Open Access

Donor Selection is a Critical Component Using Naïve Endogenous Adult Stem Cells for the Treatment of Chronic Diseases and Traumatic Injuries

Henry E Young^{1-3*}, Mark O Speight⁴⁻⁶

¹Dragonfly Foundation for Research & Development, Macon, GA 31210, USA

²Henry E Young PhD Regeneration Technologies LLC, USA

³Mercer University School of Medicine, Macon, GA 31207, USA

⁴Research Designs, Charlotte, NC 28105, USA

⁵The Charlotte Foundation for Molecular Medicine, Charlotte, NC 28105, USA

⁶Center for Wellness, Charlotte, NC 28105, USA

***Corresponding Author:** Henry E Young PhD, Chief Science Officer, Dragonfly Foundation for Research & Development, 101 Preston Ct, Suite 101, (Corporate Office), Macon, GA 31210 USA; Tel: +478-3191983; Email: young.hey1@yahoo.com

Received Date: 28-07-2020; **Accepted Date:** 26-10-2020; **Published Date:** 03-11-2020

Copyright© 2020 by Young HE, et al. All rights reserved. This is an open access article distributed under the terms of the Creative Commons Attribution License, which permits unrestricted use, distribution and reproduction in any medium, provided the original author and source are credited.

Abstract

Naïve adult endogenous stem cell transplants have been used as a substitute for embryonic stem cells and/or induced pluripotent stem cells for treating individuals with autoimmune, cardiovascular, neurological, orthopedic, pulmonary, renal and systemic chronic diseases and traumatic injuries. This is primarily due to the absence of moral and ethical issues, absence of teratoma formation when transplanting stem cells in the naïve state, readily available populations of stem cells and ease of stem cell isolation for transplant. While a majority of the ongoing clinical trials utilize autologous naïve adult endogenous stem cells for treating the individual with their own stem cells, other trials have utilized similar types of allogenic stem cells from donors for the treatment of chronic diseases. For allogeneic naïve endogenous adult stem cells to be utilized for transplant, the donor stem cells should be screened to prevent the

Young HE | Volume 1; Issue 2 (2020) | JRMBR-1(2)-009 | Clinical Trial Report

Citation: Young HE, et al. Donor Selection is a Critical Component Using Naïve Endogenous Adult Stem Cells for the Treatment of Chronic Diseases and Traumatic Injuries. J Reg Med Biol Res. 2020;1(2):1-28.

DOI: <http://dx.doi.org/10.46889/JRMBR.2020.1203>

potential for Graft Versus Host Disease (GvHD) response where the recipient may destroy the graft or the graft may destroy the recipient; to prevent inoculation of new infectious diseases into the recipient and to prevent transplantation of stem cells with deleterious gene mutations into the recipient. This paper describes the various types of adult telomerase negative and telomerase positive endogenous stem cells being used for transplantation therapies, disease entities they have treated, whether treatments utilized autologous and/or allogeneic stem cells, reported outcomes and proposed selection criteria used in the future for allogeneic adult endogenous stem cells in regenerative medicine.

Keywords

Adult; Stem Cell; Autologous; Allogeneic; Donor Selection; MSCs; VSELs; MAPCs; MUSE; TSCs; PSCs; MesoSCs; Regenerative Medicine

Introduction

Multiple studies have demonstrated that stem cells in general and naïve endogenous adult stem cells in particular are useful treatments in the field of regenerative medicine [1-15]. Adult differentiated cells, e.g., functional parenchymal cells and structural stromal cells, comprise approximately 50% of all cells in an adult (post-natal) individual [16]. Examples of functional parenchymal cells include exocrine glands, various types of muscle, pneumocytes, hepatocytes, pancreatic islet cells, neurons, nephrocytes, endothelial cells, lining cells of the gastrointestinal system, etc. Examples of structural stromal cells include loose fibrous connective tissues, endoneurium, perineurium, epineurium, endomysium, perimysium, epimysium, cardiac skeleton, organ capsules, organ trabeculae, etc. [17]. The remaining 50% of all cells in an adult individual are composed of endogenous stem cells [16].

Endogenous Telomerase Negative Stem Cells

The endogenous stem cells of an adult can be segregated into two categories based on the absence or presence of the enzyme telomerase. Approximately 40% of the adult endogenous stem cells are telomerase negative and approximately 10% are telomerase positive [16]. The enzyme telomerase is responsible for maintaining telomere number at the ends of the chromosomes during cell division. Without telomerase, once all the telomeres are lost, the cell undergoes pre-programmed cell senescence and cell death [18]. Telomerase is absent in differentiated cells and lineage committed progenitor stem cells [19]. Human telomerase negative cells at birth have a lifespan of 70 population doublings before genetically pre-programmed for cell senescence and cell death [20]. In rodents, telomerase negative cells have a lifespan of 6-8 population doublings before genetically pre-programmed for cell senescence

Young HE | Volume 1; Issue 2 (2020) | JRMBR-1(2)-009 | Clinical Trial Report

Citation: Young HE, et al. Donor Selection is a Critical Component Using Naïve Endogenous Adult Stem Cells for the Treatment of Chronic Diseases and Traumatic Injuries. J Reg Med Biol Res. 2020;1(2):1-28.

DOI: <http://dx.doi.org/10.46889/JRMBR.2020.1203>

and cell death [21]. Examples of endogenous telomerase negative stem cells are mesenchymal stem cells (MSCs), Medicinal Signalling Cells (MSCs), Marrow Stromal Cells (MSCs), Very Small Embryonic-Like Cells (VSELs), Multilineage Differentiating Stress Enduring Cells (MUSE) [14], Multipotent Adult Progenitor Cells (MAPCs), multipotent epidermal stem cells, multipotent neural progenitor stem cells, multipotent hematopoietic progenitor stem cells, tripotent adipo-chondro-osteo progenitor stem cell, bipotent adipofibroblast progenitor stem cell, bipotent hepatic oval progenitor stem cell and unipotent myoblast progenitor stem cell [10-12,22-40].

Endogenous Telomerase Positive Stem Cells

In contrast, for stem cells that are telomerase positive the number of telomeres at the ends of the chromosomes are restored after each cell division, giving the cell an almost unlimited proliferation potential as long as the cell remains undifferentiated [18]. Telomerase is present in gametes (sperm and ova), tumor cells and a small proportion (10%) of naïve adult endogenous stem cells, e.g., Ectodermal Stem Cells (EctoSCs), Mesodermal Stem Cells (MesoSCs), Endodermal Stem Cells (EndoSCs), Pluripotent Stem Cells (PSCs) and Totipotent Stem Cells (TSCs) [41-45]. In long term studies, a mesodermal stem cell clone demonstrated population doubling numbers of 2690, a pluripotent stem cell clone demonstrated population doubling numbers $> 2^{400}$ and a totipotent stem cell clone demonstrated population doubling numbers $> 2^{300}$ [42]. Throughout these studies, at start of the experiments and at every 200-300 population doublings thereafter, clones of MesoSCs, PSCs and TSCs were analyzed for any changes in karyotypic expression, confirmation of Hayflick's Limit once induced to a particular cell lineage and induction of downstream differentiated cell types [18,20]. The lower number of cell doublings for totipotent stem cells and pluripotent stem cells was due to when the telomerase positive stem cell (e.g., MesoSC, PSC, TSC) was isolated, purified and/or cloned from single cells and their respective population doubling experiments initiated, rather than their absolute number of population doublings. In any case, cell doublings > 70 (Hayflick's Limit) suggest potential for essentially unlimited proliferation potential [42].

Figure 1: Lineage map of embryonic development. Reprinted with permission from Young HE, Black Jr AC. Adult stem cells. *Anat. Rec.* 2004; 276A:75-102.

Of the 10% stem cells that are telomerase positive, ~3% are Ectodermal Stem Cells (EctoSCs) and will only form cells of the ectoderm germ layer lineage, e.g., surface ectoderm-, neural ectoderm- and neural crest-derived cells (Fig. 1). The EctoSCs will not cross over, i.e., will not transdifferentiate, into cells of either the mesodermal germ layer lineage or the endodermal germ layer lineage (Fig. 2), or dedifferentiate into pluripotent stem cells or totipotent stem cells. Approximately 3% of the telomerase positive stem cells are Mesodermal Stem Cells (MesoSCs) and will only form cells of the mesoderm germ layer lineage, e.g., lateral plate mesoderm-, intermediate mesoderm- and paraxial mesodermal-derived cells (Fig. 1). MesoSCs will not cross over, i.e., will not transdifferentiate, into cells of either the ectodermal germ layer lineage or the endodermal germ layer lineage (Fig. 2) or dedifferentiate into pluripotent stem cells or totipotent stem cells. Approximately 3% of the telomerase positive stem cells are Endodermal Stem Cells (EndoSCs) and will only form cells of the Endoderm germ layer lineage (Fig. 1). EndoSCs will not cross over, i.e., will not transdifferentiate, into cells of either the ectodermal germ layer lineage or the mesodermal germ layer lineage (Fig. 2) or dedifferentiate into pluripotent stem cells or totipotent stem cells. Approximately 0.9% of the telomerase positive stem cells are Pluripotent Stem Cells (PSCs), equivalent to the Epiblast (Fig. 1). They will form all cell types of the body across all three germ layer lineages, but will not form gametes (sperm or ova) and will not form the nucleus pulposus of the intervertebral

discs, the only adult structure of the notochord (Fig. 2), or dedifferentiate into totipotent stem cells. The remaining telomerase positive stem cells approximate 0.1% of all stem cells in the body and are termed Totipotent Stem Cells (TSCs). TSCs are equivalent to the blastocyst of the developing zygote (Fig. 1) and will form all tissues of the body, including the gametes (sperm and ova) and the nucleus pulposus of the intervertebral disc (Fig. 2). Differentiation is solely in a downstream direction and results were based on multiple studies with general and specific induction agents tested individually or in combination with clones of MSCs, EctoSCs, MesoSCs, EndoSCs, PSCs and TSCs generated by repetitive single cell clonogenic analysis (Table 1) [42-47].

Figure 2: Diagram of telomerase-positive stem cells (with an essentially unlimited proliferation potential) {above red dashed line} and telomerase-negative stem cells (which conform to Hayflick's limit of 50-70 population doublings before programmed cell senescence and death {below blue dashed line}, that are located within the body. The differentiation potential with respect to the stem cells is solely unidirectional in a downstream direction. Reprinted with permission from Young HE, Speight MO. Characterization of endogenous telomerase-positive stem cells for regenerative medicine, a review. Stem Cell Regen Med 2020; 4(2):1-14.

Induction Factor & Cell Type(s) Formed	MSCs	EctoSCs	MesoSCs	EndoSCs	PSCs	TSCs
Dexamethasone: 10^{-6} to 10^{-10} M: Mesoderm: fibroblasts, smooth muscle, cardiac muscle, skeletal muscle, unilocular white fat, multilocular brown fat, hyaline cartilage, elastic cartilage, and fibrocartilage, endochondral and cancellous bone.	Fat, Cart, Bone Only	No	Yes	No	Yes	Yes
Skeletal Muscle Morphogenetic Protein (Sk-MMP): Mesoderm: Skeletal muscle	No	No	Yes	No	Yes	Yes
Smooth Muscle Morphogenetic Protein (Sm-MMP): Mesoderm: Smooth muscle	No	No	Yes	No	Yes	Yes
Cardiac Muscle Morphogenetic Protein (CM-MMP): Mesoderm: Cardiac muscle	No	No	Yes	No	Yes	Yes
Fibroblast Morphogenetic Protein (FMP): Fibroblasts	No	No	Yes	No	Yes	Yes

Scar Fibroblast Morphogenetic protein (SFMP): Mesoderm: Scar fibroblasts	No	No	Yes	No	Yes	Yes
White Fat Morphogenetic Protein (WFMP): Mesoderm: Unilocular adipose tissue	Yes	No	Yes	No	Yes	Yes
Brown Fat Morphogenetic Protein (BFMP): Mesoderm: Multilocular adipose tissue	No	No	Yes	No	Yes	Yes
Chondrogenic Morphogenetic Protein (ChMP): Mesoderm: Fibrocartilage, elastic cartilage, hyaline cartilage, articular cartilage, growth plate cartilage	Hyaline Cart	No	Yes	No	Yes	Yes
Endochondral Bone Morphogenetic Protein (EBMP): Mesoderm: Endochondral bone formation – mesoderm to growth plate cartilage model to bone	Endoch Bone	No	Yes	No	Yes	Yes
Intramembranous Bone Morphogenetic Protein (IBMP): Mesoderm: Intramembranous bone formation – direct mesoderm to bone formation	No	No	Yes	No	Yes	Yes

Young HE | Volume 1; Issue 2 (2020) | JRMBR-1(2)-009 | Clinical Trial Report

Citation: Young HE, et al. Donor Selection is a Critical Component Using Naïve Endogenous Adult Stem Cells for the Treatment of Chronic Diseases and Traumatic Injuries. J Reg Med Biol Res. 2020;1(2):1-28.

DOI: <http://dx.doi.org/10.46889/JRMBR.2020.1203>

Bone Morphogenetic Protein-2 (BMP-2): Mesoderm: Endochondral bone formation – mesoderm to growth plate cartilage model to bone	Endoch Bone	No	Yes	No	Yes	Yes
Fibroblast Growth Factor-Alpha (FGF-a): Mesoderm: Endothelial cells	No	No	Yes	No	Yes	Yes
Transforming Growth Factor-Beta (TGF-b): Mesoderm: Fibroblasts	No	No	Yes	No	Yes	Yes
Basic-Fibroblast growth Factor (basic-FGF): Mesoderm: Fibroblasts	No	No	Yes	No	Yes	Yes
Stem Cell Factor (SCF) + Interleukin-3 (IL-3) + Interleukin-6 (IL-6) + Erythropoietin (EPO): Mesoderm: RBC colony forming units	No	No	Yes	No	Yes	Yes
Nerve Growth Factor (NGF): Ectoderm: Neurons, glial cells	No	Yes	No	No	Yes	Yes
Hepatocyte Growth Factor (HGF):	No	No	No	Yes	Yes	Yes

Endoderm: hepatocytes, oval cells (hepatic progenitor cells)						
TSC Exosome- Conditioned Medium: Totipotent stem cell lineage	No	No	No	No	No	Yes
PSC Exosome- Conditioned Medium: Pluripotent stem cell lineage	No	No	No	No	Yes	Yes
EctoSC Exosome- Conditioned Medium: Ectodermal stem cell lineage	No	Yes	No	No	Yes	Yes
MesoSC Exosome- Conditioned Medium: Mesodermal stem cell lineage	No	No	Yes	No	Yes	Yes
EndoSC Exosome- Conditioned Medium: Endodermal stem cell lineage	No	No	No	Yes	Yes	Yes
Pancreatic Islet Inductive Cocktail [12,38,40,41]: Alpha-cells (glucagon), beta-cells (insulin), delta- cells (somatostatin)	No	No	No	Yes	Yes	Yes
Nucleus Pulposus of Intervertebral Disc Exosome-Conditioned Medium: Nucleus Pulposus of IVD	No	No	No	No	No	Yes

Testicle Exosome- Conditioned Medium: Spermatogonia	No	No	No	No	No	Yes
CD cell surface markers*	CD105, CD117, CD123, CD166, MHC Class-I	CD56, CD90, MHC Class-I	CD13, CD90, MHC Class-I	CD90 MHC Class-I	CD10	CD66e
*CD cell surface markers examined were CD1a, CD2, CD3, CD4, CD5, CD7, CD8, CD9, CD10, CD11b, CD11c, CD13, CD14, CD15, CD16, CD18, CD19, CD20, CD22, CD23, CD24, CD25, CD31, CD33, CD34, CD36, CD38, CD41, CD42b, CD44, CD45, CD49d, CD55, CD56, CD57, CD59, CD61, CD62e, CD66e, CD68, CD69, CD71, CD79, CD83, CD90, CD105, CD117, CD123, FLT3 (CD135), CD166, Glycophorin-A, MHC Class-I, HLA-DR-II, FMC-7, Annexin-V, and Lin antigens.						

Table 1: Induction of Telomerase Negative Stem cells (MSCs) and Telomerase Positive Stem Cells EctoSCs, MesoSCs, EndoSCs, PSCs, TSCs) to form differentiated cells using general and specific induction agents.

Clinical Studies of Telomerase Negative and Telomerase Positive Stem Cells

With respect to telomerase negative endogenous adult stem cells, the proportion of clinical studies using mesenchymal stem cells, both autologous and allogeneic, far outweigh the number of clinical studies using very small embryonic-like stem cells, multipotent adult progenitor cells and multilineage differentiating stress enduring cells [8,48]. Examples of mesenchymal stem cell clinical studies can be subdivided into particular diseases, such as autoimmune diseases, e.g., Systemic Lupus Erythematosus (SLE), celiac disease; pulmonary diseases, e.g., Idiopathic Pulmonary Fibrosis (IPF); Chronic Obstructive Pulmonary Disease (COPD); Cardiovascular Disease (CVD); neurological diseases, e.g., Age-Related Macular Degeneration (AMD), Parkinson Disease (PD), Alzheimer's Disease (AD), Traumatic Spinal Cord Injury (TSCI), Stroke, Traumatic Brain Injury (TBI), Traumatic Blindness, Chronic Inflammatory Demyelinating Polyneuropathy (CIDP), Multiple Sclerosis (MS), Amyotrophic Lateral Sclerosis (ALS) and systemic diseases, e.g., End Stage Renal Disease (ESRD) and Chronic Kidney Disease (CKD) [49-114]. Clinical trials utilizing transplanted autologous and/or allogeneic MSCs have shown that the effect of MSCs on various disease states has been either no effect, stasis of disease progression or a slight reduction in disease progression. It has been suggested that this is due to immunomodulatory effects on the system, rather than

Young HE | Volume 1; Issue 2 (2020) | JRMBR-1(2)-009 | Clinical Trial Report

Citation: Young HE, et al. Donor Selection is a Critical Component Using Naïve Endogenous Adult Stem Cells for the Treatment of Chronic Diseases and Traumatic Injuries. J Reg Med Biol Res. 2020;1(2):1-28.

DOI: <http://dx.doi.org/10.46889/JRMBR.2020.1203>

reparative with an increase in overall function. This immunomodulatory activity has been prescribed potentially to exosomes secreted by the MSCs into the damaged tissues [26,27,49,54,58,59,77,83,87-89,91,93,97,104,105,108-110,112,115-121].

In contrast, clinical studies utilizing autologous and/or allogeneic MesoSCs, PSCs and/or TSCs have shown a definitive reparative/regenerative response in the tissues, demonstrated by a 5%-50% increase in organ(s) function(s) across all of the following diseases examined, e.g., SLE, Celiac disease, IPF, COPD, CVD, AMD, PD, AD, TSCI, stroke, TBI, traumatic blindness, CIDP, MS, ALS and CKD [122-141].

Isolation Strategies

The disparity in results between telomerase negative MSCs (e.g., no effect, stasis of disease progression, or a slight reduction in disease progression) versus telomerase positive stem cells, e.g., TSCs, PSCs and MesoSCs (restoring function of damaged tissues) might be reflected by the isolation strategies for the telomerase negative versus telomerase positive stem cells types.

The major source tissues for MSCs are bone marrow, adipose tissue and umbilical cord. The original protocol to isolate MSCs from bone marrow, was to use “long bones”, e.g., femur, tibia and/or humerus; separate the epiphysis from the diaphysis and attached metaphysis; wash out the marrow with saline, using forced pressure; homogenate the marrow; load onto a Ficoll density gradient and centrifuge to separate hematopoietic cells from the remaining mononucleated cells that were designated as MSCs [22,23]. The original protocol to separate MSCs from adipose tissue was to suction adipose tissue from an individual, which is removed as a slurry of cells. Digest the slurry with lipase, which is an enzyme that disrupts adipoblasts and adipocyte connection with the other cells. Dilute the cell suspension with tissue culture medium and fill a tissue culture flask completely full; place the tissue culture flask within a 37°C incubator horizontal; allow the adipocytes and adipoblasts to float to surface; pour off the upper layer of medium (containing the adipocytic elements) and one is left with a collection of mononucleated cells, that were termed MSCs [25]. There were three basic protocols to remove MSCs from umbilical cords. In the first procedure the MSCs were removed with the hematopoietic cells within the two umbilical arteries and one umbilical vein using pressurized saline to wash out the cells and then the MSCs separated from the blood cells by centrifugation. The second procedure isolated MSCs from Wharton’s Jelly, the tissue supporting the umbilical vessels, by “milking” Wharton’s jelly from the cord, dispersing the mononucleated cells, termed MSCs. The third procedure cut the umbilical cord into pieces, digested with enzymes to produce a slurry of cells, centrifuged to remove the enzymes and the remaining mononucleated cells were designated as MSCs [7,8,116].

Unfortunately, while these isolation procedures are easy to perform, the derived cells from each procedure are not just MSCs. Rather the isolated mononucleated cells are a heterogenous population of differentiated cells, telomerase negative stem cells and telomerase positive stem cells, with combined multilineage differentiation capabilities, secrete various growth factors

and cytokines and ability to modulate oxidative stress that can have anti-apoptotic, angiogenic, anti-inflammatory and immunomodulatory effects [142,143]. For example, bone marrow is not just hematopoietic cells and MSCs. Bone marrow is composed of hematopoietic cells, e.g., hematopoietic stem cells, RBCs and their respective cell lineages, WBCs and their respective cell lineages, chondroclasts, osteoclasts, vascular tissues, e.g., sinusoids, arteries, arterioles, venuoles, veins, all lined with endothelial cells (inner lining) and smooth muscle cells (outer layer), bone marrow stromal cells, fibroblasts, fibrocytes, adipoblasts, adipocytes, chondroblasts, chondrocytes, osteoprogenitor cells, osteoblasts, osteocytes, telomerase negative stem cells, e.g., MSCs, VSELs, MAPCs, MUSE and telomerase positive stem cells, e.g., MesoSCs, PSCs and TSCs [10-14,17,19,22,23,28-31,141,144].

Similarly, adipose tissue is not just fat cells and MSCs. White fat adipose tissue is a metabolically active tissue. It is composed of adipoblasts, adipocytes; a connective tissue framework consisting of fibroblasts and fibrocytes; nervous tissue associated cells, e.g., Schwann cells (myelin), neural processes, sensory nerve endings, neuroblasts, endoneurium, perineurium, epineurium; associated vascular tissues, e.g., endothelial cells specific for arteries, arterioles, different types of capillaries, venuoles, veins, smooth muscle cells, hematopoietic stem cells, RBCs, WBCs, monocytes, macrophages and their associated connective tissues; telomerase-negative stem cells, e.g., MSCs, VSELs, MAPCs, MUSE and telomerase-positive stem cells, e.g., EctoSCs, MesoSCs, PSCs, TSCs and MSCs [12-14,19,25,72,94,95,106,145].

Likewise, the contents of the umbilical cord are not just hematopoietic stem cells and MSCs. Rather, from inside outward the umbilical cord is composed of two umbilical arteries and one umbilical vein containing hematopoietic stem cells, MSCs and telomerase positive TSCs, PSCs and MesoSCs. The vessels are lined on the inside with endothelial cells and on the outside with smooth muscle cells. The next layer is Wharton's Jelly which consists of a hyaluronic acid extracellular matrix with embedded telomerase negative stem cells, e.g., MSCs, VSELs, MAPCs, MUSE and telomerase positive stem cells, e.g., TSCs, PSCs and MesoSCs [7,8,27,93,103,116, unpublished observations].

One might argue that if all three source tissues for mononucleated cells, designated as MSCs, e.g., bone marrow, adipose tissue and umbilical cord, also contain telomerase positive stem cells, then results between the two should be similar, but they decidedly different, i.e., immunomodulatory (MSCs) versus reparative (telomerase positive stem cells). One potential explanation for the discrepancy between the two sets of stem cells is the manner in which the cells are cryopreserved and stored for future use. Differentiated cells and telomerase negative stem cells are optimally flash frozen and stored in liquid nitrogen, -196°C (90-95% viable when thawed) [42]. This is probably due to the high cytoplasm to nuclear ratio, i.e., large amount of fluid in the cytoplasm and the chance for ice crystal formation if the cells are frozen slowly. In contrast, telomerase positive stem cells are optimally slow frozen (decrease in temperature of one degree per minute) and stored at -70°C (EctoSCs, MesoSCs and EndoSCs) to -80°C (PSCs and TSCs) (95-100% viable when thawed). The telomerase positive stem cells have a high nuclear to cytoplasmic, very little water in their cytoplasm and hence can withstand the higher

freezing and storage temperatures [42]. To test this hypothesis, we switched freezing parameters. Our clone of MSCs was slow frozen and stored at -80°C. Within 24 hours after freezing there was 5% viability of the cells when thawed. MSC viability continued to decrease to 0% with increasing time in storage. Similarly, we flash froze and stored a PSC clone (Scl-40β) in liquid nitrogen. Within 12 hours after freezing there was ~5% viability of the cells when thawed. Similar to the MSCs, with increasing storage time the viability of the PSC clone decreased to 0%. The results suggested that if mononucleated cells isolated from the source tissue were flash frozen and stored in liquid nitrogen then all potential telomerase positive stem cells in the population would be lost. Differential cryopreservation and storage at a temperature of -70°C to -80°C was another method used to rid telomerase positive stem cells from any contaminating telomerase negative stem cells in a preparation [42].

MHC Class-I and MSCs, MesoSCs, PSCs and TSCs

Studies from our lab noted that a clone of telomerase negative adult endogenous Mesenchymal Stem Cells (MSCs), generated by repetitive serial dilution clonogenic analysis, displayed CD105, CD117, CD123, CD166 and MHC Class-I cell surface markers (Table.1) [42]. In contrast, MSCs known as Medicinal Signalling Cells (MSCs) displayed CD73, CD80, CD90 and MHC Class-I cell surface markers [Review,8]. Regardless as to the MSC population analyzed, both Medicinal Signalling Cells (MSCs) displaying CD73, CD80, CD90 and Mesenchymal Stem Cells (MSCs) displaying CD105, CD117, CD123 and CD166 demonstrated the presence of MHC Class-I marker expression on their cell surfaces. Similarly, the adult endogenous telomerase positive germ layer lineage stem cells, e.g., EctoSCs, MesoSCs and EndoSCs, all displayed MHC Class-I markers on their respective cell surfaces. In contrast, adult endogenous telomerase positive PSCs and TSCs were absent of the MHC Class-I marker on their cell surfaces (Table.1) [42]. MHC Class-I is an HLA (Human Leukocyte Antigen) marker that an intact immune system uses to distinguish self from non-self [146].

A series of pre-clinical experiments were performed to ascertain whether presence or absence of the MHC Class-I marker had any effect with respect to transplanting telomerase positive stem cells. In these experiments, individual clones of TSCs, PSCs and MesoSCs were implanted into outbred animals with intact immune systems. The TSCs and PSCs incorporated into the tissues of the host animal and began regenerating previously damaged tissues [15,124,130]. In contrast, MesoSCs with the MHC Class-I cell surface marker induced an inflammatory response with subsequent scar tissue formation in the tissues [15]. The MesoSC results suggested the potential of an MHC Class-I-initiated Graft Versus Host Disease (GvHD) response, whereby allogeneic (donor) cells containing the MHC Class-I cell surface marker were recognized as non-self by an intact immune system, initiating an inflammatory response to rid the body of the offending invaders [147].

Criteria for Allogeneic Stem Cell Transplants

Chronic diseases where allogeneic stem cells from donors were transplanted into recipients for treatment included systemic lupus erythematosus, celiac disease, idiopathic pulmonary fibrosis, chronic obstructive pulmonary disease, cardiovascular disease, Alzheimer's disease and Amyotrophic lateral sclerosis. Results using allogeneic telomerase negative MSCs, expressing MHC Class-I on their cell surfaces suggested an immunomodulatory effect of the MSCs with respect to these diseases where there was either stasis of disease progression, slowed disease progression, or no effect on disease progression [7,8,50,51,55,60,61,64-76,90,92,95,96,99,103,106,107,148-150]. Another cohort of studies suggested that exosome-containing vesicles derived from MSCs were the actual mediators of the immunomodulatory response of MSCs on these diseases [26,27,49,54,58,59,77,83,87-89,91,93,97,104,105,108-110,112,115-121]. In contrast, based on the MesoSC transplantation studies, only telomerase positive TSCs and PSCs, that did not express MHC Class-I marker, were utilized for the allogeneic treatment of these same diseases [122,123,125,126,128,133,140]. The responses of the individuals were varying degrees of increase in function. These results suggested that the telomerase positive PSCs and TSCs were involved in reparative and/or regenerative activities with respect to the diseases treated.

When telomerase positive TSCs and PSCs were used as allogeneic donor cells, other criteria were recognized as important factors for choosing the appropriate donors for transplant, e.g., gender match; ABO-blood group match or O-negative universal donor; non-shared infectious diseases; deleterious genetic mutations and cancer; donor lifestyle choices; donor's ethnicity, hair pattern, hair color and personality and donor's allergies and food choices.

Gender Match

Pre-clinical animal studies examining cross gender transplants noted some rather unexpected findings [16]. When male TSCs were transplanted into females or female TSCs were transplanted into males, additional secondary sex characteristics were noted in the recipient that matched the gender of the donor. Opposite gender secondary sex characteristics did not occur when male TSCs were transplanted into males or female TSCs were transplanted into females. Totipotent stem cells have the capability to form gametes if placed into the appropriate environmental milieu and given an appropriate stimulus they will migrate to areas distant to the site of placement [15,42,127,130]. Since the adrenal cortex does secrete low levels of both androgens and estrogens, it is conceivable that transplanted allogeneic TSCs migrated to areas where secondary sex characteristics are expressed and differentiated into the appropriate tissue types under the influence of low levels of either androgens or estrogens [42]. Therefore, to prevent such an occurrence in humans, gender-match is a pre-requisite for allogeneic TSC transplant.

ABO-Blood Group-Match or O-Negative Universal Donor

Informed Consent Guidelines for allogeneic telomerase-positive stem cell harvest is to have the donor ingest Combinatorial Nutraceuticals (CN, DFRD, Macon, GA) for a minimum of 30 days prior to harvest [150]. The CN induces the native TSCs, PSCs and MesoSCs to preferentially proliferate within their connective tissue niches throughout the body. Eighteen hours before harvest the donor ingests Glacial Caps (GC, DFRD), which induce the proliferated TSCs, PSCs and MesoSCs to mobilize (reverse diapiesis) into the blood stream [152]. At harvest, 210-420cc of whole blood, containing both the blood elements and the telomerase-positive stem cells, is removed by venipuncture and the telomerase-positive stem cells are separated from the blood elements by our standardized procedure ‘FDA-mandated minimal manipulative procedures’, e.g., gravity, zeta potential and differential density gradient centrifugation, with serum, saline and sterile distilled water [122-141]. It is the blood draw that necessitates the ABO-blood group match or O-negative universal donor for allogeneic telomerase positive stem cell transplants [122,123,125,126,128,133,140]. While neither TSCs nor PSCs express MHC Class-I or HLA-DR cell surface molecules in the undifferentiated state, they will express those cell surface markers as they differentiate [42]. However, the time frame for that to occur is apparently sufficient for the host’s immune system to accept the allogeneic TSCs and PSCs as ‘self’ and not reject the differentiated cells. Year-long pre-clinical animal studies using out-bred animals with cross species transplants proved that to be the case [15,16].

Non-Shared Infectious Diseases

One of the inclusion / exclusion criteria for donors for the clinical studies is to screen both the donor and recipient for the presence of infectious diseases, e.g., cytomegalovirus, Epstein Barr virus, Hepatitis (A,B,C), HIV, etc. [151]. If the donor does not express any infectious diseases and the recipient expresses one or more infectious diseases, the donor’s TSCs and PSCs are used for transplant. Similarly, if both donor and recipient express the same infectious disease(s), then the donor’s TSCs and PSCs are used for transplant. In contrast, if the donor expresses an infectious disease that is not found in the recipient, then the donor’s TSCs and PSCs are excluded from use of that recipient.

Deleterious Genetic Mutations and Cancer

Other criteria used to exclude donors from the clinical studies is to screen the donor for deleterious genetic mutations and cancers [151]. The donor’s genome is sequenced and then cross-matched to NIH’s data base for gene sequences for germ line mutations, deleterious gene mutations and cancers, e.g., hemophilia, sickle cell anemia, retinoblastoma, familial polyposis, etc. [153]. If the donor’s genome contains one or more gene sequences for homozygous dominant, homozygous recessive, or sex-linked disorders and/or cancers, the donor is excluded from participation in the clinical studies.

Young HE | Volume 1; Issue 2 (2020) | JRMBR-1(2)-009 | Clinical Trial Report

Citation: Young HE, et al. Donor Selection is a Critical Component Using Naïve Endogenous Adult Stem Cells for the Treatment of Chronic Diseases and Traumatic Injuries. J Reg Med Biol Res. 2020;1(2):1-28.

DOI: <http://dx.doi.org/10.46889/JRMBR.2020.1203>

Donor Lifestyle Choices

Our informed consent document, which is a requirement of each participant, donor and recipient, to initial each statement and sign, specifically states the following [151].

“For a minimum of 30 days before stem cell harvest and throughout treatments to not use alcohol, tobacco products, vaping, recreational drugs, lidocaine, or chemotherapeutic agents because they KILL telomerase-positive stem cells _____.”

“Limit use of caffeine (to 95 mg per day, size of one small cup of coffee) from two weeks before to two weeks after stem cell harvest/ transplant and no caffeine during a two-week window before and after stem cell harvest/ transplant, because caffeine prevents the differentiation of the telomerase-positive stem cells _____.”

“Limit use of corticosteroids, e.g., prednisone, because it prematurely differentiates TSCs and PSCs into a mesodermal germ layer lineage _____.”

“Abstain from moderate to excessive physical activity from two weeks before to two weeks after telomerase-positive stem cell harvest and treatment because telomerase-positive stem cells will repair the most recent damaged tissue first _____.”

The lines attached for each of the above statements are for the initials of the donor or recipient, so there would be no question as to not having understood the ramifications of these and other statements within the informed consent document.

We attempted to use gender-matched, ABO-blood group matched donors that were clear of infectious diseases, genetic mutations and cancer for one of our amyotrophic lateral sclerosis patients. This was performed to increase the number of TSCs and PSCs for their treatments. After trying for eight hours (of a normal 2-3-hour procedure) to isolate telomerase-positive stem cells of any kind from our first donor, it was noted that there were no TSCs, PSCs, or MesoSCs present in her blood. At post-harvest interview she divulged that she had been celebrating the night before the stem cell harvest with her girlfriends and had gotten drunk. She stated that she had not touched a drop of alcohol for 29 days and didn’t think one day would matter.

The second attempt with a different donor was successful at isolating telomerase-positive stem cells from her blood, but at the end of one month (the usual time frame for a reduction in symptoms) there was no observable response. At post-harvest interview she stated that she was not an alcohol drinker anyway, so 30 days without alcohol didn’t matter. She also stated that she did not like coffee or tea, so abstaining from either one of them was easy. We noted at her interview she was drinking from a can of regular (caffeinated) Coke. When asked about how often she drank Coke, she stated about 10-12 Cokes every day (including during the 30-day pre-harvest period), “you could probably call me a Coke-aholic”. We surmised that that much continual caffeine probably shut down the differentiation potential of her telomerase positive TSCs and PSCs.

The third attempt with a different donor was as unsuccessful as with the first donor (i.e., no telomerase-positive stem cells in her blood). At the post-harvest interview, she stated that she does not use alcohol, tobacco products, recreational drugs, lidocaine, chemotherapeutic agents, caffeine, or corticosteroids. It was noted that on day of harvest she showed up wearing jogging clothes. When asked about this she said that ever since she had been taking the combinatorial nutraceuticals she felt so great that she would jog anywhere from 10-20 miles a day, but she limited her jogging to not more than 10 miles a day for two weeks before her harvest and including the morning before her stem cell harvest. Based on her response, we surmised that her telomerase-positive stem cells were being used by her body daily to repair microtears in her muscles and tendons and microfractures in her bones due to her jogging.

Based on the above, it is imperative to choose donors where their lifestyle choices do not supersede the informed consent document [151].

We have since given up using donors for the patient with amyotrophic lateral sclerosis and have been using cytopheresis and propagating her TSCs *ex-vivo* to maximize the numbers of telomerase-positive stem cells for her treatments [140]. In contrast, donors for individuals with SLE, IPF, COPD and CVD maintained informed consent protocols and the response in the recipients to donor TSCs and PSCs was remarkable at reversing the symptoms and increasing organ function of their respective diseases, e.g., SLE (Fig. 3 and 5), IPF (Fig. 3), COPD (Fig. 4) and CVD (Fig. 5) [122,125,126,128].

Figure 3: Endogenous telomerase-positive stem cell treatment of two individuals with Idiopathic Pulmonary Fibrosis (IPF), with baseline FEV₁ values of less than 30% (Gold-4) [154]. The female, age 80 with a baseline FEV₁ of 14%, was transplanted with a single treatment of autologous telomerase-positive stem cells (TSCs and PSCs by nebulization and MesoSCs by intravenous infusion). Within one month after treatment her FEV₁ rose to 27%

[124], and then stabilized at 25% for eight years. The male, age 61 with a baseline FEV1 of 25% was transplanted with a single autologous and three autologous/allogeneic (auto/allo) telomerase-positive stem cell treatments throughout a seven-year time frame. The autologous/allogeneic treatments consisted of pooled auto/allo-TSCs and auto/allo-PSCs by nebulization and autologous MesoSCs by intravenous infusion. His FEV1 has stabilized at approximately 70% for the past nine years (and counting). Reprinted with permission from Young HE, Speight MO. Telomerase-positive stem cells as a potential treatment for idiopathic pulmonary fibrosis. *Stem Cells Regen Med.* 2020; 4(2):1-11 [125].

Figure 4: Chronic Obstructive Pulmonary Disease (COPD) participant, with a baseline FEV1 of 30% (GOLD-3) [154], treated with multiple autologous and allogeneic telomerase-positive stem cell transplants over an eight-year time frame. Within one month following their initial autologous stem cell treatment (TSCs and PSCs nebulized, followed by MesoSCs by regular intravenous infusion into median cubital vein), their FEV1 increased to 46%, approximating a 50% increase in lung capacity [124]. During the ensuing eight-year time frame their FEV1's fluctuated from 40% to 48%, due to pneumonia followed by stem cell transplant, followed by pneumonia, followed by autologous and/or allogeneic (TSC and PSC only) stem cell transplant, and so on and so forth. After their initial stem cell transplant the individual was able to reduce supplemental oxygen from 4-L per minute to 2-L per minute for the ensuing eight years and still maintain a greater than 98% oxygen saturation of their blood. The individual succumbed to a severe case of pneumonia eight years after initial telomerase-positive stem cell treatment. Reprinted with permission from Young HE, Speight MO. Telomerase-positive stem cells as a potential treatment for chronic obstructive pulmonary disease. *Stem Cells Regen Med.* 2020; Accepted [126].

Figure 5: Systemic Lupus Erythematosus (SLE) patient's cardiac output dropped precipitously, 90% to 30%, during of ingestion of hydroxychloroquine to slow progression of SLE. At time of first stem cell transplant, cardiac output was below 25%. First stem cell transplant (autologous: TSC, PSC, and MesoSC) raised cardiac output to 25%. Second stem cell transplant from allogeneic (TSC and PSC only) 42-year-old A+ male raised cardiac output to approximately 40%. Third stem cell transplant from allogeneic 72-year-old O-negative male raise cardiac output to approximately 70%. A total of 30 adult-derived autologous and/or allogeneic telomerase-positive stem cell transplants thus far have maintained his cardiac output at approximately 70% for over nine years and counting. Reprinted with permission from Young HE, Speight MO. Cardiovascular disease treated with telomerase-positive stem cells. *Stem Cells Regen Med.* 2020; 4(2):1-8 JSCR-20-069 [128].

Donor's Ethnicity, Hair Pattern, Hair Color and Personality

Allogeneic totipotent stem cells and pluripotent stem cells have the genome of the donor and therefore the capability to recapitulate the donor's ethnicity, personality, posture, bone structure, muscle pattern, hair patterns, hair color, skin color, etc., in the recipient. Therefore, care must be taken that those possibilities are explained fully to the recipient before any allogeneic stem cells are transplanted. For example, the appearance of hair pattern, hair color and personality was seen in the individual with SLE and celiac disease following transplants of allogeneic TSCs by their intranasal delivery [122]. His first allogeneic transplant was from a 42-year-old A+ male that had a full head of auburn-colored hair and a nasty and aggressive personality. Those traits were expressed in the recipient approximately one month after treatment and was seen in the recipient as a replacement of white wispy hair to a fuller head of

Young HE | Volume 1; Issue 2 (2020) | JRMBR-1(2)-009 | Clinical Trial Report

Citation: Young HE, et al. Donor Selection is a Critical Component Using Naïve Endogenous Adult Stem Cells for the Treatment of Chronic Diseases and Traumatic Injuries. *J Reg Med Biol Res.* 2020;1(2):1-28.

DOI: <http://dx.doi.org/10.46889/JRMBR.2020.1203>

auburn-colored hair and the nasty/aggressive personality (as assessed by his spouse, in-laws, relatives and friends). His second allogeneic TSC transplant was from a 72-year-old O-negative male with full head of black hair and a mellow and laid-back personality. One month after an intranasal TSC treatment, the SLE patient's auburn hair turned black and he assumed a mellow/laid-back personality. The SLE patient received two allogeneic TSCs treatments from a 53-year old O-negative male with a full head of black hair and a caring/aggressive personality. About one month after each treatment his full head of hair remained black and he began to display a caring/aggressive personality. His second allogeneic donor, original age of donation at 72-years of age, contributed TSCs a second time, at age 75. At one month post treatment his full head of hair remained black and he assumed the mellow/laid-back personality. About four months later he received a TSC transplant from the 50-year-old A+ donor with a full head of sandy-brown colored hair and with a kind/caring personality. About one-month post-intranasal TSC treatment the SLE patient demonstrated a full head of sandy-brown colored hair and a kind/caring personality. His last allogeneic treatment came from the then 80-year-old O-negative male, still with a full head of black hair and the mellow/laid back personality. About one month after donor intranasal TSC treatment, his hair pattern, hair color and personality traits matched that of the 80-year-old donor. The SLE recipient's current personality appears to be a combination of aggressive, laid back, mellow, kind and caring, with very little if any of the 'nasty' personality traits from the first donor. Currently, his slightly thinning hair color is black and white, with some sandy-brown and a few strands of auburn. He jokes that 'the white hair is his and the other colors belong to his donors [122].

Results from a clinical study of chronic obstructive pulmonary disease [126] where treatment with allogeneic TSCs and PSCs was by nebulization and Intravenous (IV) infusion, it was noted there was no transfer of hair pattern or personality traits occurred from the donors to the recipient. Hair color was difficult to determine in the COPD individual since both the recipient and her donors had the same initial hair color when they were younger. Results from the SLE study and the COPD study suggest that only when the intranasal route of TSC infusion is utilized is there a change of hair pattern and personality in the recipient to that of the donor [122,126].

Donor's Allergies and Food Choices

Before any stem cell treatment of any kind (autologous and/or allogeneic), the SLE individual with Celiac disease was allergic to almost all foods (cooked vegetables, cooked fruits, gluten, turkey, duck, chicken, eggs, milk, cheeses, yogurt, MSG), wearables (wool, nylon, polyester, latex gloves), environmental allergens (smoke, grasses, pollens, mold, pollution), vaccines, medicines, etc. [122,123]. Since his nine allogeneic TSC and PSC stem cell treatments he has lost most of his allergies except his long-standing allergies to penicillin, contrast dye, tobacco smoke, shellfish and chocolate. He had a transitory loss of his celiac disease, a gluten allergy to deaminated gliadin peptide (antibody titer reduction from 73 to less than 1.0), during his nine allogeneic TSC and PSC transplants [122,123]. During the eight-year period of receiving

Young HE | Volume 1; Issue 2 (2020) | JRMBR-1(2)-009 | Clinical Trial Report

Citation: Young HE, et al. Donor Selection is a Critical Component Using Naïve Endogenous Adult Stem Cells for the Treatment of Chronic Diseases and Traumatic Injuries. J Reg Med Biol Res. 2020;1(2):1-28.

DOI: <http://dx.doi.org/10.46889/JRMBR.2020.1203>

allogeneic transplants he could eat a diet containing foods with gluten without any adverse side effects [123]. However, with cessation of the allogeneic transplants, his deaminated gliadin peptide titer began to rise, currently above 10 and he is again on a gluten-free diet [123]. Interestingly, he has gained an allergy to soy protein, the only allergy expressed by the O-negative male that donated telomerase-positive stem cells four times. We also noted that he has gained three food preferences to that of the same O-negative male, e.g., cooked asparagus in garlic sauce, pimento cheese and blue cheese, three foods that the recipient would not and/or could not eat due to previous food preference and/or allergies, since shortly after birth and prior to the last transplant from this donor. Based on the above observations, we would hypothesize that the SLE recipient is a chimera, with respect to hair pattern, hair color, personalities, allergies, food preferences and containing the immune systems of potentially four to five individuals [122].

Conclusion

Results using allogeneic telomerase negative MSCs, expressing MHC Class-I on their cell surfaces, demonstrated either stasis of disease progression, slowed disease progression, or no effect on disease progression with MSC transplantation [7,8,50,51,55,60,61,64-76,90,92,95,96,99,103,106,107,149-151]. These studies suggested that there was an immunomodulatory rather than a reparative effect of the MSCs with respect to the diseases treated. Another cohort of studies using chemical mediators derived from MSCs, suggested that the MSC-exosome-containing microvesicles were the actual mediators of the immunomodulatory response of MSCs on these diseases [26,27,49,54,58,59,77,83,87-89,91,93,97,104,105,108-110,112,115-121]. Since the effect of MSCs appears to be immunomodulatory rather than reparative and that exosomes from MSCs appear to drive the immunomodulatory response, it is suggested that exosome-containing vesicles derived from MSCs should be utilized to circumvent potential problems with MHC Class-I cell surface markers on allogeneic MSCs that might induce a partial to full GvHD response in the recipient, that would potentially negate its activity.

We would hypothesize that as native differentiated cells of his immune system are depleted during lupus flares that the telomerase-positive allogeneic stem cells with a “clean genome” replaced genetically defective native immune cells with cells containing the full complement of enzymes and function as they would in a normal non-autoimmune individual.

In contrast, based on the previous MesoSC transplantation studies, only telomerase positive TSCs and PSCs, that did not express MHC Class-I marker, were utilized for the allogeneic treatment of these same diseases [122,123,125,126,128,133,140]. Activated allogeneic telomerase positive TSCs and PSCs demonstrated either the repair or replacement of non-functional scar tissue and/or regenerate new functional organ parenchyma, as seen with the decrease in disease symptoms and increase in organ function in treated individuals with systemic lupus erythematosus, celiac disease, idiopathic pulmonary fibrosis, chronic obstructive pulmonary disease, cardiovascular disease, Alzheimer’s disease and Amyotrophic

lateral sclerosis [122,123,125,126,133,140]. The results suggest that allogeneic TSCs and PSCs, lacking MHC Class-I cell surface markers, are both safe and effective for increasing stem cell numbers for treatment for these chronic diseases, as long as the selection of the appropriate donor is based on gender-match, ABO blood group-match, or O-negative blood group, non-shared infectious diseases, absence of deleterious genetic mutations and life style choices of the donor. However, if allogeneic telomerase positive TSCs are utilized, then ethnicity, personality, posture, bone structure, muscle pattern, hair patterns, hair color, skin color, existing allergies and food preferences of the donor need to be acceptable to the recipient prior to transplantation.

References

1. Stocum DL. Stem cells in regenerative biology and medicine. *Wound Rep Regen*. 2001;9(6):429-42.
2. Lebowski JS, Gold J, Xu C, Funk W, Chiu CP, Carpenter MK. Human embryonic stem cells: culture, differentiation, and genetic modification for regenerative medicine applications. *Cancer J*. 2001;7(Suppl 2):S83-93.
3. Petrus-Reurer S, Bartrum H, Aronsson M. Preclinical safety studies of human embryonic stem cell-derived retinal pigment epithelial cells for the treatment of age-related macular degeneration. *Stem Cells Transl Med*. 2020;9(3):377-88.
4. Yamanaka S. Induced pluripotent stem cells: past, present, future. *Cell Stem Cell*. 2012;10(6):678-84.
5. Pei D, Xu J, Zhuang Q, Esteban MA. Induced pluripotent stem cell technology in regenerative medicine and biology. *Adv Biochem Eng Biotechnol*. 2010;123:127-41.
6. Ye L, Wang J, Teque F, Xie F, Tan Y, Kan YW, et al. Generation of HIV-1-infected patients' gene-edited induced pluripotent stem cells using feeder-free culture conditions. *Aids*. 2020;34(8):1127-39.
7. Stefanska K, Ozegowska K, Hutchings G, Popis M, Moncrieff L, Dompe C, et al. Human Wharton's jelly-cellular specificity, stemness potency, animal models, and current application in human clinical trials. *J Clin Med*. 2020;9(4):1102.
8. Menaa F, Shahrokhi S, Shatri VP. Impact and challenges of mesenchymal stem cells in medicine: an overview of the current knowledge. *Stem Cells Intl*. 2018.
9. Dominici M, Le Blanc K, Mueller I, Slaper-Cortenbach I, Marini FC, Krause DS, et al. Minimal criteria for defining multipotent mesenchymal stromal cells. *Cytotherapy*. 2006;8:315-7.
10. Kucia M, Reza R, Campbell FR, Zuba-Surma E, Majka M, Ratajczak J, et al. A population of very small embryonic-like (VSEL) CXCR4(+)SSEA-1(+)Oct-4(+) stem cells identified in adult bone marrow. *Leukemia*. 2006;20:857-69.
11. Kucia M, Halasa M, Wysoczynski M. Morphological and molecular characterization of novel CXCR4+ SSEA-4+ Oct-4+ very small embryonic-like cells purified from human cord blood: preliminary report. *Leukemia*. 2007;21:297-303.
12. Havens AM, Sun H, Shiozawa Y, Jung Y, Wang J, Mishra A, et al. Human and murine very small embryonic-like cells represent multipotent tissue progenitors, *in vitro* and *in-vivo*. *Stem Cells Dev*. 2014;23(7):689-701.
13. Jahagirdar BN, Verfaillie CM. Multipotent adult progenitor cell and stem cell plasticity. *Stem Cell Rev*. 2005;1:53-9.
14. Fisch SC, Gimeno ML, Phan JD, Simerman AA, Dumesic DA, Perone MJ, et al. Pluripotent nontumorigenic multilineage differentiating stress enduring cells (Muse cells): a seven-year retrospective. *Stem Cell Res Ther*. 2017;8(1):227.
15. Young HE, Duplaa C, Romero-Ramos M, Chesselet MF, Vourc'h P, Yost MJ, et al. Adult reserve stem cells and their potential for tissue engineering. *Cell Biochem Biophys*. 2004;40(1):1-80.

Young HE | Volume 1; Issue 2 (2020) | JRMBR-1(2)-009 | Clinical Trial Report

Citation: Young HE, et al. Donor Selection is a Critical Component Using Naïve Endogenous Adult Stem Cells for the Treatment of Chronic Diseases and Traumatic Injuries. *J Reg Med Biol Res*. 2020;1(2):1-28.

DOI: <http://dx.doi.org/10.46889/JRMBR.2020.1203>

16. Young HE, Speight MO, Black AC Jr. Functional Cells, Maintenance Cells, and Healing Cells. *J Stem Cell Res.* 2017;1(1):003:1-4.
17. Kierzenbaum AL. *Histology and Cell Biology: An Introduction to Pathology.* Mosby. 2002.
18. Zvereva MI, Shcherbakova DM, Dontsova OA. Telomerase: structure, functions, and activity regulation. *Biochemistry (Mosc).* 2010;75(13):1563-83.
19. Young HE, Black AC. Pluripotent stem cells, endogenous versus reprogrammed- a Review. *MOJ Orthop Rheumatol.* 2014;1(4):00019.
20. Hayflick L, Moorehead PS. The serial cultivation of human diploid cell strains. *Exp Cell Res.* 1961;25:585-621.
21. Rohme D. Evidence for a relationship between longevity of mammalian species and life spans of normal fibroblasts *in-vitro* and erythrocytes *in-vivo*. *Proc Natl Acad Sci USA.* 1981;78:5009-13.
22. Caplan AI. Mesenchymal stem cells. *J Orthop Res.* 1991;9:641-50.
23. Caplan AI. Review: mesenchymal stem cells: cell-based reconstructive therapy in orthopedics. *Tiss Eng.* 2005;11:1198-1211.
24. Ding DC, Shyu WC, Lin SZ. Mesenchymal stem cells. *Cell Transplant.* 2011;20:5-14.
25. Parker AM, Katz AJ. Adipose-derived stem cells for the regeneration of damaged tissues. *Expert Opin Biol Ther.* 2006;6:567-78.
26. Caplan AI. Mesenchymal stem cells: time to change the name! *Stem Cells Transl Med.* 2017;6(6):1445-51.
27. Barry FP, Murphy JM, English K, Mahon BP. Immunogenicity of adult mesenchymal stem cells: lessons from the fetal allograft. *Stem Cells Dev.* 2005;14(3):252-65.
28. Owen M. Marrow stromal cells. *J Cell Sci Suppl.* 1988;10:63-76.
29. Prockop DJ. Marrow stromal cells as stem cells for nonhematopoietic tissues. *Sci.* 1997;276(5309):71-4.
30. Jiang Y, Vaessen B, Lenvik T, Blackstad M, Reyes M, Verfaillie CM. Multipotent progenitor cells can be isolated from postnatal murine bone marrow, muscle, and brain. *Exp Hematol.* 2002;30(8):896-904.
31. Jiang Y, Jahagirdar BN, Reinhardt RL, Schwartz RE, Keene CD, Ortiz-Gonzalez XR, et al. Pluripotency of mesenchymal stem cells derived from adult marrow. *Nature.* 2002;418(6893):41-9.
32. Watt FM. Epidermal stem cells in culture. *J Cell Sci Suppl.* 1988;10:85-94.
33. Young HE. Adult stem cells. *Anat Rec A Discov Mol Cell Evol Biol.* 2004;276:75-102.
34. Ren Q, Yang CP, Liu Z, Sugino K, Mok K, He Y, et al. Stem cell-intrinsic, seven-up-triggered temporal factor gradients diversify intermediate neural progenitors. *Curr Biol.* 2017;27(9):1303-13.
35. Weissman IL, Heimfeld S, Soangrude G. Hematopoietic stem cell purification. *Immunol Today.* 1989;10(6):184-5.
36. Dzierzak E, Bigas A. Blood development: hematopoietic stem cell dependence and independence. *Cell Stem Cell.* 2018;22(5):639-51.
37. Uchida N, Weissman IL. Searching for hematopoietic stem cells: evidence that Thy-1.1 low Lin-Sca-1+ cells are the only stem cells in C57BL/Ka-Thy-1.1 bone marrow. *J Exp Med.* 1992;175(1):175-84.
38. Pittenger MF, Mackay AM, Beck SC, Jaiswal RK, Douglas R, Mosca JD, et al. Multilineage potential of adult human mesenchymal stem cells. *Sci.* 1999;284(5411):143-7.
39. Vierck JL, McNamara JP, Dodson MV. Proliferation and differentiation of progeny of ovine unilocular fat cells (adipofibroblasts). *In Vitro Cell Dev Biol Anim.* 1996;32(9):564-72.
40. Petersen BE, Bowen WC, Patrene KD, Mars WM, Sullivan AK, Murase NA, et al. Bone marrow as a potential source of hepatic oval cells. *Sci.* 1999;284(5417):1168-70.
41. Mauro A. Satellite cell of skeletal muscle fibers. *J Biophys Biochem Cytol.* 1961;9(2):493-5.
42. Bryan TM, Englezou A, Dunham MA, Reddel RR. Telomere length dynamics in telomerase-positive immortal human cell populations. *Exp Cell Res.* 1998;293(2):370-8.
43. Young HE, Speight MO. Characterization of endogenous telomerase-positive stem cells for regenerative medicine, a review. *Stem Cell Regen Med.* 2020;4(2):1-14.
44. Young HE, Duplaa C, Young TM, Floyd JA, Reeves ML, Davis KH, et al. Clonogenic analysis reveals reserve stem cells in postnatal mammals I. Pluripotent mesenchymal stem cells. *Anat Rec.* 2001;263(4):350-60.

Young HE | Volume 1; Issue 2 (2020) | JRMBR-1(2)-009 | Clinical Trial Report

Citation: Young HE, et al. Donor Selection is a Critical Component Using Naïve Endogenous Adult Stem Cells for the Treatment of Chronic Diseases and Traumatic Injuries. *J Reg Med Biol Res.* 2020;1(2):1-28.

DOI: <http://dx.doi.org/10.46889/JRMBR.2020.1203>

45. Young HE, Duplaa C, Yost MJ, Henson NL, Floyd JA, Detmer K, et al. Clonogenic analysis reveals reserve stem cells in postnatal mammals II. Pluripotent epiblastic-like stem cells. *Anat Rec*. 2004;277(1):178-203.
46. Young HE, Black AC Jr. Adult-derived stem cells [III. Totipotent blastomere-like stem cells]. *Minerva Biotechnologica Cancer Gene Mechanisms and Gene Therapy Reviews*. 2005;17(1):55-63.
47. Bonner-Weir, Taneja M, Weir GC, Tatarkiewicz K, Song KH, Sharma A, et al. In-vitro cultivation of human islets from expanded ductal tissue. *Proc Natl Acad Sci*. 2000;97(14):7999-8004.
48. Young HE, Linnios JI, Lochner F, McCommon G, Cope LA, Black Jr AC. Pancreatic islet composites secrete insulin in response to a glucose challenge. *J Stem Cell Res*. 2017;1(1):1-12.
49. "ClinicalTrials.gov". <https://clinicaltrials.gov/> [Last Accessed on November 01, 2020].
50. Choi M, Ban T, Rhim T. Therapeutic use of stem cell transplantation for cell replacement of cytoprotective effect of microvesicle released from mesenchymal stem cell. *Mol Cells*. 2014;37(2):133-9.
51. Moheb-Alian A, Forouzes F, Rostami-Nejad M, Rostami K. Mesenchymal stem cells as potential therapeutic approaches in celiac disease. *Gastroenterol Hepatol Bed Bench*. 2016;9(1):S1-7.
52. Ciccocioppo R, Cangemi GC, Roselli EA, Kruzliak P. Are stem cells a potential therapeutic tool in coeliac disease? *Cell Mol Life Sci*. 2015;72(7):1317-29.
53. Jacob R, Sirbu-Boeti P, Jacob S. Stem cell therapies for gastrointestinal and liver diseases. *Chirurgia (Bucur)*. 2009;104(2):131-40.
54. Al-Toma A, Mulder CJJ. Review article: stem cell transplantation for the treatment of gastrointestinal diseases-current applications and future perspectives. *Aliment Pharmacol Ther*. 2007;26(Supple 2):77-89.
55. Gonzalez MA, Gonzalez-Rey E, Rico L, Büscher D, Delgado M. Adipose-derived mesenchymal stem cells alleviate experimental colitis by inhibiting inflammatory and autoimmune responses. *Gastroenterol*. 2009;136(3):978-89.
56. Chambers DC, Enever D, Ilic N, Sparks L, Whitelaw K, Ayres J et al. A phase 1b study of placenta-derived mesenchymal stromal cells in patients with idiopathic pulmonary fibrosis. *Respirol*. 2014;19(7):1013-8.
57. Ghadiri M, Young PM, Traini D. Cell-based therapies for the treatment of idiopathic pulmonary fibrosis (IPF) disease. *Expert Opin Biol Ther*. 2016;16(3):375-87.
58. Barczyk M, Schmidt M, Mattoli S. Stem cell-based therapy in idiopathic pulmonary fibrosis. *Stem Cell Rev Resp*. 2015;11(4):598-620.
59. Siegel G, Schafer R, Dazzi F. The immunosuppressive properties of mesenchymal stem cells. *Transplantation*. 2009;87(9S):S45-9.
60. Liu M, Ren D, Wu D, Zheng J, Tu W. Stem cell and idiopathic pulmonary fibrosis: mechanisms and treatment. *Curr Stem Cell Res Ther*. 2015;10(6):466-76.
61. Purdon S, Patete CL, Glassberg MK. Multipotent mesenchymal stromal cells for pulmonary fibrosis? *Am J Med Sci*. 2019;357(5):390-3.
62. Toonkel RL, Hare JM, Matthay MA, Glassberg MK. Mesenchymal stem cells and idiopathic pulmonary fibrosis. Potential for clinical testing. *Am J Respir Crit Care Med*. 2013;188(2):133-40.
63. Tzouveleakis A, Toonkel R, Karamitsakos T. Mesenchymal stem cells for the treatment of idiopathic pulmonary fibrosis. *Front Med (Lausanne)*. 2018;5:142.
64. Lu Q, El-Hashash AHK. Cell-based therapy for idiopathic pulmonary fibrosis. *Stem Cell Invest*. 2019;6:22.
65. Li X, Yue S, Luo Z. Mesenchymal stem cells in idiopathic pulmonary fibrosis. *Oncotarget*. 2017;8(6):102600-16.
66. Glassberg MK, Minkiewicz J, Toonkel RL, Simonet ES, Rubio GA, DiFede D, et al. Allogeneic human mesenchymal stem cells in patients with idiopathic pulmonary fibrosis via intravenous delivery (ATHER): a phase I safety clinical trial. *Chest*. 2017;151(5):971-81.
67. Weiss, Casaburi R, Flannery R, LeRoux-Williams M, Tashkin DP. A placebo-controlled, randomized trial of mesenchymal stem cells in COPD. *Chest*. 2013;143(6):1590-8.
68. Balkissoon R. Stem cell therapy for COPD: where are we? *Chronic Obstruc Pulm Dis*. 2018;5(2):148-53.
69. Sun Z, Li F, Zhou X. Stem cell therapies for chronic obstructive pulmonary disease: current status of pre-clinical studies and clinical trials. *J Thorac Dis*. 2018;10(2):1084-98.
70. Cheng SL, Lin CH, Yao CL. Mesenchymal stem cell administration in patients with chronic obstructive pulmonary disease: state of the science. *Stem Cells Int*. 2017;2017:8916570.

Young HE | Volume 1; Issue 2 (2020) | JRMBR-1(2)-009 | Clinical Trial Report

Citation: Young HE, et al. Donor Selection is a Critical Component Using Naïve Endogenous Adult Stem Cells for the Treatment of Chronic Diseases and Traumatic Injuries. *J Reg Med Biol Res*. 2020;1(2):1-28.

DOI: <http://dx.doi.org/10.46889/JRMBR.2020.1203>

71. Fishman JE, Kim GJ, Kyeong NY, Goldin JG, Glassberg MK. Intravenous stem cell dose and changes in quantitative lung fibrosis and DLCO in the ATHER trial: a pilot study. *Eur Rev Med Pharmacol Sci*. 2019;23(17):7568-72.
72. Geiger S, Hirsch D, Hermann FG. Cell therapy for lung disease. *Eur Respir Rev*. 2017;28:26(144).
73. Bateman ME, Strong AL, Gimble JM, Bunnell BA. Concise review: Using fat to fight disease: A systematic review of nonhomologous adipose-derived stromal/stem cell therapies. *Stem Cells*. 2018;36(9):1311-28.
74. Broekman W, Khedoe PP, Schepers K, Roelofs H, Stolk J, Hiemstra PS. Mesenchymal stromal cells: a novel therapy for the treatment of chronic obstructive pulmonary disease? *Thorax*. 2018;73(6):565-74.
75. Kokturk N, Yildirim F, Gulhan PY, Oh YM. Stem cell therapy in chronic obstructive pulmonary disease. How far is it to the clinic? *Am J Stem Cells*. 2018;7(3):56-71.
76. Kruk DMLW, Hejink IH, Slebos DJ, Timens W, Nick H. Mesenchymal stem cells to regenerate emphysema: on the horizon? *Respiration*. 2018;96(2):148-58.
77. Cruz FF, Rocco PRM. The potential role of mesenchymal stem cell therapy of chronic lung disease. *Expert Rev Respir Med*. 2020;14(1):31-9.
78. Bari E, Ferrarotti I, Torre ML, Corsico AG, Perteghella S. Mesenchymal stem/stromal cell secretome for lung regeneration: The long way through “pharmaceuticalization” for the best formulation. *J Control Release*. 2019;309:11-24.
79. Bosman A, Edel MJ, Blue G, Dilley RJ, Harvey RP, Winlaw DS. Bioengineering and Stem Cell Technology in the Treatment of Congenital Heart Disease. *J Clin Med*. 2015;4(4):768-81.
80. Goradel NH, Ghiyami-Hour, Negahdari B, Malekshahi ZV, Hashemzahi M, Masoudifar A, et al. Stem Cell Therapy: a new therapeutic option for cardiovascular diseases. *J Cell Biochem*. 2017;119(1):95-104.
81. Muller P, Lemcke H, David R. Stem cell therapy in heart diseases - cell types, mechanisms and improvement strategies. *Cell Physiol Biochem*. 2018;48(6):2607-55.
82. Cialo-Pakuluk A, Marycz K. A promising tool in retina regeneration: current perspectives and challenges when using mesenchymal progenitor stem cells in veterinary and human ophthalmological applications. *Stem Cell Rev Rep*. 2017;13(5):598-602.
83. Park SS, Moisseive E, Bauer G, Anderson JD, Grant MB, Zam A, et al. Advances in bone marrow stem cell therapy for retinal dysfunction. *Prog Retin Eye Res*. 2017;56:148-65.
84. Klingeborn M, Dismuke WM, Rickman CB, Stamer WD. Roles of exosomes in the normal and diseased eye. *Prog Retin Eye Res*. 2017;58:158-77.
85. Ding SSL, Subbiah SK, Ali Kahn MS, Farhana A, Mok PL. Empowering mesenchymal stem cells for ocular degenerative disorders. *Int J Mol Sci*. 2019;20(7):1784.
86. Borkowska-Kuczkowska A, Shugocka D, Swiatkowska-Flis B. The use of mesenchymal stem cells for the treatment of progressive retinal diseases: a review. *Regen Med*. 2019;14(4):321-9.
87. Bakondi B, Girman S, Lu B, Wang S. Multimodal delivery of isogenic mesenchymal stem cell yields synergistic protection from retinal degeneration and vision loss. *Stem Cells Transl Med*. 2017;6(2):444-57.
88. Chang YH, Wu KC, Harn HJ, Lin SZ, Ding DC. Exosomes and stem cells in degenerative disease diagnosis and therapy. *Cell Transplant*. 2018;27(3):349-63.
89. Conese M, Cassano R, Gavini E, Trapani G, Rassu G, Sanna E, et al. Harnessing stem cells and neurotrophic factors with novel technologies in the treatment of Parkinson's Disease. *Curr Stem Cell Res Ther*. 2019;14(7):549-69.
90. Vilaça-Faria H, Salgado AJ, Teixeira FG. Mesenchymal stem cells-derived exosomes: a new possible therapeutic strategy for Parkinson's disease? *Cells*. 2019;8(2):118.
91. Chakari-Khiavi F, Dolati S, Chakari-Khiavi A, Abbaszadeh H, Aghebati-Maleki L, Poulak T, et al. Prospects for the application of mesenchymal stem cells in Alzheimer's disease treatment. *Life Sci*. 2019;231:116564.
92. Elia CA, Losurdo M, Malosio ML, Coco S. Extracellular vesicles from mesenchymal stem cells exert pleiotropic effects on amyloid- β , inflammation, and regeneration: A spark of hope for Alzheimer's disease from tiny structures? *Bioessays*. 2019;41(4):e1900199.
93. Kang JM, Yeon BK, Cho SJ, Suh YH. Stem cell therapy for Alzheimer's disease: a review of recent clinical trials. *J Alzheimers Dis*. 2016;23(1):76.

94. Ding M, Shen Y, Wang P, Xie Z, Xu S, Zhu Z, et al. Exosomes isolated from human umbilical cord mesenchymal stem cells alleviate neuroinflammation and reduce amyloid-beta deposition by modulating microglial activation in Alzheimer's disease. *Neurochem Res.* 2018;43(11):2165-77.
95. Gao S, Guo X, Zhao S, Jin Y, Zhou F, Yuan P, et al. Differentiation of human adipose-derived stem cells into neuron/motorneuron-like cells for cell replacement therapy of spinal cord injury. *Cell Death Dis.* 2019;10(8):1-5.
96. Bydon M, Dietz AB, Goncalves S, Moinuddin FM, Alvi MA, Goyal A, et al. CELLTOP Clinical trial: first report from a phase 1 trial of autologous adipose tissue-derived mesenchymal stem cells in the treatment of paralysis due to traumatic spinal cord injury. *Mayo Clin Proc.* 2020;95(2):406-14.
97. Mendonca MVP, Larocca TF, de Freitas Souza BS, Villarreal CF, Silva LF, Matos AC, et al. Safety and neurological assessments after autologous transplantation of bone marrow mesenchymal stem cells in subjects with chronic spinal cord injury. *Stem Cell Res Ther.* 2014;5(6):126.
98. Dabrowska S, Andrzejewska A, Lukomska B, Janowski M. Neuroinflammation as a target for treatment of stroke using mesenchymal stem cells and extracellular vesicles. *J Neuroinflammation.* 2019;16(1):178.
99. Lucia Maria Ferri A, Bersano A, Lisini D, Boncoraglio G, Frigerio S, Parati E. Mesenchymal stem cells for ischemic stroke: progress and possibilities. *Curr Med Chem.* 2016;23(16):1598-608.
100. Zheng H, Zhang B, Chhatbar PY, Dong Y, Alawieh A, Lowe F, et al. Mesenchymal stem cell therapy in stroke: A systemic review of the literature in pre-clinical and clinical research. *Cell Transplant.* 2018;27(12):1723-30.
101. Wang F. Transplanting mesenchymal stem cells for treatment of ischemic stroke. *Cell Transplant.* 2018;27(12):1825-34.
102. Hasan A, Deeb G, Rahal R, Atwi K, Mondello S, Marei HE, et al. Mesenchymal stem cells in the treatment of traumatic brain injury. *Front Neurol.* 2017;8:28.
103. Das M. Mesenchymal stem cell therapy for the treatment of traumatic brain injury: progress and prospects. *Rev Neurosci.* 2019;30(8):839-55.
104. Qi L, Xue X, Sun J, Wu Q, Wang H, Guo Y, Sun B, et al. The promising effects of transplanted umbilical cord mesenchymal stem cells on the treatment in traumatic brain injury. *J Craniofac Surg.* 2018;29(7):1689-92.
105. Mead B, Tomarev S. Bone marrow-derived mesenchymal stem cells-derived exosomes promote survival of retinal ganglion cells through miRNA-dependent mechanisms. *Stem Cells Transl Med.* 2017;6(4):1273-85.
106. Pan D, Chang X, Xu M, Zhang M, Zhang S, Wang Y, et al. UMSC-derived exosomes promote retinal ganglion cells survival in a rat model of optic nerve crush. *J Chem Neuroanat.* 2019;96:134-9.
107. Fernandez O, Izquierdo G, Fernández V, Leyva L, Reyes V, Guerrero M, et al. Adipose-derived Mesenchymal Stem Cells (AdMSC) for the treatment of secondary-progressive multiple sclerosis: A triple blinded, placebo controlled, randomized phase I/II safety and feasibility study. *PLoS One.* 2018;13(5):e0195891.
108. Xiao J, Yang R, Biswas S, Qin X, Zhang M, Deng W. Mesenchymal stem cells and induced pluripotent stem cells as therapies for multiple sclerosis. *Int J Mol Sci.* 2015;16(5):9283-302.
109. Dahbour S, Jamali F, Alhattab D, Al-Radaideh A, Ababneh O, Al-Ryalat N, et al. Mesenchymal stem cells and conditioned medium in the treatment of multiple sclerosis patients: clinical, ophthalmological and radiological assessments of safety and efficacy. *CNS Neurosci Ther.* 2017;23(11):866-74.
110. Bonafede R, Mariotto R. ALS pathogenesis and therapeutic approaches: the role of mesenchymal stem cells and extracellular vesicles. *Front Cell Neurosci.* 2017;11:80.
111. Petrou P, Gothelf Y, Argov Z, Gotkine M, Levy YS, Kassis I, et al. Safety and clinical effects of mesenchymal stem cells secreting neurotrophic factor transplantation in patients with Amyotrophic Lateral Sclerosis: results of phase 1/2 and 2a clinical trials. *JAMA Neurol.* 2016;73(3):337-44.
112. Matejkova N. Characterisation of mesenchymal stem cells for patients with amyotrophic lateral sclerosis. *J Clin Pathol.* 2018;71(8):735-42.
113. Aghajani Nargesi A, Lerman LO, Eirin A. Mesenchymal stem cell-derived extracellular vesicles for kidney repair: current status and looming challenges. *Stem Cell Res Ther.* 2017;8(1):273.

114. Morigi M, Rota C, Remuzzi G. Mesenchymal stem cells in kidney repair. *Methods Mol Biol.* 2016;1416:89-107.
115. Casiraghi F, Perico N, Cortinovis M, Remuzzi G. Mesenchymal stromal cells in renal transplantation: opportunities and challenges. *Nat Rev Nephrol.* 2016;12(4):241-53.
116. Siegel G, Schafer R, Dazzi F. The immunosuppressive properties of mesenchymal stem cells. *Transplantation.* 2009;87:S45-9.
117. Janczewski AM, Wojtkiewicz J, Malinowska E, Doboszyńska A. Can youthful mesenchymal stem cells from Wharton's jelly bring a breath of fresh air for COPD? *Int J Mol Sci.* 2017;18(11):E2449.
118. Mendt M. Mesenchymal stem cell-derived exosomes for clinical use. *Bone Marrow Transplant.* 2019;54(Suppl 2):789-92.
119. Kumar P, Kandoi S, Misra R, Vijayalakshmi S, Rajagopal K, Verma RS. The mesenchymal stem cell secretome: a new paradigm towards cell-free therapeutic mode in regenerative medicine. *Cytokine & Growth Factor Rev.* 2019;46:1-9.
120. Jiang W, Xu J. Immune modulation by mesenchymal stem cells. *Cell Prolif.* 2020;53(1):e12712.
121. Wang M, Yuan Q, Xie L. Mesenchymal stem cell-based immunomodulation: properties and clinical application. *Stem Cells Intl.* 2018;2018:3057624.
122. Hicok KH, Vangness T, Dordevic M. Exosome origins: why the cell source matters. *Stem Cell & Regen Med.* 2020;4(1):1-4.
123. Young HE, Speight MO. Allogeneic and autologous telomerase-positive stem cells as a potential treatment for systemic lupus erythematosus. *Stem Cells Regen Med.* 2020;4(2):1-9.
124. Young HE, Speight MO. Allogeneic telomerase-positive stem cells as a treatment for celiac disease. *Stem Cells Regen Med.* 2020;4(2):1-7.
125. Young, Black GF, Coleman JA. Pulmonary diseases and adult healing cells: from bench top to bedside. *J Stem Cell Res.* 2017;1(2)003:1-9.
126. Young HE, Speight MO. Telomerase-positive stem cells as a potential treatment for idiopathic pulmonary fibrosis. *Stem Cells Regen Med.* 2020;4(2):1-11.
127. Young HE, Speight MO. Telomerase-positive stem cells as a potential treatment for chronic obstructive pulmonary disease. *Stem Cells Regen Med.* 2020;4(2):1-7.
128. Young, Speight MO, Williams SE. Adult healing cells and cardiovascular disease: From bench top to bedside. *J Stem Cell Res.* 2017;1(3)002:1-8.
129. Young HE, Speight MO. Cardiovascular disease treated with telomerase-positive stem cells. *Stem Cells Regen Med.* 2020;4(2):1-8.
130. Young HE, Speight MO, Williams SE, Black Jr AC. Age-related macular degeneration treated with autologous telomerase-positive totipotent stem cells. *Stem Cells Regen Med.* 2020;4(2):1-4.
131. Young HE, Speight MO, Williams SE, Black Jr AC. Adult stem cells: from bench-top to bedside. In: *Tissue Regeneration: Where Nanostructure Meets Biology*, 3DBiotech, North Brunswick, NJ. 2013;1:1-60.
132. Young HE, Hyer L, Black Jr AC, Robinson Jr JS. Treating Parkinson disease with adult stem cells. *J Neurol Disord.* 2013;1(2):1-8.
133. Young HE, Speight MO. Treating Parkinson disease with autologous telomerase-positive stem cells. 2020.
134. Young HE, Speight MO. Alzheimer's dementia treated with autologous and allogeneic telomerase-positive stem cells. 2020.
135. Young HE, Speight MO. Traumatic spinal cord injury treated with autologous telomerase-positive stem cells. 2020
136. Young HE, Speight MO. Stroke treated with autologous telomerase-positive stem cells. 2020.
137. Young HE, Speight MO. Traumatic brain injury treated with autologous telomerase-positive stem cells. 2020
138. Young HE, Speight MO. Traumatic blindness treated with autologous telomerase-positive stem cells. 2020.
139. Young HE, Speight MO. Chronic inflammatory demyelinating polyneuropathy treated with autologous telomerase-positive stem cells. 2020.
140. Young HE, Speight MO. Multiple sclerosis treated with autologous telomerase-positive stem cells. *Stem Cells Regen Med.* 2020.

Young HE | Volume 1; Issue 2 (2020) | JRMBR-1(2)-009 | Clinical Trial Report

Citation: Young HE, et al. Donor Selection is a Critical Component Using Naïve Endogenous Adult Stem Cells for the Treatment of Chronic Diseases and Traumatic Injuries. *J Reg Med Biol Res.* 2020;1(2):1-28.

DOI: <http://dx.doi.org/10.46889/JRMBR.2020.1203>

141. Speight MO, Young HE. Are telomerase-positive autologous and allogeneic stem cells a potential treatment for amyotrophic lateral sclerosis -Laboratory Abnormalities of Uncertain Significance (ALS-LAUS). 2020.
142. Speight MO, Young HE. Chronic kidney disease treated with autologous telomerase-positive stem cells. 2020.
143. Strioga M, Viswanathan S, Darinskas A, Slaby O, Michalek J. Same or not the same? Comparison of adipose tissue-derived versus bone marrow-derived mesenchymal stem and stroma cells. *Stem Cells Dev.* 2012;21(14):2724-52.
144. Wolmarans E, Mellet J, Ambele MA, Durandt C, Pepper MS. Heterogeneity of cell therapy products. *S Afr Med J.* 2019;109(8 Suppl 1):S25-9.
145. Young HE, Henson NL, Black GF. Stage-specific embryonic antigen-4-positive cells and carcinoembryonic antigen cell adhesion molecule-1-positive cells are located in the bone marrow of the adult rat. *J Stem Cell Res.* 2017;1(2)001:1-3.
146. Young HE, Limnios IJ, Lochner F, McCommon G, Black GF, Coleman J, et al. Healing cells in the dermis and adipose tissue of the adult pig. *J Stem Cell Res.* 2017;1(2)004:1-5.
147. Abbas AK, Lichtman AH, Pillai S. In: cellular and molecular Immunology. Elsevier, Saunders. 2012:6.
148. Kumar V, Abbas AK, Fausto M. In: Robbins and Cotran pathologic basis of Disease. Elsevier, Saunders. 2010;226-30.
149. Ondreika A, Jagadeesh D. Enteropathy-associated T-cell lymphoma. *Curr Hematol Malig Rep.* 2016;11(6):504-13.
150. Bolli R, Chugh AR, D'Amario D, Loughran JH, Stoddard MF, Ikram S, et al. Effect of cardiac stem cells in patients with ischemic cardiomyopathy: initial results of the SCIPIO trial. *Lancet.* 2011;378(9806):1847-57.
151. Brown C, McKee C, Bakshi S, Walker K, Hakman E, Halassy S, et al. Mesenchymal stem cells: cell therapy and regeneration potential. *J Tissue Eng Regen Med.* 2019;13(9):1738-55.
152. Young HE, Speight MO. Informed consent guidelines for optimizing the use of telomerase-positive stem cells for regenerative medicine. *J Regen Med Biol Res.* 2020;1(1):1-20.
153. Young HE, Lochner F, Lochner D. Primitive stem cells in adult human peripheral blood. *J Stem Cell Res.* 2017; 1(2)001:1-8.
154. http://www.ncbi.nlm.nih.gov/pmc/gene_sequences [Last accessed on November 01, 2020].
155. American Thoracic Society. Standards for the diagnosis and management of individuals with alpha-1 antitrypsin deficiency. *Amer J Resp Care Med.* 2003;168:818-900.