularly for signs of a cytopathic effect (CPE) over a period of 14 or 28 days (with a passage after a period of 14 days) with two haemadsorption assays carried out with each of the three

erythrocyte species. The 28-day period will be used for detection of cytomegalovirus (CMV). At the MCB level, in vivo viral testing is performed by a contract provider (BioReliance; protocol 005002: "In Vivo: Suckling and Adult Mice, Guinea Pigs, Embry. Hen Eggs"). This assay is used routinely to check for inapparent viruses in cell banks. This assay is run in compliance with the U.S. FDA Good Laboratory Practice regulations (21 CFR Part 58). For final formulation, there is an excipient that is used in one of the preferred embodiments. The final product contains ERC re-suspended in Isolyte S Multi-Electrolyte Solution (B. Braun Medical, Irvine, CA) with 10% dimethyl sulfoxide (DMSO) as a cryopreservative. Any small amounts of medium which may remain in the product are safe for infusion. No testing for residual reagents is performed. Testing is performed using the US Pharmacopeia standard for basic sterility USP/CFR 610.12 GMP. Flow cytometry is used to validate the potency by marking CD90, CD105 positive (>90%), CD45, CD34 negative (<5%). A 2mL aliquot of expended media from the culture is shipped to LABS, Inc for endotoxin testing. See appendix VI for LABS, Inc FDA certifications. The USP/CFR 610.12 GMP (BASIC STERILITY) testing method is used for sterility. Potency is tested by the supernatant stimulation of HUVEC proliferation. Supernatant from the culture of 1 million cells is cultured for 48 hours to stimulate proliferation by > 150% in a standard culture. During manufacture of stem cells, there are processes and procedures to ensure the quality of the product. These processes and procedures are validated and reviewed to continuously control the integrity of our products. The following are process control measures which maintain control over our product and are designed to prevent contamination or transmission of infectious disease. Standard Operating Procedures or written policies and procedures are developed and written with a standard format and are reviewed annually. Clinical outcomes are also monitored which collects patient data on adverse events of a patient. These events are part of the quality system internal assessment schedule to be reviewed as applicable events happen. Change control is procedures for how to properly implement changes. These changes are documented and approved. Materials used in the processing of our products are from qualified suppliers. Materials are received and handled according to our written procedures. Critical materials are traceable to the product as per our procedures. Equipment used for any purposes is maintained according to manufacturer guidelines and Good Laboratory Practices. Records are maintained of all maintenance and services rendered such as annual calibration. equipment taken

out of service is documented and return to service is also documented. Critical equipment is monitored according to our quality control and operational procedures. Cleaning and sanitation methods are defined for critical equipment. Equipment is validated for use before placed into service. Equipment is calibrated and maintained according to manufacturer's recommendations, regulatory requirements, and accrediting standards. Documentation is kept for each piece of equipment regarding identification number, repairs, scheduled calibration, and disposition. Critical equipment is traceable to the processing of an individual product. The manufacturing processes for ERC are qualified through validation of processes and procedures with the end goal of producing ERC doses for use. Please see the appendices for the actual validations. Validation of the clean room was obtained through certification by Ace Lab Systems, Inc.

[0031] The cell type generated according to the above description is characterized by expression of unique molecules. This is in contrast to other types of stem cells. The most commercially developed stem cell type outside of the hematopoietic sphere is the bone marrow derived mesenchymal stem cell. This cell population expresses significantly higher concentrations of the following genes as compared to bone marrow mesenchymal cells: somatostatin receptor 1, forkhead box L2, FAM105A, synaptopodin 2-like, anoctamin 4, spondin 2, CARD16, VAT1L, indolethylamine N-methyltransferase, deiodinase, iodothyronine, type II (DIO2), aldehyde dehydrogenase 1 family, member A1, 5-hydroxytryptamine (serotonin) receptor 2B, caspase recruitment domain family, member 17, Rho GTPase activating protein 20, zinc finger and BTB domain containing 46 (ZBTB46), synaptopodin 2-like (SYNPO2L), transcript variant 1, mRNA, chromosome 13 open reading frame 15 (C13orf15), mRNA, homeobox D11 (HOXD11), mRNA, oxidized low density lipoprotein (lectin-like) receptor 1 (OLR1), transcript variant 2, mRNA, homeobox D10 (HOXD10), mRNA, Pregnancy specific beta-1-glycoprotein 4, matrix metalloproteinase 3 (stromelysin 1, progelatinase) (MMP3), mRNA, actin filament associated protein 1-like 2 (AFAP1L2), transcript variant 2, mRNA, SH3-domain GRB2-like (endophilin) interacting protein 1 (SGIP1), mRNA, solute carrier family 7 (cationic amino acid transporter, y+ system), member 2 (SLC7A2), transcript variant 1, mRNA, pregnancy specific beta-1-glycoprotein 8 (PSG8), transcript variant 3, mRNA, Wilms tumor 1 (WT1), transcript variant F, mRNA, platelet-derived growth

factor beta polypeptide (PDGFB), transcript variant 1, mRNA, forkhead box F1 (FOXF1), mRNA, mannan-binding lectin serine peptidase 1 (C4/C2 activating component of Ra-reactive factor) (MASP1), transcript variant 1, mRNA, deiodinase, iodothyronine, type II (DIO2), transcript variant 4, mRNA, G protein-coupled receptor 126 (GPR126), transcript variant b1, mRNA, stimulated by retinoic acid gene 6 homolog (mouse) (STRA6), transcript variant 6, mRNA, hydroxysteroid (11-beta) dehydrogenase 1 (HSD11B1), transcript variant 2, mRNA, RAS guanyl releasing protein 2 (calcium and DAG-regulated) (RASGRP2), transcript variant 4, mRNA, membrane bound O-acyltransferase domain containing 1 (MBOAT1), mRNA, LON peptidase N-terminal domain and ring finger 2 (LONRF2), mRNA, interferon-induced protein with tetratricopeptide repeats 2 (IFIT2), mRNA, cathepsin C (CTSC), transcript variant 3, mRNA, caspase 1, apoptosis-related cysteine peptidase (interleukin 1, beta, convertase) (CASP1), transcript variant beta, mRNA, integrin, alpha 4 (antigen CD49D, alpha 4 subunit of VLA-4 receptor) (ITGA4), mRNA, integrin, alpha 6 (ITGA6), transcript variant 1, mRNA, contactin 3 (plasmacytoma associated) (CNTN3), mRNA, synaptophysin-like 2 (SYPL2), mRNA, Rho GTPase activating protein 25 (ARHGAP25), transcript variant 4, mRNA, potassium voltage-gated channel, Shal-related subfamily, member 2 (KCND2), mRNA, S100 calcium binding protein A4 (S100A4), transcript variant 1, mRNA, chemokine (C-C motif) receptor-like 2 (CCRL2), transcript variant 2, mRNA, integrin, alpha 6 (ITGA6), transcript variant 2, mRNA, guanylate binding protein 4 (GBP4), mRNA, multiple C2 domains, transmembrane 1 (MCTP1), transcript variant S, mRNA, interferon-induced protein with tetratricopeptide repeats 2 (IFIT2), mRNA, C1q and tumor necrosis factor related protein 9 (C1QTNF9), mRNA, progesterone receptor (PGR), transcript variant 2, mRNA, hypothetical LOC646113 (FLJ43390), non-coding RNA. zinc finger and BTB domain containing 46 (ZBTB46), mRNA, interferon-induced protein with tetratricopeptide repeats 3 (IFIT3), transcript variant 1, mRNA, microphthalmia-associated transcription factor (MITF), transcript variant 2, mRNA, interleukin 24 (IL24), transcript variant 4, mRNA, neuronal pentraxin I (NPTX1), mRNA, integrin, alpha 4 (antigen CD49D, alpha 4 subunit of VLA-4 receptor) (ITGA4), mRNA, WT1 antisense RNA (non-protein coding) (WT1-AS), non-coding RNA, microphthalmia-associated transcription factor (MITF), transcript variant 2, mRNA, sterile alpha motif domain containing 12 (SAMD12), transcript variant 1, mRNA, chromosome 7 open reading frame 58 (C7orf58), transcript variant 1, mRNA, phospholipase B domain

containing 1 (PLBD1), mRNA, podocalyxin-like (PODXL), transcript variant 2, mRNA, interleukin 8 (IL8), mRNA, chromosome 7 open reading frame 58 (C7orf58), transcript variant 2, mRNA, protein kinase, cAMP-dependent, regulatory, type II, beta (PRKAR2B), mRNA, chromosome 8 open reading frame 4 (C8orf4), mRNA, stimulated by retinoic acid gene 6 homolog (mouse) (STRA6), transcript variant 5, mRNA, progesterone receptor (PGR), transcript variant 2, mRNA, angiopoietin 2 (ANGPT2), transcript variant 2, mRNA, synaptophysin-like 2 (SYPL2), mRNA, retinoic acid receptor responder (tazarotene induced) 2 (RARRES2), mRNA, claudin 1 (CLDN1), mRNA, sal-like 1 (Drosophila) (SALL1), transcript variant 1, mRNA, calcium channel, voltage-dependent, T type, alpha 1H subunit (CACNA1H), transcript variant 2, mRNA, armadillo repeat containing 4 (ARMC4), mRNA, phosphatidylinositol-specific phospholipase C, X domain containing 3 (PLCXD3), mRNA, G protein-coupled receptor, family C, group 5, member A (GPC5A), mRNA, GATA binding protein 2 (GATA2), transcript variant 1, mRNA, actin filament associated protein 1-like 1 (AFAP1L1), transcript variant 1, mRNA, ST6 (alpha-N-acetyl-neuraminyl-2,3-beta-galactosyl-1, 3)-N-acetylgalactosaminide alpha-2,6-sialyltransferase 5 (ST6GALNAC5), mRNA, H19, imprinted maternally expressed transcript (non-protein coding) (H19), non-coding RNA, sphingosine-1-phosphate receptor 3 (S1PR3), mRNA, protein kinase, cAMP-dependent, regulatory, type II, beta (PRKAR2B), mRNA, interleukin 7 receptor (IL7R), mRNA, calcium/calmodulin-dependent protein kinase IG (CAMK1G), mRNA, homeobox A11 (HOXA11), mRNA, renin (REN), mRNA, transcription factor AP-2 gamma (activating enhancer binding protein 2 gamma) (TFAP2C), mRNA, cathepsin C (CTSC), transcript variant 2, mRNA, STAM binding protein-like 1 (STAMBPL1), mRNA, Hypothetical protein LOC254057, adrenomedullin (ADM), mRNA, tenascin XB (TNXB), transcript variant XB-S, mRNA, KH domain containing, RNA binding, signal transduction associated 3 (KHDRBS3), mRNA, solute carrier family 35, member F3 (SLC35F3), mRNA, collagen, type IV, alpha 6 (COL4A6), transcript variant B, mRNA, protocadherin 7 (PCDH7), transcript variant a, mRNA, chromosome 10 open reading frame 58 (C10orf58), transcript variant 1, mRNA, fibroblast growth factor 9 (glia-activating factor) (FGF9), mRNA, sushi domain containing 3 (SUSD3), mRNA, melanoma associated antigen (mutated) 1-like 1 (MUM1L1), transcript variant 2, mRNA, keratin 18 pseudogene (FLJ40504), non-coding RNA, C-type lectin domain family 14, member A (CLEC14A), mRNA, 1-

acylglycerol-3-phosphate O-acyltransferase 9 (AGPAT9), mRNA, phosphodiesterase 8B (PDE8B), transcript variant 3, mRNA, ArfGAP with dual PH domains 2 (ADAP2), mRNA, Keratin 18, family with sequence similarity 65, member C (FAM65C), mRNA, androgen receptor (AR), transcript variant 1, mRNA, phosphodiesterase 9A (PDE9A), transcript variant 2, mRNA, Intercellular adhesion molecule 1, monoglyceride lipase (MGLL), transcript variant 2, mRNA, HOXA11 antisense RNA 1 (non-protein coding) (HOXA11-AS1), antisense RNA, receptor (chemosensory) transporter protein 4 (RTP4), mRNA, reticulon 4 receptor (RTN4R), mRNA, Keratin pseudogene, annexin A3 (ANXA3), mRNA, RAS guanyl releasing protein 2 (calcium and DAG-regulated) (RASGRP2), transcript variant 3, mRNA, serum deprivation response (SDPR), mRNA, collagen, type XIII, alpha 1 (COL13A1), transcript variant 21, mRNA, v-ets erythroblastosis virus E26 oncogene homolog 2 (avian) (ETS2), mRNA, ADAM metallopeptidase domain 8 (ADAM8), transcript variant 3, mRNA, prostate collagen triple helix (PCOTH), transcript variant 1, mRNA, family with sequence similarity 124A (FAM124A), transcript variant 1, mRNA, interferon, alpha-inducible protein 27 (IFI27), transcript variant 2, mRNA, hypothetical protein MGC16121 (MGC16121), non-coding RNA, egf-like module containing, mucin-like, hormone receptor-like 2 (EMR2), transcript variant 4, mRNA, RAS guanyl releasing protein 2 (calcium and DAG-regulated) (RASGRP2), transcript variant 3, mRNA, KH domain containing, RNA binding, signal transduction associated 3 (KHDRBS3), mRNA, chromosome 9 open reading frame 47 (C9orf47), transcript variant 1, mRNA, family with sequence similarity 162, member B (FAM162B), mRNA, sodium channel, voltage-gated, type IX, alpha subunit (SCN9A), mRNA, glutaredoxin (thioltransferase) (GLRX), transcript variant 2, mRNA, four jointed box 1 (Drosophila) (FJX1), mRNA, chromosome 10 open reading frame 58 (C10orf58), transcript variant 1, mRNA, archaelysin family metallopeptidase 1 (AMZ1), mRNA, laminin, alpha 5 (LAMA5), mRNA, myosin XVI (MYO16), transcript variant 2, mRNA, SH3-domain GRB2-like (endophilin) interacting protein 1 (SGIP1), mRNA, nuclear receptor subfamily 2, group F, member 1 (NR2F1), mRNA, GULP, engulfment adaptor PTB domain containing 1 (GULP1), mRNA, actin binding LIM protein family, member 3 (ABLIM3), mRNA, transmembrane protein 154 (TMEM154), mRNA, germ cell associated 1 (GSG1), transcript variant 1, mRNA, suppressor of cytokine signaling 2 (SOCS2), mRNA, GULP, engulfment adaptor PTB domain containing 1 (GULP1), mRNA, integrin,

alpha 4 (antigen CD49D, alpha 4 subunit of VLA-4 receptor) (ITGA4), mRNA, DENN/MADD domain containing 2A (DENND2A), mRNA, interferon-induced protein with tetratricopeptide repeats 1 (IFIT1), transcript variant 2, mRNA, C-type lectin domain family 2, member B (CLEC2B), mRNA, hairy and enhancer of split 5 (Drosophila) (HES5), mRNA, chromosome 7 open reading frame 58 (C7orf58), transcript variant 2, mRNA, Keratin 18, cathepsin C (CTSC), transcript variant 1, mRNA, G protein-coupled receptor 183 (GPR183), mRNA, Mitogen-activated protein kinase kinase kinase 8 caspase recruitment domain family, member 9 (CARD9), transcript variant 2, mRNA, nidogen 1 (NID1), mRNA, adenosine monophosphate deaminase 3 (AMPD3), transcript variant 3, mRNA, opioid growth factor receptor-like 1 (OGFRL1), mRNA, interferon induced transmembrane protein 1 (9-27) (IFITM1), mRNA, interleukin 2 receptor, beta (IL2RB), mRNA, tripartite motif containing 14 (TRIM14), transcript variant 1, mRNA, acyl-CoA synthetase short-chain family member 1 (ACSS1), nuclear gene encoding mitochondrial protein, mRNA, RNA binding motif protein 24 (RBM24), transcript variant 3, mRNA, stathmin-like 2 (STMN2), transcript variant 1, mRNA, GULP, engulfment adaptor PTB domain containing 1 (GULP1), mRNA, secreted and transmembrane 1 (SECTM1), mRNA, betaine-homocysteine S-methyltransferase 2 (BHMT2), transcript variant 1, mRNA, lymphocyte-activation gene 3 (LAG3), mRNA, transmembrane protein 51 (TMEM51), transcript variant 1, mRNA, guanine nucleotide binding protein (G protein), gamma 11 (GNG11), mRNA, CD163 molecule-like 1 (CD163L1), mRNA, major histocompatibility complex, class I, F (HLA-F), transcript variant 2, mRNA, endoplasmic reticulum metalloproteinase 1 (ERMP1), mRNA, cytochrome b5 reductase 2 (CYB5R2), mRNA, mitogen-activated protein kinase kinase kinase 5 (MAP3K5), mRNA, interleukin 20 (IL20), mRNA, T-box 3 (TBX3), transcript variant 1, mRNA, adrenergic, alpha-1D-, receptor (ADRA1D), mRNA, leucine rich repeat containing 8 family, member C (LRRC8C), mRNA, folate receptor 3 (gamma) (FOLR3), mRNA, tumor necrosis factor receptor superfamily, member 21 (TNFRSF21), mRNA, actin binding LIM protein family, member 3 (ABLIM3), mRNA, CD44 molecule (Indian blood group) (CD44), transcript variant 7, mRNA, phosphatidylinositol-3,4,5-trisphosphate-dependent Rac exchange factor 1 (PREX1), mRNA, tripartite motif containing 14 (TRIM14), transcript variant 1, mRNA, aldehyde dehydrogenase 1 family, member A1 (ALDH1A1), mRNA, adaptor-related protein complex 1, mu 2 subunit (AP1M2),

mRNA, integrin, alpha 1 (ITGA1), mRNA, mitogen-activated protein kinase kinase 5 (MAP3K5), mRNA, serpin peptidase inhibitor, clade B (ovalbumin), member 2 (SERPINB2), transcript variant 2, mRNA, scavenger receptor class B, member 1 (SCARB1), transcript variant 1, mRNA, homeobox D9 (HOXD9), mRNA, G protein-coupled receptor, family C, group 5, member B (GPC5B), mRNA, Rho guanine nucleotide exchange factor (GEF) 16 (ARHGEF16), mRNA, adrenergic, alpha-2A-, receptor (ADRA2A), mRNA, intercellular adhesion molecule 4 (Landsteiner-Wiener blood group) (ICAM4), transcript variant 2, mRNA, guanine nucleotide binding protein (G protein), gamma 4 (GNG4), transcript variant 1, mRNA, BCL2-like 10 (apoptosis facilitator) (BCL2L10), mRNA, monoglyceride lipase (MGLL), transcript variant 1, mRNA, Furry homolog (Drosophila) phorbol-12-myristate-13-acetate-induced protein 1 (PMAIP1), mRNA, transmembrane and tetratricopeptide repeat containing 1 (TMTC1), transcript variant 1, mRNA, collagen, type IV, alpha 5 (COL4A5), transcript variant 1, mRNA, disrupted in renal carcinoma 3 (DIRC3), non-coding RNA, Rho GDP dissociation inhibitor (GDI) beta (ARHGDIB), mRNA, oxytocin receptor (OXTR), mRNA, tumor necrosis factor receptor superfamily, member 6b, decoy (TNFRSF6B), mRNA, cytochrome b5 reductase 2 (CYB5R2), mRNA, peptidase M20 domain containing 2 (PM20D2), mRNA, shroom family member 3 (SHROOM3), mRNA, family with sequence similarity 46, member C (FAM46C), mRNA, nuclear factor of kappa light polypeptide gene enhancer in B-cells inhibitor, epsilon (NFKBIE), mRNA, tumor necrosis factor receptor superfamily, member 6b, decoy (TNFRSF6B), mRNA.

Examples

Example I Generation of Clinical Grade Endometrial Regenerative Cells

[0032] ERC menstrual blood derived, expanded cells characterized by plastic adherent cells possessing a mesenchymal-like morphology and expressing the markers CD90 and CD105, while lacking expression of CD14, CD34, and CD45.

[0033] Cells are delivered frozen in DME/F-12 media with DMSO. Cells are thawed, washed by centrifugation according to protocol.

[0034] Cryocyte bags will be filled with cellular product from cell bank that has been generated and tested for mycoplasma contamination, sterility, viability and

endotoxin content. Filling of Cryocyte bags will be performed by General Biotechnology with cells previously expanded from the working cell bank to passage 9. Cells are resuspended in 100mL of Isolyte S Multi-Electrolyte Solution (B. Braun Medical). Each Cryocyte bag will contain 110 million cells in a volume of 100 ml. Approximately 110 million cells are needed per clinical dose, accounting for a 10% extra volume that may be lost due to spillage.

[0035] Collection of menstrual blood is performed according to a modification of our published procedure (Meng et al. Journal of Translational Medicine 2007, 5:57) under aseptic conditions. Manufacturing procedures take place in the General BioTechnology class 10,000 clean production suite. Each technician must properly gown when entering in the GMP room. Before entry into the clean lab area, the technician obtains a bunny suit in the ante room. After the hood of the bunny suit is placed on, they obtain a mouth covering and place on, making sure that all hair is fully covered under the hood and mouth covering. The technician then puts on a pair of sterile powder free gloves, and can enter the clean lab space with the thawed vial.

[0036] Environmental monitoring is performed in the Class 10,000 clean room. The clean room uses Biological Safety Cabinets (BSC) which maintains a Class 5 environment. BSC are certified annually by an outside qualified vender. Settling plates are performed quarterly with acceptable criteria based on USP. Two settling plates are placed in the BSC during processing for a minimum of 30 minutes. Also as a negative control, a covered settling plate will be placed inside the BSC at the same time After the settling plate has been in the BSC, evaluate the plate for presence of bacterial colonies, Colony Forming Units (cfu), by allowing the plate to incubate for 48 hours. Levels requiring alert are more than 1 colony per plate. Incubator temperature should be 36-38o C. TSA plates are used to evaluate the wide spectrum of possible bacteria present. Prepared plates stored in their original wrapping at 2 – 8°C should be warmed to room temperature prior to use. The product is validated from the time of manufacture to be stable at room temperature (25°C) for 192 h (8 days).

[0037] Additionally the clean room is monitored for room temperature and particle counts. Acceptable room temperature is between 15 and 30 degrees Celsius.

A MetOne Aerocet 531 particle counter and is used to evaluate the particles in the air of the clean room. It is used to confirm that the number of loose particles in the air is less than 10,000 0.5 micron particles per ft³. The particle counter is run on a weekly basis in the three major areas of the clean room space. It runs for 30 minutes in the gowning area, on the counter inside the clean room space and inside the hood.

[0038] After each use of the clean room, the BSC is wiped down with 5.25% bleach then followed by a 70% isopropyl alcohol. Countertops inside the clean room space are wiped down with 70% isopropyl alcohol each day. Once a week all surfaces inside the clean room, including floor, are wiped down with enzymatic cleaner LpH using a dry disposable cloth. Yearly, all walls and ceiling are clean with a lint roller, and all soft walls are cleaned with 70% isopropyl alcohol.

[0039] Before laboratory technicians are allowed into the clean room, a gowning competency must be passed. RODAC plates are utilized to assess the competency of the technician. The acceptable limits of CFU/ plate are listed in the table below. This is again repeated quarterly for all qualified technicians.

[0040] Menstrual Blood Mononuclear Cell Isolation begins with the delivery of the sample to the processing lab. Washing Tube containing the menstrual blood sample is topped up to 50 ml with PBS in the Biological Safety Cabinet and cells are washed by centrifugation at 500 g for 10 minutes at room temperature, which produced a cell pellet at the bottom of the conical tube. Under sterile conditions supernatant is decanted and the cell pellet is gently dissociated by tapping until the pellet appeared liquid. The pellet is resuspended in 50 ml of PBS and gently mixed so as to produce a uniform mixture of cells in PBS. The cells are washed again by centrifugation at 500g for 10 minutes at room temperature. Under sterile conditions, the supernatant is decanted and the cell pellet is resuspended in 15mL complete DME/F-12 media (Hyclone) supplemented with 10% Fetal Bovine Serum (Atlas Biologicals specified to have Endotoxin level: ≤ 100 EU/ml (levels routinely ≤ 10 EU/ml) and hemoglobin level: ≤ 30 mg/dl (levels routinely ≤ 25 mg/dl). The serum lot used is sequestered and one lot is used for all experiments. Additionally, the media is supplemented with 1% penicillin/streptomycin and 0.1% amphotericin B. The sample is then plated in a T75 flask and placed in a 37°C incubator. Media is

changed after 24 hours, and then every 2-3 days at the discretion of the laboratory staff.

[0041] Once cells reach 70-80% confluence they are passaged for expansion after which they are frozen down for quarantine (minimum 2 vials) and a culture screen will be completed. The expended media from the culture will be sent for sterility and mycoplasma testing. Cells from the sample are aliquotted and frozen in Cryocyte bags at a concentration of 110 million cells per bag.

[0042] Screening and collection is performed under approval of the local IRB. Donors are screened according to federal regulation 21 CFR1271 regarding allogeneic cell product. Specifically, healthy, non-smoking, female volunteers between 18-30 years of age sign informed consent form for providing menstrual blood sample. The volunteers undergo a standard medical history and examination including evaluation for malignancy, diabetes, leukemia, heart disease. Hematology, biochemistry, and physical examination require no abnormalities. Patients are required to be negative for anti-HIV-1, HIV-2, hepatitis B surface antigen, hepatitis B core antibody, Treponema pallidum (syphilis), CJD, antibody to trypanosome cruzi, anti-HTLV-II, Gonorrhea and Chlamydia. A collection of raw laboratory data will remain at the site and a donor case report forms are available for inspection.

Inclusion Criteria

[0043] Menstruating women between the ages of 18 and 30

Exclusion Criteria

[0044] History of Toxic Shock Syndrome, Current tobacco use, Diabetes, Positive Communicable Disease Screen (Hepatitis B or C, syphilis, chlamydia, HIV, chlamydia, gonorrhea), Alcohol or drug abuse, Unable to disclose health history of blood-related relatives.

Example 2: Administration of ERC using Retrograde Venous Sinus Method

[0045] Cryocyte bags are filled with cellular product from cell bank that has been generated and tested for mycoplasma contamination, sterility, viability and

endotoxin content. Filling of Cryocyte bags is performed with cells previously expanded from the working cell bank to passage 9. Cells are resuspended in 100mL of Isolyte S Multi-Electrolyte Solution (B. Braun Medical). Each Cryocyte bag will contain 110 million cells in a volume of 100 ml. Approximately 110 million cells are needed per clinical dose, accounting for a 10% extra volume that may be lost due to spillage.

[0046] Using aseptic technique and local anesthesia, a 8 French sheath is inserted into the most distal portion femoral vein, followed by a 8x40 balloon -7 French Catheter guided by a wire using standard procedures. Once in the inferior vena cave the catheter is advanced into the right atrium and then rotated along the posterial atrial wall to a site just above the septal leaflet or the tricuspid valve. Gentle advancement of the catheter allows it to enter the coronary sinus where the balloon is place in a non-obstructing mid-position. The balloon should be positioned in the coronary sinus in one of the following positions as determined by the treating physician's clinical judgment: 1) Coronary Sinus, 2) Middle Cardiac Vein, 3) Lesser (small) Cardiac Vein, and 4) Great Cardiac Vein (See Attachments 3 & 4).

[0047] The particular characteristics of case may require the placement of the balloon in a position other than these four positions. The actual placement will be reported to determine the frequency of this occurrence. Once in place, the single balloon will be inflated and the total volume of 40mL will be divided into four 10 mL syringes and the ECR's will be infused into the coronary sinus for a total of 5minutes. The balloon will remain inflated for 10 minutes after infusion to permit the migration of the nucleated cells into the cardiac tissue.

Example 3: Clinical Trial Administration of ERC using Retrograde Venous Sinus Method

[0048] A 60 patient dose-escalating clinical trial is performed to assess efficacy of ERC delivered using the retrograde administration technique in the context of the current patent. The therapeutic solution involves the various doses of ERC administered in a solution of isolyte, which arrives frozen at the site in 10% DMSO. Patients are included in the study if they meet the following criteria: Age 18 years

and ability to understand the planned treatment, suffer from Congestive Heart Failure, Left ventricular ejection fraction $\leq 40\%$ by echocardiogram, per ECHO completed 30 days prior to treatment, Symptomatic heart failure NYHA class III or IV, Able to comply with all study-related visits, Able to tolerate ALL study procedures, able to give Informed Consent, Negative for HcG with a serum pregnancy test, Patients with controlled diabetes mellitus ($\text{HbA1c} < 9.0\%$), Hematocrit $\geq 28.0\%$, White Blood Cell count $\leq 14,000$, Platelet count $\geq 50,000$, Life expectancy of 6 months or more in the opinion of the investigator, Serum bilirubin, ALT, AST ≤ 2.5 time the upper level of normal, Controlled blood pressure (systolic blood pressure ≤ 140 and a diastolic blood pressure of ≤ 90 mmHG) and established anti-hypertensive therapy as necessary prior to entry into the study, Patient has received stable, standard medical therapy for at least one month with no new medications to treat the disease introduced in the last month, Pre-existing condition (e.g. thromboembolic risk, diabetes, hypercholesterolemia are adequately controlled in the opinion of the investigator), Fertile patients (male and female) must agree to use an appropriate form of contraception while participating in the study. Furthermore, patients who fall into the exclusion criteria will not be allowed in the study. The exclusion criteria are as follows: Female who is pregnant or nursing, or of child bearing potential and is not using a reliable birth control method, or who intend to become pregnant during the tenure of this study, History of prior radiation exposure for oncological treatment, History of Bone Marrow Disorder (especially NHL, MDS), History of abnormal bleeding or clotting, History of Liver Cirrhosis, End stage renal disease (Creatinine ≤ 3.0 mg / dl) and/or dialysis, Acute Myocardial Infarction < 1 week from treatment date, Active clinical infection being treated by antibiotics within one week of enrollment, Inability or unwillingness to comply with the treatment protocol, follow-up, research tests, or give consent, History of life-threatening arrhythmias, except if an automated implantable cardioverter defibrillator (AICD) is implanted, Life expectancy < 6 months due to concomitant illnesses, Known cancer and undergoing treatment; chemotherapy and/or radiotherapy, Patients receiving treatment with hematopoietic growth factors (e.g., EPO, G-CSF), Patients who can not stop anticoagulation therapy (warfarin) 72hrs prior to infusion, Patients who can not stop anti-platelet therapy (clopidogrel) 7 days prior infusion, Prior admission for substance abuse, Body Mass Index (BMI) of 40 kg/m² or greater, Patient receiving experimental medication or participating in another clinical study within 30 days of signing the

informed consent, In the opinion of the investigator or the sponsor, the patient is unsuitable for cellular therapy, Known allergy or sensitivity to contrast agents used in imaging procedures.

[0049] The primary objective of this feasibility study is to provide clinical data to demonstrate the safety and efficacy of Endometrial Regenerative Cells (ERC) in treating patients diagnosed with congestive heart failure (CHF). The secondary objective is to demonstrate that the infusion of Endometrial Regenerative Cells (ERC) into the coronary sinus is safe as assessed by adverse event records. Additionally, the study aims to assess the effect of the infusion of ERC's on the clinical course of angina and heart failure as measured by QOL questionnaire, Minnesota Living with Heart Failure, NYHA and CCS classification and SPECT. Another secondary objective is to assess the effect of the infusion of ERC's on heart function as measured by left ventricular ejection fraction (LVEF) and left ventricular end-diastolic diameter (LVEDD) by ECHO. Additionally, the study aims to assess the effect of the infusion ERC's of on the area of ischemia as measured by myocardial SPECT studies and ECHO.

[0050] The study examines safety throughout the study period with the use of direct evaluation and patient reporting during study visits or patient-initiated telephone contacts. The types, frequencies, severity, and duration of any reported adverse event or abnormalities in clinical laboratory values, physical examinations, vital signs, or special cardiovascular evaluations will be assessed. The changes from baseline are summarized. Specific safety data to be summarized includes, Major Cardiac Adverse Events, Adverse Events/Serious Adverse Events, Elevation of Cardiac Enzymes post-infusion, Complete blood count, Physical assessment/vital signs, ECG, ECHO, MRI or SPECT Abnormalities.

[0051] In the study, efficacy is assessed at 3, 6, and 12 months by monitoring therapeutic changes by: a) Reduction (or lack of an increase) in LVESV compared to baseline measured by echocardiography; b) Changes in LVEF compared to baseline measured by echocardiography; c) Change in Stress LVEF compared to baseline by SPECT (at 6 months only); d) Newly formed ischemia verified by SPECT or MRI (at 6 months only); e) Change in LVEDV compared to baseline measured by

echocardiography; f) Change in NYHA from baseline; g) Change in CCS from baseline; h) Change in Minnesota Living with Heart Failure Questionnaire (MLHFQ) from baseline.

[0052] Cell administration will be performed using clinical grade ERC come from healthy, non-smoking, female volunteers between 18-30 years of age who have signed an Informed Consent Form (ICF). Individual(s) who have signed the ICF provide a menstrual blood sample blood sample at Indiana University Hospital under approval of the local IRB for clinical use. The volunteers undergo a standard medical history and examination including evaluation for malignancy, diabetes, leukemia, heart disease. Hematology, biochemistry, and physical examination require no abnormalities. Volunteer donors are required to be negative for anti-HIV-1, HIV-2, hepatitis B surface antigen, hepatitis B core antibody, Treponema pallidum (syphilis), Creutzfeldt-Jakob Disease (CJD), antibody to trypanosome cruzi, and anti-HTLV-II. A collection of raw laboratory data will remain at the site and a donor case report forms are available for inspection. At the manufacturing laboratory, the cells are isolated and prepared as previously described and a seed culture will be established. Because of the source of the cells, antibiotics must be used in the initial seed culture. Once the seed culture is established, a sub-culture is prepared through 3 passages without antibiotics and the culture will then be tested for sterility (USP/CFR 610.12 GMP) and mycoplasma. Next, expansion will begin in a class 10,000 clean room in T-225 flasks. The cells are re-screened for sterility and mycoplasma and flow cytometry for CD90, 105 (positive) and CD45, CD34 (negative). Cells are stored in CellSeal® closed system cryovials (VialCo, USA). The dose for clinical administration will be packaged in Cryocyte™ bags (Baxter, USA). Cell suspensions will be cryopreserved in a commercially available cryopreservative (10% DMSO solution, CS10, BioLife Solutions, USA) by control rate freezing at -1°C/minute from 22°C to -80°C followed by plunging into liquid nitrogen (LN2).

[0053] Using aseptic technique and local anesthesia, a 8 French sheath is inserted into the most distal portion femoral vein, followed by a 8x40 balloon -7 French Catheter guided by a wire using standard procedures. Once in the inferior vena cave the catheter is advanced into the right atrium and then rotated along the posterial atrial wall to a site just above the septal leaflet or the tricuspid valve. Gentle

advancement of the catheter allows it to enter the coronary sinus where the balloon is place in a non-obstructing mid-position. The balloon should be positioned in the coronary sinus in one of the following positions as determined by the treating physician's clinical judgment: 1) Coronary Sinus, 2) Middle Cardiac Vein, 3) Lesser (small) Cardiac Vein, and 4) Great Cardiac Vein (See Attachments 3 & 4).

[0054] The particular characteristics of case may require the placement of the balloon in a position other than these four positions. The actual placement will be reported to determine the frequency of this occurrence. Once in place, the single balloon will be inflated and the total volume of 40mL will be divided into four 10 mL syringes and the ERC's or Carrier-Solution depending on patient randomization will be infused into the coronary sinus for a total of 5 minutes. The balloon will remain inflated for 10 minutes after infusion to permit the migration of the nucleated cells into the cardiac tissue.

[0055] Patients in the treatment group will have baseline data established at the conclusion of screening and date of randomization will be determined to be Day 0 for this cohort. The treatment must occur within 72 hours of date of randomization. Treatment occurring after 72 hour will be considered a protocol deviation, screening laboratory assessments and screening EKG will have to be repeated. Follow-up data will be gathered for treatment patients at day of treatment, discharge, 3 month, 6 month, and 1 year. Patients in the control group will receive catheter procedure with a carrier solution. Patients in the control group will not receive ERC.

[0056] Patients in the control group will have baseline data established at the conclusion of screening and date of randomization will be determined to be Day 0 for this cohort. The treatment must occur within 72 hours of date of randomization. Treatment occurring after 72 hour will be considered a protocol deviation, screening laboratory assessments and screening EKG will have to be repeated. Patients in the control group may be offered the opportunity to cross-over after completing at least 6 months of this trial. However, before a cross-over option becomes available, an independent data and safety monitoring board (DSMB) and the sponsor will review 6-month safety and feasibility data from the first 10 treatment patients and risk-benefit profile in order to assess the value and utility of a such a protocol. If a cross-over option becomes available, the investigators will assess the status of an individual

control patient, discuss the cross-over option with the patient, and will ensure the patient meets the eligibility criteria of the cross-over in order to qualify for treatment.

[0057] Treatment is performed in all 60 patients without serious adverse events. The dose escalation of 50, 100, and 200 million cells per patient is performed without adverse events. Incidence of MACE is significantly lower in patients receiving ERC compared to placebo. An increase in myocardial perfusion, quality of life, and ejection fraction is noticed in the treatment group but not in the placebo control.

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[0058]

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CLAIMS:

1. A solution useful for the treatment of cardiovascular disorders comprising: a) a nucleic acid capable of inducing the process of RNA interference (RNAi); and/or b) a cellular population.
2. The solution of claim 1, wherein said solution is administered: a) intravenously; b) epicardially; c) endocardially; d) intracoronarily; and e) retrograde into the coronary sinus.
3. The solution of claim 1, wherein said nucleic acids capable of inducing RNAi are selected from a group comprising of: a) short hairpin RNA; b) short interfering RNA; and c) virally expressed RNA.
4. The solution of claim 1, wherein said nucleic acids capable of inducing RNAi are designed to decrease expression of inflammatory mediators.
5. The solution of claim 1, wherein said nucleic acids capable of inducing RNAi are designed to decrease expression of fibrosis producing molecules.
6. The solution of claim 1, wherein said nucleic acids capable of inducing RNAi are designed to decrease expression of apoptosis stimulating molecules.
7. The solution of claim 4, wherein said nucleic acids capable of inducing RNAi are designed to decrease expression of inflammatory mediators are comprised of complementary sequences of nucleic acids, said nucleic acids capable of stimulating RNAi, said sequences having homology to genes selected from a group comprising of: ABCF1, BCL6, C3, C4A, CEBPB, CRP, ICEBERG, IL1R1, IL1RN, IL8RB, LTB4R, TOLLIP, IFNA2, IL10RA, IL10RB, IL13, IL13RA1, IL5RA, IL9, IL9R, CD40LG (TNFSF5), IFNA2, IL10, IL13, IL17C, IL1A, IL1B, IL1F10, IL1F5, IL1F6, IL1F7, IL1F8, IL1F9, IL22, IL5, IL-6, IL8, IL9, IL-18, IL-33, LTA, LTB, MIF, SCYE1, SPP1, TNF, CCL13 (mcp-4), CCR1, CCR2, CCR3, CCR4, CCR5, CCR6, CCR7, CCR8, CCR9, CX3CR1, IL8RA, XCR1 (CCXCR1), C5, CCL1 (I-309), CCL11 (eotaxin), CCL13 (mcp-4), CCL15 (MIP-1d), CCL16 (HCC-4), CCL17 (TARC), CCL18 (PARC), CCL19, CCL2 (mcp-1), CCL20 (MIP-3a), CCL21 (MIP-

2), CCL23 (MIPF-1), CCL24 (MIPF-2 / eotaxin-2), CCL25 (TECK) , CCL26, CCL3 (MIP-1a), CCL4 (MIP-1b), CCL5 (RANTES), CCL7 (mcp-3), CCL8 (mcp-2), CXCL1, CXCL10 (IP-10), CXCL11 (I-TAC / IP-9), CXCL12 (SDF1), CXCL13, CXCL14, CXCL2, CXCL3, CXCL5 (ENA-78 / LIX), CXCL6 (GCP-2), CXCL9, IL13, and IL8.

8. The solution of claim 5, wherein said nucleic acids capable of inducing RNAi are designed to decrease expression of fibrosis stimulating molecules are comprised of complementary sequences of nucleic acids, said nucleic acids capable of stimulating RNAi, said sequences having homology to genes selected from a group comprising of: ACTA2 (a-SMA), AGT, CTGF, CCL11 (Eotaxin), CCL2 (MCP-1), CCL3 (MIP-1a), GREM1, IL13, IL13RA2, IL4, IL5, SNAI1 (Snail), COL1A2, COL3A1, LOX, MMP1, MMP13, MMP14, MMP2 (Gelatinase A), MMP3, MMP8, MMP9, PLAU (uPA), PLG, SERPINA1 (a1-antitrypsin), SERPINE1 (PAI-1), SERPINH1, TIMP1, TIMP2, TIMP3, TIMP4, ITGA1, ITGA2, ITGA3, ITGAV, ITGB1, ITGB3, ITGB5, ITGB6, ITGB8, BMP7, CAV1, DCN, ENG (EVI-1), GREM1, INHBE, LTBP1, SMAD2, SMAD3, SMAD4, SMAD6, SMAD7, TGFB1, TGFB2, TGFB3, TGFB1 (ALK5), TGFB2, TGIF1, THBS1, and THBS2.

9. The solution of claim 6, wherein said nucleic acids capable of inducing RNAi are designed to decrease expression of apoptosis stimulating molecules are comprised of complementary sequences of nucleic acids, said nucleic acids capable of stimulating RNAi, said sequences having homology to genes selected from a group comprising of: CASP1 (ICE), CASP10 (MCH4), CASP14, CASP2, CASP3, CASP4, CASP5, CASP6, CASP7, CASP8, CASP9, CFLAR (CASPER), CRADD, PYCARD (TMS1/ASC), ABL1, AKT1, BAD, BAK1, BAX, BCL2L11, BCLAF1, BID, BIK, BNIP3, BNIP3L, CASP1 (ICE), CASP10 (MCH4), CASP14, CASP2, CASP4, CASP6, CASP8, CD70 (TNFSF7), CIDEB, CRADD, FADD, FASLG (TNFSF6), HRK, LTA (TNFB), NOD1 (CARD4), PYCARD (TMS1/ASC), RIPK2, TNF, TNFRSF10A, TNFRSF10B (DR5), TNFRSF25 (DR3), TNFRSF9, TNFSF10 (TRAIL), TNFSF8, TP53, TP53BP2, TRADD, TRAF2, TRAF3, and TRAF4.

10. The solution of claim 1, wherein a gene or plurality of genes associated with angiogenesis are administered as part of the solution.

11. The solution of claim 10, wherein said genes are introduced by a means selected from: a) naked DNA administration; b) liposomal DNA administration; c) viral administration d) ultrasound based administration; e) microbubble based administration; and f) nanoparticle based administration.

12. The solution of claim 10, wherein said genes are administered either as a plasmid, as mRNA, or as proteins.

13. The solution of claim 10, wherein said genes are selected from a group comprising of: FGF, VEGF, SDF-1, VEGFR, NRP-1, Ang1, Ang2, PDGF (BB-homodimer), PDGFR, TGF- β , endoglin, TGF- β receptors, MCP-1, integrins α V β 3, α V β 5, α 5 β 1, VE-cadherin, CD31, ephrin, ANGPTL3, BAI1, COL4A3, IL8, LAMA5, NRP1, NRP2, STAB1, plasminogen activators, ANGPTL4, PECAM1, PF4, PROK2, SERPINF1, TNFAIP2, HAND2, SPHK1, CCL11, CCL2, CXCL1, CXCL10, CXCL3, CXCL5, CXCL6, CXCL9, IFNA1, IFNB1, IFNG, IL1B, IL6, MDK, TNF, plasminogen activator inhibitor-1, eNOS, COX-2, AC133, Id1/Id3, ANGPT1, ANGPT2, ANPEP, TYMP, EREG, FGF1, FGF2, FIGF, FLT1, JAG1, KDR, S1PR1, EFNA1, EFNA3, EFNB2, EGF, EPHB4, FGFR3, HGF, IGF1, ITGB3, PDGFA, TEK, TGFA, TGFB1, TGFB2, TGFB1, LAMA5, CCL11, CCL2, CDH5, COL18A1, S1PR1, ENG, ITGAV, ITGB3, THBS1, LECT1, LEP, MMP2, MMP9, PLAUG, PLG, TIMP1, TIMP2, AKT1, HIF1A, HPSE, ID1, ID3, NOTCH4, PTGS1, TIMP3, THBS2, NRP1, NRP2, PGF, PLXDC1, STAB1, VEGFA, VEGFC,

14. The solution of claim 1, wherein a gene or plurality of genes associated with inhibition of apoptosis are administered as part of the solution.

15. The solution of claim 14, wherein said genes are introduced by a means selected from: a) naked DNA administration; b) liposomal DNA administration; c) viral administration d) ultrasound based administration; e) microbubble based administration; and f) nanoparticle based administration.

16. The solution of claim 14, wherein said genes are administered either as genes, as mRNA, or as proteins.

17. The solution of claim 14, wherein said genes are selected from a group comprising of: obestatin, XIAP, survivin, BCL-2, BCL-XL, GATA-4, IGF-1, EGF, heme-oxygenase-1, NF-kB, akt, pi3-k, and epha-2.

18. The solution of claim 1, wherein said cellular population in said solution is a monocytic cell.

19. The solution of claim 1, wherein said monocytic cell population may be autologous, allogeneic, or xenogeneic to the recipient.

20. The solution of claim 1, wherein said cell population is a stem cell.

21. The solution of claim 20, wherein said stem cell population is autologous, allogeneic, or xenogeneic to the recipient.

22. The solution of claim 1, wherein said stem cell comprises a cell selected from a group containing: a) a progenitor cell; b) a pluripotent stem cell; c) an induced pluripotent stem cell; d) a hematopoietic stem cell; e) a very small embryonic like stem cell; f) a mesenchymal stem cell; g) an endometrial regenerative cell; h) a progenitor cell; and i) a monocyte.

23. The solution of claim 22, wherein said stem cells are selected from a group comprising of: embryonic stem cells, cord blood stem cells, placental stem cells, bone marrow stem cells, amniotic fluid stem cells, neuronal stem cells, circulating peripheral blood stem cells, mesenchymal stem cells, germinal stem cells, adipose tissue derived stem cells, exfoliated teeth derived stem cells, hair follicle stem cells, dermal stem cells, parthenogenically derived stem cells, reprogrammed stem cells and side population stem cells.

24. The solution of claim 22, wherein said embryonic stem cells are totipotent.

25. The solution of claim 24, wherein said embryonic stem cells express one or more antigens selected from a group consisting of: stage-specific embryonic antigens (SSEA) 3, SSEA 4, Tra-1-60 and Tra-1-81, Oct-3/4, Cripto, gastrin-releasing peptide (GRP) receptor, podocalyxin-like protein (PODXL), Rex-1, GCTM-2, Nanog, and human telomerase reverse transcriptase (hTERT).

26. The solution of claim 23, wherein said cord blood stem cells are multipotent and capable of differentiating into endothelial, smooth muscle, and neuronal cells.

27. The solution of claim 23, wherein said cord blood stem cells are identified based on expression of one or more antigens selected from a group comprising: SSEA-3, SSEA-4, CD9, CD34, c-kit, OCT-4, Nanog, and CXCR-4

28. The solution of claim 27, wherein said cord blood stem cells do not express one or more markers selected from a group comprising of: CD3, CD34, CD45, and CD11b.

29. The solution of claim 23, wherein said placental stem cells are isolated from the placental structure.

30. The solution of claim 29, wherein said placental stem cells are identified based on expression of one or more antigens selected from a group comprising: Oct-4, Rex-1, CD9, CD13, CD29, CD44, CD166, CD90, CD105, SH-3, SH-4, TRA-1-60, TRA-1-81, SSEA-4 and Sox-2.

31. The solution of claim 23, wherein said bone marrow stem cells comprise of bone marrow mononuclear cells.

32. The solution of claim 31, wherein said bone marrow stem cells are selected based on the ability to differentiate into one or more of the following cell types: endothelial cells, smooth muscle cells, and neuronal cells.

33. The solution of claim 32, wherein said bone marrow stem cells are selected based on expression of one or more of the following antigens: CD34, c-kit, flk-1, Stro-1, CD105, CD73, CD31, CD146, vascular endothelial-cadherin, CD133 and CXCR-4.

34. The solution of claim 33, wherein said bone marrow stem cells are enriched for expression of CD133.

35. The solution of claim 23, wherein said amniotic fluid stem cells are isolated by introduction of a fluid extraction means into the amniotic cavity under ultrasound guidance.

36. The solution of claim 35, wherein said amniotic fluid stem cells are selected based on expression of one or more of the following antigens: SSEA3, SSEA4, Tra-1-60, Tra-1-81, Tra-2-54, HLA class I, CD13, CD44, CD49b, CD105, Oct-4, Rex-1, DAZL and Runx-1.

37. The solution of claim 36, wherein said amniotic fluid stem cells are selected based on lack of expression of one or more of the following antigens: CD34, CD45, and HLA Class II.

38. The solution of claim 23, wherein said neuronal stem cells are selected based on expression of one or more of the following antigens: RC-2, 3CB2, BLB, Sox-2hh, GLAST, Pax 6, nestin, Muashi-1, NCAM, A2B5 and prominin.

39. The solution of claim 23, wherein said circulating peripheral blood stem cells are characterized by ability to proliferate in vitro for a period of over 3 months.

40. The solution of claim 23, wherein said circulating peripheral blood stem cells are characterized by expression of CD34, CXCR4, CD117, CD113, and c-met.

41. The solution of claim 40, wherein said circulating peripheral blood stem cells lack substantial expression of differentiation associated markers.

42. The solution of claim 41, wherein said differentiation associated markers are selected from a group comprising of CD2, CD3, CD4, CD11, CD11a, Mac-1, CD14, CD16, CD19, CD24, CD33, CD36, CD38, CD45, CD56, CD64, CD68, CD86, CD66b, and HLA-DR.

43. The solution of claim 23, wherein said mesenchymal stem cells express one or more of the following markers: STRO-1, CD105, CD54, CD106, HLA-I markers, vimentin, ASMA, collagen-1, fibronectin, LFA-3, ICAM-1, PECAM-1, P-selectin, L-selectin, CD49b/CD29, CD49c/CD29, CD49d/CD29, CD61, CD18, CD29, thrombomodulin, telomerase, CD10, CD13, STRO-2, VCAM-1, CD146, and THY-1.

44. The solution of claim 43, wherein said mesenchymal stem cells do not express substantial levels of HLA-DR, CD117, and CD45.

45. The solution of claim 23, wherein said mesenchymal stem cells are derived from a group selected of: bone marrow, adipose tissue, umbilical cord blood, placental tissue, peripheral blood mononuclear cells, differentiated embryonic stem cells, and differentiated progenitor cells.

46. The solution of claim 23, wherein said germinal stem cells express markers selected from a group comprising of: Oct4, Nanog, Dppa5 Rbm, cyclin A2, Tex18, Stra8, Dazl, beta1- and alpha6-integrins, Vasa, Fragilis, Nobox, c-Kit, Sca-1 and Rex1.

47. The solution of claim 23, wherein said adipose tissue derived stem cells express markers selected from a group comprising of: CD13, CD29, CD44, CD63, CD73, CD90, CD166, Aldehyde dehydrogenase (ALDH), and ABCG2.

48. The solution of claim 47, wherein said adipose tissue derived stem cells are a population of purified mononuclear cells extracted from adipose tissue capable of proliferating in culture for more than 1 month.

49. The solution of claim 23, wherein said exfoliated teeth derived stem cells express markers selected from a group comprising of: STRO-1, CD146 (MUC18), alkaline phosphatase, MEPE, and bFGF.

50. The solution of claim 23, wherein said hair follicle stem cells express markers selected from a group comprising of: cytokeratin 15, Nanog, and Oct-4.

51. The solution of claim 23, wherein said hair follicle stem cells are capable of proliferating in culture for a period of at least one month.

52. The solution of claim 23, wherein said hair follicle stem cells secrete one or more of the following proteins when grown in culture: basic fibroblast growth factor (bFGF), endothelin-1 (ET-1) and stem cell factor (SCF).

53. The solution of claim 23, wherein said dermal stem cells express markers selected from a group comprising of: CD44, CD13, CD29, CD90, and CD105.

54. The solution of claim 23, wherein said dermal stem cells are capable of proliferating in culture for a period of at least one month.

55. The solution of claim 23, wherein said parthenogenically derived stem cells are generated by addition of a calcium flux inducing agent to activate an oocyte followed by enrichment of cells expressing markers selected from a group comprising of SSEA-4, TRA 1-60 and TRA 1-81.

56. The solution of claim 23, wherein said reprogrammed stem cells are selected from a group comprising of: cells subsequent to a nuclear transfer, cells subsequent to a cytoplasmic transfer, cells treated with a DNA methyltransferase inhibitor, cells treated with a histone deacetylase inhibitor, cells treated with a GSK-3 inhibitor, cells induced to dedifferentiate by alteration of extracellular conditions, and cells treated with various combination of the mentioned treatment conditions.

57. The solution of claim 56, wherein said nuclear transfer comprises introducing nuclear material to a cell substantially enucleated, said nuclear material deriving from a host whose genetic profile is sought to be dedifferentiated.

58. The solution of claim 56, wherein said cytoplasmic transfer comprises introducing cytoplasm of a cell with a dedifferentiated phenotype into a cell with a differentiated phenotype, such that said cell with a differentiated phenotype substantially reverts to a dedifferentiated phenotype.

59. The solution of claim 56, wherein said DNA demethylating agent is selected from a group comprising of: 5-azacytidine, psammaplin A, and zebularine.

60. The solution of claim 56, wherein said histone deacetylase inhibitor is selected from a group comprising of: valproic acid, trichostatin-A, trapoxin A and depsipeptide.

61. The side population cells of claim 23, wherein said cells are identified based on expression multidrug resistance transport protein (ABCG2) or ability to efflux intracellular dyes such as rhodamine-123 and or Hoechst 33342.

62. The side population cells of claim 61, wherein said cells are derived from tissues such as pancreatic tissue, liver tissue, smooth muscle tissue, striated muscle tissue, cardiac muscle tissue, bone tissue, bone marrow tissue, bone spongy tissue, cartilage tissue, liver tissue, pancreas tissue, pancreatic ductal tissue, spleen tissue, thymus tissue, Peyer's patch tissue, lymph nodes tissue, thyroid tissue, epidermis tissue, dermis tissue, subcutaneous tissue, heart tissue, lung tissue, vascular tissue, endothelial tissue, blood cells, bladder tissue, kidney tissue, digestive tract tissue, esophagus tissue, stomach tissue, small intestine tissue, large intestine tissue, adipose tissue, uterus tissue, eye tissue, lung tissue, testicular tissue, ovarian tissue, prostate tissue, connective tissue, endocrine tissue, and mesentery tissue.

63. The solution of claim 22, wherein said committed progenitor cells are selected from a group comprising of: cardiac progenitor cells, endothelial progenitor cells, neuronal progenitor cells, and hematopoietic progenitor cells.

64. The solution of claim 63, wherein said committed endothelial progenitor cells are purified from the bone marrow.

65. The solution of claim 64, wherein said committed endothelial progenitor cells are purified from peripheral blood.

66. The solution of claim 65, wherein said committed endothelial progenitor cells are purified from peripheral blood of a patient whose committed endothelial progenitor cells are mobilized by administration of a mobilizing agent or therapy.

67. The solution of claim 1, wherein a histone deacetylase inhibitor is added at a sufficient concentration to induce an anti-fibrotic/regenerative effect.

68. The solution of claim 67, wherein said histone deacetylase inhibitor is selected from a group comprising of: a) valproic acid; b) phenylbutyrate; c) trichostatin A; and d) AR42.

69. The solution of claim 1, wherein the cell population administered is an endometrial regenerative cell.

70. The solution of claim 69, wherein said endometrial regenerative cell expresses substantially higher amounts of the following genes as compared to bone marrow derived mesenchymal stem cells: somatostatin receptor 1, forkhead box L2, FAM105A, synaptopodin 2-like, anoctamin 4, spondin 2, CARD16, VAT1L, indolethylamine N-methyltransferase, deiodinase, iodothyronine, type II (DIO2), aldehyde dehydrogenase 1 family, member A1, 5-hydroxytryptamine (serotonin) receptor 2B, caspase recruitment domain family, member 17, Rho GTPase activating protein 20, zinc finger and BTB domain containing 46 (ZBTB46), synaptopodin 2-like (SYNPO2L), transcript variant 1, mRNA, chromosome 13 open reading frame 15 (C13orf15), mRNA, homeobox D11 (HOXD11), mRNA, oxidized low density lipoprotein (lectin-like) receptor 1 (OLR1), transcript variant 2, mRNA, homeobox D10 (HOXD10), mRNA, Pregnancy specific beta-1-glycoprotein 4, matrix metalloproteinase 3 (stromelysin 1, progelatinase) (MMP3), mRNA, actin filament associated protein 1-like 2 (AFAP1L2), transcript variant 2, mRNA, SH3-domain

GRB2-like (endophilin) interacting protein 1 (SGIP1), mRNA, solute carrier family 7 (cationic amino acid transporter, y+ system), member 2 (SLC7A2), transcript variant 1, mRNA, pregnancy specific beta-1-glycoprotein 8 (PSG8), transcript variant 3, mRNA, Wilms tumor 1 (WT1), transcript variant F, mRNA, platelet-derived growth factor beta polypeptide (PDGFB), transcript variant 1, mRNA, forkhead box F1 (FOXF1), mRNA, mannan-binding lectin serine peptidase 1 (C4/C2 activating component of Ra-reactive factor) (MASP1), transcript variant 1, mRNA, deiodinase, iodothyronine, type II (DIO2), transcript variant 4, mRNA, G protein-coupled receptor 126 (GPR126), transcript variant b1, mRNA, stimulated by retinoic acid gene 6 homolog (mouse) (STRA6), transcript variant 6, mRNA, hydroxysteroid (11-beta) dehydrogenase 1 (HSD11B1), transcript variant 2, mRNA, RAS guanyl releasing protein 2 (calcium and DAG-regulated) (RASGRP2), transcript variant 4, mRNA, membrane bound O-acyltransferase domain containing 1 (MBOAT1), mRNA, LON peptidase N-terminal domain and ring finger 2 (LONRF2), mRNA, interferon-induced protein with tetratricopeptide repeats 2 (IFIT2), mRNA, cathepsin C (CTSC), transcript variant 3, mRNA, caspase 1, apoptosis-related cysteine peptidase (interleukin 1, beta, convertase) (CASP1), transcript variant beta, mRNA, integrin, alpha 4 (antigen CD49D, alpha 4 subunit of VLA-4 receptor) (ITGA4), mRNA, integrin, alpha 6 (ITGA6), transcript variant 1, mRNA, contactin 3 (plasmacytoma associated) (CNTN3), mRNA, synaptophysin-like 2 (SYPL2), mRNA, Rho GTPase activating protein 25 (ARHGAP25), transcript variant 4, mRNA, potassium voltage-gated channel, Shal-related subfamily, member 2 (KCND2), mRNA, S100 calcium binding protein A4 (S100A4), transcript variant 1, mRNA, chemokine (C-C motif) receptor-like 2 (CCRL2), transcript variant 2, mRNA, integrin, alpha 6 (ITGA6), transcript variant 2, mRNA, guanylate binding protein 4 (GBP4), mRNA, multiple C2 domains, transmembrane 1 (MCTP1), transcript variant S, mRNA, interferon-induced protein with tetratricopeptide repeats 2 (IFIT2), mRNA, C1q and tumor necrosis factor related protein 9 (C1QTNF9), mRNA, progesterone receptor (PGR), transcript variant 2, mRNA, hypothetical LOC646113 (FLJ43390), non-coding RNA. zinc finger and BTB domain containing 46 (ZBTB46), mRNA, interferon-induced protein with tetratricopeptide repeats 3 (IFIT3), transcript variant 1, mRNA, microphthalmia-associated transcription factor (MITF), transcript variant 2, mRNA, interleukin 24 (IL24), transcript variant 4, mRNA, neuronal pentraxin I (NPTX1), mRNA, integrin, alpha 4 (antigen CD49D, alpha 4 subunit of VLA-4 receptor) (ITGA4), mRNA, WT1

antisense RNA (non-protein coding) (WT1-AS), non-coding RNA, microphthalmia-associated transcription factor (MITF), transcript variant 2, mRNA, sterile alpha motif domain containing 12 (SAMD12), transcript variant 1, mRNA, chromosome 7 open reading frame 58 (C7orf58), transcript variant 1, mRNA, phospholipase B domain containing 1 (PLBD1), mRNA, podocalyxin-like (PODXL), transcript variant 2, mRNA, interleukin 8 (IL8), mRNA, chromosome 7 open reading frame 58 (C7orf58), transcript variant 2, mRNA, protein kinase, cAMP-dependent, regulatory, type II, beta (PRKAR2B), mRNA, chromosome 8 open reading frame 4 (C8orf4), mRNA, stimulated by retinoic acid gene 6 homolog (mouse) (STRA6), transcript variant 5, mRNA, progesterone receptor (PGR), transcript variant 2, mRNA, angiopoietin 2 (ANGPT2), transcript variant 2, mRNA, synaptophysin-like 2 (SYPL2), mRNA, retinoic acid receptor responder (tazarotene induced) 2 (RARRES2), mRNA, claudin 1 (CLDN1), mRNA, sal-like 1 (Drosophila) (SALL1), transcript variant 1, mRNA, calcium channel, voltage-dependent, T type, alpha 1H subunit (CACNA1H), transcript variant 2, mRNA, armadillo repeat containing 4 (ARMC4), mRNA, phosphatidylinositol-specific phospholipase C, X domain containing 3 (PLCXD3), mRNA, G protein-coupled receptor, family C, group 5, member A (GPRC5A), mRNA, GATA binding protein 2 (GATA2), transcript variant 1, mRNA, actin filament associated protein 1-like 1 (AFAP1L1), transcript variant 1, mRNA, ST6 (alpha-N-acetyl-neuraminyl-2,3-beta-galactosyl-1, 3)-N-acetylgalactosaminide alpha-2,6-sialyltransferase 5 (ST6GALNAC5), mRNA, H19, imprinted maternally expressed transcript (non-protein coding) (H19), non-coding RNA, sphingosine-1-phosphate receptor 3 (S1PR3), mRNA, protein kinase, cAMP-dependent, regulatory, type II, beta (PRKAR2B), mRNA, interleukin 7 receptor (IL7R), mRNA, calcium/calmodulin-dependent protein kinase IG (CAMK1G), mRNA, homeobox A11 (HOXA11), mRNA, renin (REN), mRNA, transcription factor AP-2 gamma (activating enhancer binding protein 2 gamma) (TFAP2C), mRNA, cathepsin C (CTSC), transcript variant 2, mRNA, STAM binding protein-like 1 (STAMBPL1), mRNA, Hypothetical protein LOC254057, adrenomedullin (ADM), mRNA, tenascin XB (TNXB), transcript variant XB-S, mRNA, KH domain containing, RNA binding, signal transduction associated 3 (KHDRBS3), mRNA, solute carrier family 35, member F3 (SLC35F3), mRNA, collagen, type IV, alpha 6 (COL4A6), transcript variant B, mRNA, protocadherin 7 (PCDH7), transcript variant a, mRNA, chromosome 10 open reading frame 58 (C10orf58), transcript variant 1, mRNA,

fibroblast growth factor 9 (glia-activating factor) (FGF9), mRNA, sushi domain containing 3 (SUSD3), mRNA, melanoma associated antigen (mutated) 1-like 1 (MUM1L1), transcript variant 2, mRNA, keratin 18 pseudogene (FLJ40504), non-coding RNA, C-type lectin domain family 14, member A (CLEC14A), mRNA, 1-acylglycerol-3-phosphate O-acyltransferase 9 (AGPAT9), mRNA, phosphodiesterase 8B (PDE8B), transcript variant 3, mRNA, ArfGAP with dual PH domains 2 (ADAP2), mRNA, Keratin 18, family with sequence similarity 65, member C (FAM65C), mRNA, androgen receptor (AR), transcript variant 1, mRNA, phosphodiesterase 9A (PDE9A), transcript variant 2, mRNA, Intercellular adhesion molecule 1, monoglyceride lipase (MGLL), transcript variant 2, mRNA, HOXA11 antisense RNA 1 (non-protein coding) (HOXA11-AS1), antisense RNA, receptor (chemosensory) transporter protein 4 (RTP4), mRNA, reticulon 4 receptor (RTN4R), mRNA, Keratin pseudogene, annexin A3 (ANXA3), mRNA, RAS guanyl releasing protein 2 (calcium and DAG-regulated) (RASGRP2), transcript variant 3, mRNA, serum deprivation response (SDPR), mRNA, collagen, type XIII, alpha 1 (COL13A1), transcript variant 21, mRNA, v-ets erythroblastosis virus E26 oncogene homolog 2 (avian) (ETS2), mRNA, ADAM metallopeptidase domain 8 (ADAM8), transcript variant 3, mRNA, prostate collagen triple helix (PCOTH), transcript variant 1, mRNA, family with sequence similarity 124A (FAM124A), transcript variant 1, mRNA, interferon, alpha-inducible protein 27 (IFI27), transcript variant 2, mRNA, hypothetical protein MGC16121 (MGC16121), non-coding RNA, egf-like module containing, mucin-like, hormone receptor-like 2 (EMR2), transcript variant 4, mRNA, RAS guanyl releasing protein 2 (calcium and DAG-regulated) (RASGRP2), transcript variant 3, mRNA, KH domain containing, RNA binding, signal transduction associated 3 (KHDRBS3), mRNA, chromosome 9 open reading frame 47 (C9orf47), transcript variant 1, mRNA, family with sequence similarity 162, member B (FAM162B), mRNA, sodium channel, voltage-gated, type IX, alpha subunit (SCN9A), mRNA, glutaredoxin (thioltransferase) (GLRX), transcript variant 2, mRNA, four jointed box 1 (Drosophila) (FJX1), mRNA, chromosome 10 open reading frame 58 (C10orf58), transcript variant 1, mRNA, archaeysin family metallopeptidase 1 (AMZ1), mRNA, laminin, alpha 5 (LAMA5), mRNA, myosin XVI (MYO16), transcript variant 2, mRNA, SH3-domain GRB2-like (endophilin) interacting protein 1 (SGIP1), mRNA, nuclear receptor subfamily 2, group F, member 1 (NR2F1), mRNA, GULP, engulfment adaptor PTB domain containing 1 (GULP1),

mRNA, actin binding LIM protein family, member 3 (ABLIM3), mRNA, transmembrane protein 154 (TMEM154), mRNA, germ cell associated 1 (GSG1), transcript variant 1, mRNA, suppressor of cytokine signaling 2 (SOCS2), mRNA, GULP, engulfment adaptor PTB domain containing 1 (GULP1), mRNA, integrin, alpha 4 (antigen CD49D, alpha 4 subunit of VLA-4 receptor) (ITGA4), mRNA, DENN/MADD domain containing 2A (DENND2A), mRNA, interferon-induced protein with tetratricopeptide repeats 1 (IFIT1), transcript variant 2, mRNA, C-type lectin domain family 2, member B (CLEC2B), mRNA, hairy and enhancer of split 5 (Drosophila) (HES5), mRNA, chromosome 7 open reading frame 58 (C7orf58), transcript variant 2, mRNA, Keratin 18, cathepsin C (CTSC), transcript variant 1, mRNA, G protein-coupled receptor 183 (GPR183), mRNA, Mitogen-activated protein kinase kinase kinase 8 caspase recruitment domain family, member 9 (CARD9), transcript variant 2, mRNA, nidogen 1 (NID1), mRNA, adenosine monophosphate deaminase 3 (AMPD3), transcript variant 3, mRNA, opioid growth factor receptor-like 1 (OGFRL1), mRNA, interferon induced transmembrane protein 1 (9-27) (IFITM1), mRNA, interleukin 2 receptor, beta (IL2RB), mRNA, tripartite motif containing 14 (TRIM14), transcript variant 1, mRNA, acyl-CoA synthetase short-chain family member 1 (ACSS1), nuclear gene encoding mitochondrial protein, mRNA, RNA binding motif protein 24 (RBM24), transcript variant 3, mRNA, stathmin-like 2 (STMN2), transcript variant 1, mRNA, GULP, engulfment adaptor PTB domain containing 1 (GULP1), mRNA, secreted and transmembrane 1 (SECTM1), mRNA, betaine--homocysteine S-methyltransferase 2 (BHMT2), transcript variant 1, mRNA, lymphocyte-activation gene 3 (LAG3), mRNA, transmembrane protein 51 (TMEM51), transcript variant 1, mRNA, guanine nucleotide binding protein (G protein), gamma 11 (GNG11), mRNA, CD163 molecule-like 1 (CD163L1), mRNA, major histocompatibility complex, class I, F (HLA-F), transcript variant 2, mRNA, endoplasmic reticulum metalloproteinase 1 (ERMP1), mRNA, cytochrome b5 reductase 2 (CYB5R2), mRNA, mitogen-activated protein kinase kinase kinase 5 (MAP3K5), mRNA, interleukin 20 (IL20), mRNA, T-box 3 (TBX3), transcript variant 1, mRNA, adrenergic, alpha-1D-, receptor (ADRA1D), mRNA, leucine rich repeat containing 8 family, member C (LRRC8C), mRNA, folate receptor 3 (gamma) (FOLR3), mRNA, tumor necrosis factor receptor superfamily, member 21 (TNFRSF21), mRNA, actin binding LIM protein family, member 3 (ABLIM3), mRNA, CD44 molecule (Indian blood group) (CD44),

transcript variant 7, mRNA, phosphatidylinositol-3,4,5-trisphosphate-dependent Rac exchange factor 1 (PREX1), mRNA, tripartite motif containing 14 (TRIM14), transcript variant 1, mRNA, aldehyde dehydrogenase 1 family, member A1 (ALDH1A1), mRNA, adaptor-related protein complex 1, mu 2 subunit (AP1M2), mRNA, integrin, alpha 1 (ITGA1), mRNA, mitogen-activated protein kinase kinase kinase 5 (MAP3K5), mRNA, serpin peptidase inhibitor, clade B (ovalbumin), member 2 (SERPINB2), transcript variant 2, mRNA, scavenger receptor class B, member 1 (SCARB1), transcript variant 1, mRNA, homeobox D9 (HOXD9), mRNA, G protein-coupled receptor, family C, group 5, member B (GPRC5B), mRNA, Rho guanine nucleotide exchange factor (GEF) 16 (ARHGEF16), mRNA, adrenergic, alpha-2A-, receptor (ADRA2A), mRNA, intercellular adhesion molecule 4 (Landsteiner-Wiener blood group) (ICAM4), transcript variant 2, mRNA, guanine nucleotide binding protein (G protein), gamma 4 (GNG4), transcript variant 1, mRNA, BCL2-like 10 (apoptosis facilitator) (BCL2L10), mRNA, monoglyceride lipase (MGLL), transcript variant 1, mRNA, Furry homolog (Drosophila) phorbol-12-myristate-13-acetate-induced protein 1 (PMAIP1), mRNA, transmembrane and tetratricopeptide repeat containing 1 (TMTC1), transcript variant 1, mRNA, collagen, type IV, alpha 5 (COL4A5), transcript variant 1, mRNA, disrupted in renal carcinoma 3 (DIRC3), non-coding RNA, Rho GDP dissociation inhibitor (GDI) beta (ARHGDIB), mRNA, oxytocin receptor (OXTR), mRNA, tumor necrosis factor receptor superfamily, member 6b, decoy (TNFRSF6B), mRNA, cytochrome b5 reductase 2 (CYB5R2), mRNA, peptidase M20 domain containing 2 (PM20D2), mRNA, shroom family member 3 (SHROOM3), mRNA, family with sequence similarity 46, member C (FAM46C), mRNA, nuclear factor of kappa light polypeptide gene enhancer in B-cells inhibitor, epsilon (NFKBIE), mRNA, tumor necrosis factor receptor superfamily, member 6b, decoy (TNFRSF6B), mRNA.

71. The solution of claim 69, wherein said endometrial regenerative cell is extracted from the endometrium by means of an endometrial biopsy.

72. The solution of claim 69, wherein said endometrial regenerative cell is extracted from the menstrual blood.

73. The solution of claim 69, wherein said endometrial regenerative cell is extracted from the menstrual blood by means of density centrifugation.

74. The solution of claim 69, wherein said endometrial regenerative cell is extracted from the menstrual blood by means of culture expansion.

75. The solution of claim 69, wherein said endometrial regenerative cell is extracted from the menstrual blood by means of culture expansion.

76. The solution of claim 69, wherein said endometrial regenerative cell is purified for high expression of CD73 from a population of endometrial cells that express markers selected from CD29, CD41a, CD44, CD90, and CD105, and having an ability to proliferate at a rate of 0.5-1.5 doublings per 24 hours in a growth medium.

77. The solution of claim 69, wherein said endometrial regenerative cell is purified for high expression of somatostatin receptor 1 from a population of endometrial cells that express markers selected from CD29, CD41a, CD44, CD90, and CD105, and having an ability to proliferate at a rate of 0.5-1.5 doublings per 24 hours in a growth medium.

78. The solution of claim 69, wherein said endometrial regenerative cell is purified for high expression of spondin 2 from a population of endometrial cells that express markers selected from CD29, CD41a, CD44, CD90, and CD105, and having an ability to proliferate at a rate of 0.5-1.5 doublings per 24 hours in a growth medium.

79. The solution of claim 69, wherein said endometrial regenerative cell is purified for high expression of anoctamin 4 from a population of endometrial cells that express markers selected from CD29, CD41a, CD44, CD90, and CD105, and having an ability to proliferate at a rate of 0.5-1.5 doublings per 24 hours in a growth medium.

80. The solution of claim 69, wherein said endometrial regenerative cell is purified for high expression of aldehyde dehydrogenase from a population of endometrial cells that express markers selected from CD29, CD41a, CD44, CD90, and CD105, and

having an ability to proliferate at a rate of 0.5-1.5 doublings per 24 hours in a growth medium.

81. The solution of claim 69, wherein said endometrial regenerative cell is purified for high expression of 5-hydroxytryptamine receptor 2B from a population of endometrial cells that express markers selected from CD29, CD41a, CD44, CD90, and CD105, and having an ability to proliferate at a rate of 0.5-1.5 doublings per 24 hours in a growth medium.

82. The solution of claim 1, wherein activity of stem cells is assessed in vitro before administration of said stem cells.

83. The solution of claim 82, wherein said stem cell activity is selected from a group of activities comprising of: a) cardiac differentiation ability; b) cytokine production activity; c) immune modulatory activity; d) angiogenic activity; e) endothelial differentiation activity.

84. The solution of claim 83, wherein said cardiac differentiation activity is quantified by culture of said stem cells in a cardiac-inductive media, followed by assessment of the number of cardiomyocytes generated.

85. The solution of claim 83, wherein said cytokine production activity is assessed by quantification of cytokine genes produced by said stem cells, either in basal culture or under induced conditions such as exposure to hypoxia, said cytokines including growth factors.

86. The solution of claim 83, wherein said immune modulatory activity is assessed by quantification of stimulation of allogeneic immunity, using assays such as the stimulation of mixed lymphocyte reaction, and/or by quantification of ability to inhibit an ongoing immune response, such as suppression of ongoing mixed lymphocyte reaction or response of T cell clones against cognate antigen and antigen presenting cell.

87. The solution of claim 83, wherein said angiogenic activity is quantified by ability of said stem cell to stimulate proliferation of human umbilical vein endothelial cells

(HUVEC), or stimulate production of blood vessels in an in vivo model such as the corneal assay or the chorionic allantoic member assay.

88. The solution of claim 83, wherein said endothelial differentiation activity is quantified by ability of said stem cell to differentiate into endothelial cells in the presence of endothelial-inductive media.

89. The solution of claim 1, wherein said cells are exposed to hypoxia prior to administration with the purpose of augmenting therapeutic properties of said cells.

90. The solution of claim 1, wherein said cells are exposed to hyperthermia prior to administration with the purpose of augmenting therapeutic properties of said cells.

91. The solution of claim 1, wherein said cells are exposed to a cytokine and/or growth factor environment prior to administration with the purpose of augmenting therapeutic properties of said cells.

92. The solution of claim 1, wherein said cells are transfected with a gene in order to enhance therapeutic properties of said cells, said genes being capable of stimulating a group of activities selected from: a) angiogenesis; b) inhibition of apoptosis; c) inhibition of fibrosis; and d) inhibition of inflammation.

93. The solution of claim 92, wherein said cells are augmented in angiogenic activity by transfection with a gene or genes selected from a group comprising of: FGF, VEGF, SDF-1, VEGFR, NRP-1, Ang1, Ang2, PDGF (BB-homodimer), PDGFR, TGF- β , endoglin, TGF- β receptors, MCP-1, integrins α V β 3, α V β 5, α 5 β 1, VE-cadherin, CD31, ephrin, ANGPTL3, BAI1, COL4A3, IL8, LAMA5, NRP1, NRP2, STAB1, plasminogen activators, ANGPTL4, PECAM1, PF4, PROK2, SERPINF1, TNFAIP2, HAND2, SPHK1, CCL11, CCL2, CXCL1, CXCL10, CXCL3, CXCL5, CXCL6, CXCL9, IFNA1, IFNB1, IFNG, IL1B, IL6, MDK, TNF, plasminogen activator inhibitor-1, eNOS, COX-2, AC133, Id1/Id3, ANGPT1, ANGPT2, ANPEP, TYMP, EREG, FGF1, FGF2, FIGF, FLT1, JAG1, KDR, S1PR1, EFNA1, EFNA3, EFNB2, EGF, EPHB4, FGFR3, HGF, IGF1, ITGB3, PDGFA, TEK, TGFA, TGFB1, TGFB2, TGFB1, LAMA5, CCL11, CCL2, CDH5, COL18A1, S1PR1, ENG, ITGAV, ITGB3, THBS1, LECT1, LEP, MMP2, MMP9, PLA1, PLG, TIMP1,

TIMP2, AKT1, HIF1A, HPSE, ID1, ID3, NOTCH4, PTGS1, TIMP3, THBS2, NRP1, NRP2, PGF, PLXDC1, STAB1, VEGFA, VEGFC.

94. The solution of claim 92, wherein said cells are increased in resistance to apoptosis by transfecting with a nucleic acid capable of inducing RNAi to genes associated with apoptosis comprised of complementary sequences of nucleic acids, said nucleic acids capable of stimulating RNAi, said sequences having homology to genes selected from a group comprising of: CASP1 (ICE), CASP10 (MCH4), CASP14, CASP2, CASP3, CASP4, CASP5, CASP6, CASP7, CASP8, CASP9, CFLAR (CASPER), CRADD, PYCARD (TMS1/ASC), ABL1, AKT1, BAD, BAK1, BAX, BCL2L11, BCLAF1, BID, BIK, BNIP3, BNIP3L, CASP1 (ICE), CASP10 (MCH4), CASP14, CASP2, CASP4, CASP6, CASP8, CD70 (TNFSF7), CIDEB, CRADD, FADD, FASLG (TNFSF6), HRK, LTA (TNFB), NOD1 (CARD4), PYCARD (TMS1/ASC), RIPK2, TNF, TNFRSF10A, TNFRSF10B (DR5), TNFRSF25 (DR3), TNFRSF9, TNFSF10 (TRAIL), TNFSF8, TP53, TP53BP2, TRADD, TRAF2, TRAF3, and TRAF4.

95. The solution of claim 92, wherein said cells are increased in resistance to apoptosis by transfection with anti-apoptotic genes, said genes selected from a group of genes comprising of: obestatin, XIAP, survivin, BCL-2, BCL-XL, GATA-4, IGF-1, EGF, heme-oxygenase-1, NF-kB, akt, pi3-k, and epha-2.

96. The solution of claim 92, wherein said cells are enhanced in resistance to fibrosis by transfection with nucleic acids capable of inducing RNAi to genes associated with fibrosis, said genes selected from a group comprising of: ACTA2 (α -SMA), AGT, CTGF, CCL11 (Eotaxin), CCL2 (MCP-1), CCL3 (MIP-1a), GREM1, IL13, IL13RA2, IL4, IL5, SNAIL (Snail), COL1A2, COL3A1, LOX, MMP1, MMP13, MMP14, MMP2 (Gelatinase A), MMP3, MMP8, MMP9, PLA1 (uPA), PLG, SERPINA1 (α 1-antitrypsin), SERPINE1 (PAI-1), SERPINH1, TIMP1, TIMP2, TIMP3, TIMP4, ITGA1, ITGA2, ITGA3, ITGAV, ITGB1, ITGB3, ITGB5, ITGB6, ITGB8, BMP7, CAV1, DCN, ENG (EVI-1), GREM1, INHBE, LTBP1, SMAD2, SMAD3, SMAD4, SMAD6, SMAD7, TGFB1, TGFB2, TGFB3, TGFB1 (ALK5), TGFB2, TGIF1, THBS1, and THBS2.

97. The solution of claim 92, wherein said cells are enhanced in resistance to inflammation by transfection with nucleic acids capable of inducing RNAi to genes associated with inflammation, said genes selected from a group comprising of: ABCF1, BCL6, C3, C4A, CEBPB, CRP, ICEBERG, IL1R1, IL1RN, IL8RB, LTB4R, TOLLIP, IFNA2, IL10RA, IL10RB, IL13, IL13RA1, IL5RA, IL9, IL9R, CD40LG (TNFSF5), IFNA2, IL10, IL13, IL17C, IL1A, IL1B, IL1F10, IL1F5, IL1F6, IL1F7, IL1F8, IL1F9, IL22, IL5, IL-6, IL8, IL9, IL-18, IL-33, LTA, LTB, MIF, SCYE1, SPP1, TNF, CCL13 (mcp-4), CCR1, CCR2, CCR3, CCR4, CCR5, CCR6, CCR7, CCR8, CCR9, CX3CR1, IL8RA, XCR1 (CCXCR1), C5, CCL1 (I-309), CCL11 (eotaxin), CCL13 (mcp-4), CCL15 (MIP-1d), CCL16 (HCC-4), CCL17 (TARC), CCL18 (PARC), CCL19, CCL2 (mcp-1), CCL20 (MIP-3a), CCL21 (MIP-2), CCL23 (MPIF-1), CCL24 (MPIF-2 / eotaxin-2), CCL25 (TECK) , CCL26, CCL3 (MIP-1a), CCL4 (MIP-1b), CCL5 (RANTES), CCL7 (mcp-3), CCL8 (mcp-2), CXCL1, CXCL10 (IP-10), CXCL11 (I-TAC / IP-9), CXCL12 (SDF1), CXCL13, CXCL14, CXCL2, CXCL3, CXCL5 (ENA-78 / LIX), CXCL6 (GCP-2), CXCL9, IL13, and IL8.

98. The solution of claim 1, wherein a monoclonal antibody capable of inhibiting inflammatory changes is administered as part of said solution.

99. The solution of claim 98, wherein said monoclonal antibody is selected from a group of monoclonal antibodies inhibiting targets selected from a group comprising of: TLR-2, TLR3, TLR-4, TLR-5, TLR-7, TLR8, TLR9, C3, C4A, CEBPB, CRP, ICEBERG, IL1R1, IL1RN, IL8RB, LTB4R, TOLLIP, IFNA2, IL10RA, IL10RB, IL13, IL13RA1, IL5RA, IL9, IL9R, CD40LG (TNFSF5), IFNA2, IL10, IL13, IL17C, IL1A, IL1B, IL1F10, IL1F5, IL1F6, IL1F7, IL1F8, IL1F9, IL22, IL5, IL-6, IL8, IL9, IL-18, IL-33, LTA, LTB, MIF, SCYE1, SPP1, TNF, CCL13 (mcp-4), CCR1, CCR2, CCR3, CCR4, CCR5, CCR6, CCR7, CCR8, CCR9, CX3CR1, IL8RA, XCR1 (CCXCR1), C5, CCL1 (I-309), CCL11 (eotaxin), CCL13 (mcp-4), CCL15 (MIP-1d), CCL16 (HCC-4), CCL17 (TARC), CCL18 (PARC), CCL19, CCL2 (mcp-1), CCL20 (MIP-3a), CCL21 (MIP-2), CCL23 (MPIF-1), CCL24 (MPIF-2 / eotaxin-2), CCL25 (TECK) , CCL26, CCL3 (MIP-1a), CCL4 (MIP-1b), CCL5 (RANTES), CCL7 (mcp-3), CCL8 (mcp-2), CXCL1, CXCL10 (IP-10), CXCL11 (I-TAC / IP-9), CXCL12 (SDF1), CXCL13, CXCL14, CXCL2, CXCL3, CXCL5 (ENA-78 / LIX), CXCL6 (GCP-2), CXCL9, IL13, and IL8.

100. The solution of claim 1, wherein said solution is administered by the steps of: a) inserting a balloon catheter into the coronary sinus, said catheter containing a guide wire; b) inflating said balloon in the mid portion of the coronary sinus to create a stagnation of blood flow; and c) administering said therapeutic solution in a retrograde manner across the balloon against the coronary venous circulation.

101. The solution of claim 100, wherein said catheter is inserted by cannulation of the femoral vein with a sheath of approximately 7 French.

102. The solution of claim 100, wherein said catheter is inserted by cannulation of the femoral vein with a sheath of approximately 7 French, a catheter of approximately 6 French is placed into the coronary sinus, a hydrophilic guide wire of approximately 0.035 mm is placed in the interventricular or lateral vein, and said balloon is inflated at a pressure approximately 1 to 2 atm in order to allow for stagnation of coronary circulation for a time period of approximately 10 minutes, with said therapeutic solution being injected at a rate of approximately 10 ml per minute

103. A therapeutic agent comprising an isolated cell derived from the endometrium in a liquid media useful for treatment of ischemic conditions.

104. The therapeutic agent of claim 103, wherein said cell is extracted by endometrial biopsy, curettage, or from isolated endometrium after hysterectomy.

105. The therapeutic agent of claim 103, wherein said liquid media is a composition capable of substantially maintaining viability of said endometrially-derived cell.

106. The therapeutic agent of claim 103, wherein said endometrially-derived cell is extracted from the menstrual blood.

107. The therapeutic agent of claim 103, wherein endometrial derived cells are cultured in a liquid media and produce PDGF, MMP-3, GM-CSF and Angiopoietin-2 at a higher rate than bone marrow mesenchymal stem cells cultured under similar conditions.

108. The method of claim 1, wherein stem cells, are administered in absence of nucleic acids via retrograde administration into the coronary sinus.

109. The method of claim 108, wherein said method of retrograde administration comprises: a) inserting a balloon catheter into the coronary sinus, said catheter containing a guide wire; b) inflating said balloon in the mid portion of the coronary sinus to create a stagnation of blood flow; and c) administering the cell population in a retrograde fashion across the balloon against the coronary venous circulation in a manner sufficient to cause uptake of the cells by cardiac tissue.

110. The method of claim 108, wherein said catheter is inserted by cannulation of the femoral vein with a sheath of approximately 7 French, a catheter of approximately 6 French is placed into the coronary sinus, a hydrophilic guide wire of approximately 0.035 mm is placed in the interventricular or lateral vein, and said balloon is inflated at a pressure approximately 1 to 2 atm in order to allow for stagnation of coronary circulation for a time period of approximately 10 minutes, with said therapeutic solution being injected at a rate of approximately 10 ml per minute.

111. A method of inhibiting rejection of a cardiac graft comprising administering a nucleic acid capable of suppressing gene expression of rejection-associated genes through the steps of: a) inserting a balloon catheter into the coronary sinus, said catheter containing a guide wire; b) inflating said balloon in the mid portion of the coronary sinus to create a stagnation of blood flow; and c) administering said nucleic acids in a retrograde manner across the balloon against the coronary venous circulation.

112. The method of claim 111, wherein said catheter is inserted by cannulation of the femoral vein with a sheath of approximately 7 French, a catheter of approximately 6 French is placed into the coronary sinus, a hydrophilic guide wire of approximately 0.035 mm is placed in the interventricular or lateral vein, and said balloon is inflated at a pressure approximately 1 to 2 atm in order to allow for stagnation of coronary circulation for a time period of approximately 10 minutes, with said therapeutic solution being injected at a rate of approximately 10 ml per minute.

113. A method of treat peripheral artery disease comprising the steps of: a) 1. A solution useful for the treatment of cardiovascular disorders comprising: a) a nucleic acid capable of inducing the process of RNA interference (RNAi); and/or b) a cellular population.

114. A method for the treatment of a peripheral artery disorder, comprising administration of a cellular population comprising endometrial regenerative cells intramuscularly.