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Age-Related Macular Degeneration Treated with Autologous Telomerase-Positive Totipotent Stem Cells

Henry E. Young[1-3]* and Mark O. Speight[4-6]

[1]*Dragonfly Foundation for Research & Development, Macon, GA 31210 USA.*

[2]*Henry E Young PhD Regeneration Technologies LLC.*

[3]*Mercer University School of Medicine, Macon, GA 31207 USA.*

[4]*Research Designs, Charlotte, NC 28105 USA.*

[5]*The Charlotte Foundation for Molecular Medicine, Charlotte, NC 28105 USA.*

[6]*Center for Wellness, Charlotte, NC 28105 USA.*

***Correspondence:**

Henry E. Young PhD, Chief Science Officer, Dragonfly Foundation for Research & Development, 101 Preston Ct, Suite 101, (Corporate Office), Macon, GA 31210 USA; Tel: 1+478-319-1983, Fax; 1+478-743-2080.

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ABSTRACT

Age-related macular degeneration (AMD) is an insidious disease characterized by gradual worsening of symptoms, which in time results in a loss of visual acuity in the central area of vision. Macular degeneration does not result in complete blindness, because peripheral vision remains. However, loss of central vision can make it difficult to perform daily activities, such as reading, driving, recognizing faces, etc. There are two forms of macular degeneration, wet and dry. Wet macular degeneration occurs in about 20% of the cases and can be treated pharmacologically. Dry macular degeneration occurs in about 80% of all cases. It has no known treatment or cure. Currently, the Holy Grail for regenerative medicine for diseases and/or disorders with no known cure involves the use of stem cells. Three types of stem cells have been proposed to treat individuals with macular degeneration, e.g., mesenchymal stem cells, embryonic stem cells, and induced pluripotent stem cells. We propose a fourth possibility; endogenous adult-derived telomerase-positive totipotent stem cells (TSCs). Autologous TSCs were used to treat four individuals with macular degeneration that had lost their central visual acuity. Two subjects had their central visual acuity restored. The third had serious heart comorbidity and the TSCs treated their body instead, and the fourth individual was non-compliant. The results demonstrated both safety and efficacy (50%) for treating macular degeneration with TSCs.

Introduction

Age-related macular degeneration (AMD) presents with partial to complete loss of vision in the center of the visual field (Figure 1) [1,2]. This corresponds to degeneration in the macula, located in the fovea centralis, which is the area of highest visual acuity of the eye [3]. The area of the macula comprises about 2% of the total retina, with the remaining 98% of the retina devoted to peripheral vision, which remains unaffected by the disease. Even though a small percentage of the retina is composed of the macula, almost half of the visual cortex is devoted to processing information from the macula [3].

In 2015, AMD affected 6.2 million people worldwide and was the fourth leading cause of partial blindness. It occurs most commonly in people above 50 years of age. Aging, especially above 50-years-of-age, family history, smoking, hypertension, atherosclerosis, high cholesterol, abdominal obesity, fat intake, and UV light contributing factors and play a role in macular degeneration, which is due to damage of the macula of the retina [1,2,4-7]. Early on there are no symptoms, but with aging, people experience a gradual worsening of symptoms. Macular degeneration does not result in complete blindness, because peripheral vision remains. However, loss of central vision can make it difficult to perform daily activities, i.e., recognize faces, drive, read, etc. [4].

Figure 1. A, Normal Vision; B, Macular Degeneration Vision

National Eye Institute, National Institute of Health

Diagnosis of macular degeneration can be made by complete ocular examination. There are three basic progressional stages: early, middle, and late, with the late stage divided into "wet" and "dry" forms. People with the "wet" form can experience acute onset, while those with the "dry" form experience gradual loss of central vision [1].

There is no known cure or treatment for restoration of vision once it is lost. There are methods to slow the progression of the disease, i.e., anti-VEGF (vascular endothelial growth factor) medication injected into the eye, laser coagulation, or photodynamic therapy, for those with late stage "wet" macular degeneration [8,9]. Dietary supplements may slow progression, but antioxidants and minerals do not appear to be useful in this regard. In contrast, there are no known treatments for "dry" AMD [1,2,4,10].

Potential Stem Cell Treatments

Both retinal pigmented epithelium (RPE) and photoreceptor replacement therapies are being examined as treatment modalities for AMD [11]. The source of these cells includes embryonic stem cells [12-14] and induced pluripotent stem cells [15-22]. Mesenchymal stem cells are viewed as a potential immunomodulatory exosome treatment modality for wet and dry macular degeneration [7,9,21-26].

Adult-derived autologous telomerase-positive stem cells, e.g., totipotent stem cells (TSCs), pluripotent stem cells (PSCs) and mesodermal stem cells (MesoSCs) have been extensively characterized in multiple species of animals, including humans, from newborns to geriatric-individuals [27]. Unique characteristics of these stem cells include the presence of the telomerase enzyme when the stem cells are in their naïve quiescent undifferentiated state; essentially an unlimited proliferation potential until the cells begin to differentiate; loss of the telomerase enzyme during their induced differentiation; induced differentiation in culture into a minimum of 66 distinct cell types of all three embryonic germ layer lineages, e.g., ectoderm, mesoderm, and endoderm, plus spermatogonia and notochord. Autologous telomerase-positive TSCs, PSCs, and MesoSCs have been used for treating individuals with Parkinson's disease [28,29] cardiovascular disease [30,31] chronic obstructive pulmonary disease [32,33] idiopathic pulmonary fibrosis [32,34] celiac disease [35] and systemic lupus erythematosus [36]. These safety and efficacy clinical studies suggested the potential for telomerase-positive stem cells for the treatment of individuals with loss of visual acuity due to age-related macular degeneration. Since telomerase-positive adult stem cells act to restore damaged or missing cells and tissues by repair and/or regeneration, it was hypothesized that these particular stem cells would migrate to the retina and restore function to the macula of the fovea centralis.

Materials and Methods

Autologous adult-derived telomerase-positive stem cells, e.g., totipotent stem cells (TSCs), pluripotent stem cells (PSCs), and mesodermal stem cells (MesoSCs) were tested in IRB-approved study protocols for age-related macular degeneration. Inclusion criteria were any male or female, 18 to 120 years of age, and lack of any serious comorbidity [37]. Exclusion criteria were (1) use of alcohol, tobacco products, vaping, recreational drugs, lidocaine, or chemotherapeutic agents; (2) limited use of caffeine and corticosteroids; (3) limited moderate to strenuous exercising inside a two-week window before to a two-week window after stem cells transplant; (4) cancer within the last five years [37]. All individuals treated initialed and signed their respective informed consent documents [37].

Stem cell recipients were mandated to follow the informed consent guidelines for telomerase-positive stem cells for clinical therapy [37]. These guidelines consisted of a defined protocol to maximize the number of telomerase-positive stem cells for harvest and subsequent repair of the tissues, and included first, avoidance of alcohol, tobacco products, vaping, recreational drugs, lidocaine, and chemotherapeutic agents because they kill telomerase-positive stem cells; and second, limiting the use of caffeine and corticosteroids because they alter the differentiative capabilities of telomerase-positive stem cells. Participants were required to ingest combinatorial nutraceuticals (CN) (DFRD, Macon, GA) daily for a minimum of 30 days prior to initial harvest and then throughout subsequent treatments of recipient to increase proliferation of telomerase-positive stem cells within the person's own connective tissues; additional concerns involved staying well hydrated two weeks before stem cell harvest; limit moderate to excessive exercising during a two-week window around the time of stem cell harvest/treatment to maximize directed repair responses; and ingesting glacial caps (GC, DFRD) 18 hours before stem cell harvest to mobilize stem cells into the blood stream.

The harvesting of the telomerase-positive stem cells occurred using venipuncture, withdrawing 210 to 420cc's of blood, based on body weight of the individual. The telomerase-positive stem cells were separated from the blood cells utilizing FDA-mandated minimal manipulative procedures, utilizing gravity, zeta potential, and differential buoyant density gradient centrifugation with serum, saline, and distilled water. The telomerase-positive stem cells were segregated into individual populations of TSCs, PSCs, and MesoSCs, and activated. The TSCs were concentrated into two aliquots of 0.2cc's each. The subjects' nostrils were cleaned with 0.65% sterile saline to remove mucus. The subject was placed into the reversed Trendelenburg position (nostrils pointing upward)

and one aliquot applied to each nostril in a dropwise fashion. The subject remained in the reversed Trendelenburg position for an additional five minutes after the second application to ensure that the TSCs had sufficient time to migrate to the olfactory bulbs lying just dorsal to the cribriform plate, and then placed into an upright position. The PSCs and MesoSCs were pooled and diluted into 250cc's of sterile normal heparin/saline and infused into an accessible vein, usually the median cubital vein, by regular intravenous infusion (IV). The subject was cautioned to rest the remainder of their stem cell treatment day and undergo only light physical activity for the next 7 days after treatment.

Results

Four females 60 to 80 years of age developed age-related macular degeneration that resulted in loss of central visual acuity. In two individuals, their central visual acuity was completely restored following two autologous telomerase-positive stem cell treatments (2/4 = 50% efficacy). The other two did not respond to two telomerase-positive stem cell treatments with respect to restoring their visual acuity. One subject had an unrecognized severe comorbidity that we postulate the telomerase-positive stem cells repaired instead, as her cardiac output increased by 5% after each treatment. The other subject was non-compliant, smoking and drinking alcohol before, during, and after her stem cell treatments.

Discussion

Age-related macular degeneration (AMD) has an insidious onset. Symptoms gradually worsen with time leading to loss of visual loss in the central visual field (Fig. 1). Macular degeneration does not result in complete blindness, because peripheral vision remains. However, loss of central vision can make it difficult to perform daily activities, i.e., reading, driving, recognizing faces, etc. [4]. The "wet" version of AMD can be treated with pharmacological agents infused by intravitreal injection [8]. However, there are no known treatments for "dry" AMD [1,2,4,10].

Stem cells have been touted as the "holy grail" as a potential treatment modality for diseases and disorders with no known treatments and/or cures [39,40]. Stem cells have been proposed to treat diseases such as retinitis pigmentosa (RP), Stargardt's disease (juvenile macular degeneration), and the dry form of age-related macular degeneration [11].

Mesenchymal stem cells are viewed as a potential immunomodulatory exosome treatment modality for wet and dry macular degeneration [7,9,22-26]. One of the major problems with mesenchymal stem cells is the variability in isolation procedures leading to uncertainty as to the nature of the cells that are defined as being "mesenchymal stem cells" for any reported study. For example, mesenchymal stem cells have been isolated from adipose tissue. Adipose tissue is not formed by white fat cells (unilocular adipocytes) and mesenchymal stem cells alone. There are many other cell types present, e.g., (1) fibrocytes and their progenitor cells, fibroblasts; (2) different types of endothelial cells lining capillaries, arterioles, venioles, and lymphatic vessels and their progenitor cells, endothelioblasts; (3) blood elements within the capillaries, RBCs, WBCs, and platelets; (4) perivascular cells; (5) smooth muscle cells lining outside of arterioles and venules, and their progenitor cells, myoblasts; (6) multipotent adult progenitor cells (MAPCs; (7) very small embryonic-like stem cells (VSELs); (8) sensory nerve endings; (9) Schwann cells; (10) ectodermal stem cells (EctoSCs), and their progenitor cells, ectodermal progenitor cells; (11) endodermal stem cells (EndoSCs), and their progenitor cells, endodermal progenitor cells; (12) mesodermal stem cells (MesoSCs), and their progenitor cells, mesodermal progenitor cells; (13) germ layer lineage stem cells (GLSCs); (14) epiblastic-like pluripotent stem cells (ELSCs); (15) corona-like pluripotent stem cells (CLSCs); (16) halo-like pluripotent stem cells (HLSCs); (17) totipotent stem cells (TSCs); and (18) mesenchymal stem cells (MSCs), a tri-potent progenitor cell that can give rise to fat, cartilage, and bone. [3,27,43-45]. Except for cloning, using repetitive single cell clonogenic analysis [27] or isolation of mesenchymal stem cells using cell surface antibodies to CD105, CD117, and CD123 [46] by either flow sorting, magnetic bead sorting, or panning [27] it is extremely difficult to isolate a relatively pure population of mesenchymal stem cells for testing, much less for clinical applications.

Similar problems arise when attempting to isolate mesenchymal stem cells from bone marrow. Bone marrow is not limited red marrow and mesenchymal stem cells. Bone marrow is composed of red marrow containing hematopoietic generating cells, osteoprogenitor cells, osteoblasts, osteoclasts, marrow stromal cells, and yellow marrow (fat) containing all the above cell types, except nerve fibers and Schwann cells [3,27,43-45,47,48]. As stated above, except for cloning, using repetitive single cell clonogenic analysis, or isolation of mesenchymal stem cells using cell surface antibodies to CD105, CD117, and CD123 [27,46] it is extremely difficult to isolate a relatively pure population of mesenchymal stem cells for testing, much less for clinical treatments.

Umbilical cords have been utilized to generate mesenchymal stem cells. However, an umbilical cord is not composed of just the baby's blood and mesenchymal stem cells. The cell types present with respect to an umbilical cord include the mother's RBCs, WBCs, platelets (attached to outside of cord); the outer covering consisting of syncytiotrophoblast and cytotrophoblast; extraembryonic somatic mesoderm; Hoffbauer's cells; endothelial cells lining arteries and vein, and their progenitor cells, endothelioblasts; smooth muscle cells and their progenitor myoblasts; ectodermal stem cells (EctoSCs), and their progenitor cells, ectodermal progenitor cells; endodermal stem cells (EndoSCs), and their progenitor cells, endodermal progenitor cells; mesodermal stem cells (MesoSCs), and their progenitor cells, mesodermal progenitor cells; germ layer lineage stem cells (GLSCs); epiblastic-like pluripotent stem cells (ELSCs); corona-like pluripotent stem cells (CLSCs); halo-like pluripotent stem cells (HLSCs); and totipotent stem cells (TSCs) [3,27,45,49]. As stated above, except for cloning, using repetitive single cell clonogenic analysis, or isolation of mesenchymal stem cells using cell surface antibodies to CD105, CD117, and CD123 [27,46] it is extremely difficult to

isolate a relatively pure population of mesenchymal stem cells for testing, much less for clinical applications.

Two potential routes of delivery have been proposed for autologous and/or allogeneic mesenchymal stem cells to treat macular degeneration, e.g., intravitreal injection [9,25,26] and intranasal infusion [50,51]. One questions the rationale for injecting a cell type that will differentiate into fat, cartilage, or bone, into the posterior chamber of the eye. Cases of unilateral and bilateral blindness were reported by individuals injected in such a manner at an FDA Conference on Stem Cells [42].

In contrast, intranasal infusion of MSCs necessitates the use of a hyperosmolarity substance, such as mannitol, to shrink the olfactory epithelial cells, forming channels to allow passage of the larger MSCs past the blood brain barrier and into the central nervous system. If the hyperosmolarity procedure is performed just once in individuals at or older than puberty, the potential harm is negligible. However, if the hyperosmolarity procedure is performed two or more times in individuals at or older than puberty then permanent channels are created between the olfactory epithelial cells that have the potential for an increase in bacterial and/or viral meningitis in these hyperosmolarity-treated individuals [27,50-54].

In contrast, knowing that the telomerase-positive stem cells utilized represent less than 4% of all the stem cells in the body [38] e.g., TSCs < 0.1%, PSCs < 0.9%, and MesoSCs < 3%, an alternative regimen was devised to isolate the cells. Standardized procedures were utilized for all treatments, e.g., neurological, cardiovascular, pulmonary, autoimmune, systemic, and orthopedic, with a set of guidelines [37] to maximize telomerase-positive stem cell proliferation in their connective tissue niches. Initially, the subject would ingest a combinatorial nutraceutical (CN) for 30 days prior to harvest and throughout their treatments. By proliferating their telomerase-positive stem cells in situ within all their connective tissue niches throughout their body the absolute number of telomerase-positive stem cells was increased in their blood 16,000 times above baseline. Eighteen hours before harvest, the subject ingests glacial caps, which causes a reverse diapedesis of the telomerase-positive stem cells from their connective tissue niches into the blood stream in a bell-shaped curve, with the peak release at 18 hours post ingestion [37]. Glacial caps further increase telomerase-positive stem cell numbers in the blood by a factor of six at the 18-hour time point.

This results in a total increase of 9.6×10^4 above baseline of telomerase-positive stem cells for harvest. Harvest of telomerase-positive stem cells is/was by simple venipuncture, withdrawing 210-420cc's of blood, based on individual's body weight. The released telomerase-positive stem cells are separated from the RBCs, WBCs, and platelets by zeta potential, gravity, and differential buoyant density gradient centrifugation using serum, saline, and distilled water. The telomerase-positive stem cells are segregated into relatively pure populations of totipotent stem cells (ultra-small-TSCs and small-TSCs), pluripotent stem cells (PSCs, e.g., HLSCs, CLSCs, ELSCs, and GLSCs), and mesodermal stem cells (MesoSCs) [27] and activated. Activation outside the body takes approximately 2 hours, while activation inside the body takes about 2 weeks. The populations are then further processed and recombined based on the particular treatment to be given. In this case, neurological, in which the TSCs are concentrated into 2 x 0.2cc aliquots. The participant washes the mucus from their nose with 0.65% sterile saline, the participant is placed into a reverse Trendelenburg position and each aliquot given by intranasal infusion, one into each nostril. The PSCs and MesoSCs are suspended in 250cc's of sterile normal heparin/saline and given by regular intravenous infusion in an accessible vein, usually the median cubital vein.

As noted in the Results section, two of four individuals with macular degeneration had complete restoration of their central visual acuity after two "neurological" treatments with telomerase-positive stem cells. Of the remaining two individuals, one had an unrecognized serious heart problem that was repaired instead, increasing their cardiac output by 5% after each treatment. Previous studies have shown that if individuals have a life-threatening condition, their body will treat that condition first no matter where the activated stem cells are placed within the body [30,36,55]. The other individual was non-compliant, smoking and drinking before, during, and after their telomerase-positive stem cell two treatments. Since we know that smoking and drinking will kill actively dividing telomerase-positive stem cells [37,55] there were probably no viable telomerase-positive stem cells available for repair of their macular degeneration.

Both retinal pigmented epithelium (RPE) and photoreceptor replacement therapies are being examined as treatment modalities for AMD [11]. Source of these cells include embryonic stem cells [12-14] and induced pluripotent stem cells [15-22].

Early studies implanting naïve embryonic stem cells and induced pluripotent stem cells demonstrated the formation of teratomas, i.e., cancerous collections of cells, around the implant [39]. Teratoma formation is caused by the inherent pre-programming of these cells to form all tissues of the embryo. Outside the uterus and away from the normal checks and balances of normal development, there is no regulation of development and a mass of differentiated cell types occurs. To circumvent teratoma formation it was discovered that one could induce one or more particular cell types to differentiate within embryonic stem cells [56,57] and induced pluripotent stem cells. The particular cell types formed could then be isolated in a relative pure form. At this point in time, the inherent pre-programming to form every cell type is circumvented, teratoma formation is prevented, and result, in this instance, is retinal pigmented epithelium and photoreceptor cells [12-22]. The next steps were to develop a matrix for adherence of the cell types and the implantation the cell/matrix into the eye to restore visual acuity [22].

There are three issues with using embryonic stem cells for any kind of regenerative medicine, e.g., moral, ethical, and graft

versus host response. Using embryonic stem cells means one is using allogeneic (non-self) stem cells for treatments. And unless immunosuppressants are utilized [12] there is the chance for a graft versus host response in the individual [58,59] whereby either the host kills the graft or the graft kills the host.

Induced pluripotent stem cells, starting with differentiated cells from the recipient prior to insertion of the Yamanaka genes [39] presents no problems with respect to moral or ethical or graft versus host response, since the origin of the cells to be transplanted is identical to the recipient of the transplant [16]. However, a potential change in immunogenicity of differentiated host cells that were reconfigured into iPSCs with insertion of embryonic genes has come into question [15] resulting in the potential for a graft versus host response [58,59].

We offer an alternative solution to the use of either mesenchymal stem cells, embryonic stem cells, or induced pluripotent stem cells for the restoration of visual acuity in patients with macular degeneration. That alternative solution is the use endogenous autologous adult-derived telomerase positive stem cells as the treatment modality. Since these telomerase-positive stem cells are autologous, there is no ethical, moral, or immunogenicity issues with respect to their use. We have used autologous (self) telomerase-positive stem cells as the treatment modality in neurological (Parkinson disease) [28,29] cardiovascular (Myocardial Infarction) [30,31] pulmonary (chronic obstructive pulmonary disease and idiopathic pulmonary fibrosis) [32-34] autoimmune (systemic lupus erythematosus) [36] and orthopedic disorders (osteoarthritis) [40] without any immunogenicity problems for as long as more than nine years and counting after transplant. We have also used endogenous allogeneic (non-self-donor) adult-derived telomerase positive stem cells as the treatment modality for neurological (Alzheimer's dementia) [41] pulmonary (chronic obstructive pulmonary disease and idiopathic pulmonary fibrosis) [33,34] and systemic (systemic lupus erythematosus and celiac disease) [35,36] disorders. However, use of allogeneic telomerase-positive stem cells necessitates use of gender-matched, ABO blood group-matched donors free of infectious diseases and free of deleterious genetic mutations [37,55].

There are many unique attributes of telomerase-positive stem cells:

- **The Telomerase Enzyme**

Telomerase enzyme [27] imparts essentially an unlimited number of population doublings until the telomerase enzyme is lost due to differentiation of the cell to become a telomerase-negative progenitor stem cell [60]. At that point in time the cell begins its potential of 70 population doublings with a biological clock starting at zero [61].

- **Quiescence**.

Their default state without use of any inhibitors to prevent premature differentiation is quiescence. Telomerase-positive stem cells are not preprogrammed to form anything. Rather, they respond to local environmental cues to dictate their activity state, be it proliferation, migration, activation, or induction. They respond as long as they are in the presence of a factor that dictates their activity state. Once that factor is removed, they stop the activity and return to a quiescent state until another factor is present to dictate their activity state. This sequence of activity state to quiescence to activity state to quiescence continues until they commit to becoming a more differentiated progenitor stem cell [62].

- **Differentiative Capabilities**

Totipotent stem cells will form any cell/tissue of the body, including the gametes and the nucleus pulposus of the intervertebral disc, which is the only adult derivative of the notochord (the primary inducer of the embryo). Pluripotent stem cells will from any cell/tissue of the body, except the gametes and the adult derivative of the notochord [27].

- **Unique and efficient tissue regenerative capacity**

Telomerase-positive stem cells have a unique ability to replace and/or regenerate only what is missing from the tissue/organ, and nothing more. In other words, there is no overgrowth of missing cells or tissues or structures within the tissue or organ. Once all the cells/tissues that need replacement are present, the unused telomerase-positive stem cells migrate to adjacent connective tissues and assume their default, quiescent and naïve state [62].

- **Younger chronological age of replacement tissues (turning back the biological clock)**

When telomerase-positive stem cells are utilized to replace damaged or missing cells, those replacement cells have a younger chronological age than the tissues which they are implanted. The reason for the apparent chronological age difference is that the newly minted differentiated cells have a chronological age of zero (0) population doublings. In other words, these are essentially newborn cells within an individual that has already accumulated 20-60 or more population doublings, depending on the age of the individual at time of implantation. And, as these "newborn" cells begin to develop they demonstrate phenotypic expression markers and extracellular matrices indicative of their chronological age biological clock (i.e., population doublings).

Some rather peculiar side effects have been noted in individuals receiving multiple transplants of autologous and/or allogeneic telomerase-positive stem cells These side effects include a change in hair pattern and hair color to that of a younger version of the donor (self or non-self) of the stem cells as well as loss of wrinkles [36]. These apparent side effects correspond to younger cells producing "younger phenotypic expression patterns" in an older aged individual.

We have seen this particular phenomenon in three individuals, two males and one female [31,33,36]. One male, 68 years of age, is our systemic lupus erythematosus subject. Since 2011 he has been transplanted 30 times, with nine allogeneic transplants and 21 autologous transplants. He has no visible wrinkles, smooth skin, and subsequent changes in hair color to that of his four donors' hair colors of auburn, black, light brown, and black. Before his

first allogeneic transplant his hair was sparse and white. A month after his first allogeneic transplant his fuller head of hair turned auburn in color. A month after his second allogeneic transplant his hair went from auburn to black. His third allogeneic donor also had black hair. And a month after his fourth allogeneic transplant, his donor had light brown hair, his hair changed from black to light brown. Then with the next allogeneic transplant his hair color returned to black. Currently the SLE participant's hair color is predominantly black and white with some light brown and a few auburn hairs in the mix [36].

The female was one of our COPD participants. She had 16 telomerase-positive stem cell transplants, four were allogeneic and 12 were autologous, over the course of eight years. She demonstrated loss of wrinkles and change in hair color, to a younger version of herself and her donors all had the same hair color as younger individuals [33].

The other male has not undergone any removal and reinfusion of telomerase-positive stem cells. Rather he has been on the combinatorial nutraceuticals (CN) daily since March of 2019. After undergoing five separate coronary arterial bypass graft surgeries and placement of 15 drug eluting stents, he had a massive heart attack in March of 2019. He left the hospital on the heart transplant list with a cardiac output of less than 10%. On the combinatorial nutraceutical formulation for four months his cardiac output rose to 35% and his name was removed from the heart transplant list. By March of 2020 his cardiac output was up to 50% [31]. He says he feels great, he plays golf weather permitting, and he wants to stay on the formulation. He was mostly bald with a few strands of white hair in March of 2019. He is getting his hair back slowly, and it is his original hair color. He is slowly losing his wrinkles. His wife, daughter, and son have commented on his renewed vitality and his "younger" appearance and hair color.

Apparently, it is the current perception in the literature that induced pluripotent stem cells (iPSCs) are the most versatile source of stem cells for regenerative medicine [18]. We would propose that another cell is better able to fit that description, e.g., endogenous adult-derived telomerase-positive totipotent stem cells (TSCs) [27,29-36,38-41].

As shown in Table 1, Both TSCs and iPSCs are telomerase-positive and therefore have an unlimited proliferation potential. Both TSCs and iPSCs will respond to proliferation factors, induction factors, and inhibition factors. Both TSCs and iPSCs can be transplanted as an autologous cell/tissue by intravitreal injection or surgical implantation. This is where their similarities end. Their default state, without the use of inhibitors, is quiescence for TSCs and spontaneous differentiation for iPSCs. Both can be implanted, with the TSCs as a naïve undifferentiated cell population, whereas, the iPSCs have to be pre-induced into one of more differentiated cell types, otherwise, teratoma formation occurs.

While both TSCs and iPSCs can be transplanted as an allogeneic cell/tissue, the TSCs train the recipient's immune system to accept the donor telomerase-positive stem cells (e.g., TSCs and PSCs) as self [38]. In contrast, as a future differentiated cell type, the implanted iPSCs need immunosuppressants to prevent a graft versus host response [21]. TSCs can be given by intranasal infusion without the use of a hyperosmolarity solution, due to their extremely small size, 0.1 to 2 microns, which enable them to squeeze past the olfactory epithelial cells. Differentiated iPSCs are significantly larger than TSCs and necessitate the use of a hyperosmolarity solution, if intranasal is the preferred route of administration, otherwise intravitreal injection or surgical implantation is utilized [14-18,21,22]. When implanted into intact undamaged tissue, the TSCs will remain quiescent. In contrast, the iPSCs will form their pre-induced cell types. When implanted into damaged tissues, the TSCs will repair all the damage cells/tissues across all three primary germ layer lineages, gametes, and/or nucleus pulposus of intervertebral disc. In contrast, iPSCs will only form their pre-induced cell types. The preferred route of delivery for naïve telomerase-positive totipotent stem cells is intranasal delivery without the use of a hyperosmolarity agent, which is significantly less invasive than direct injection into the posterior chamber of the eye or surgical implantation of iPSCs [14-18,21,22].

Attribute	Totipotent Stem Cells	Induced Pluripotent Stem Cells
Telomerase	Present	Present
Proliferation Potential	Unlimited	Unlimited
Differentiation Capability	Totipotent	Pluripotent
Default State w/o inhibitors	Quiescence	Spontaneous Differentiation
Teratoma Formation	No	Yes
Implantation	Naive	Pre-Induced
Respond to Proliferation Factor	Yes	Yes
Respond to Induction Factor	Yes	Yes
Respond to Inhibition Factor	Yes	Yes
Implanted as Naïve Stem Cell	Yes	No
Autologous Implant	Yes	Yes
Allogeneic Implant	Yes	Only with immunosuppressants
Induce Graft vs Host Response	No	Yes
Intravitreal Injection	Yes	Yes
Surgical Implantation	Yes	Yes
Intranasal	Yes	No
Implanted into intact tissue	Quiescence	Pre-Induced cell types
Implanted into damaged tissues	Repair damage to all cell types	Form pre-induced cell types

Table 1: Comparison of attributes between telomerase-positive totipotent stem cells (TSCs) and telomerase-positive induced pluripotent stem cells (iPSCs).

Conclusion

Age-related macular degeneration (AMD) is an insidious disease with a gradual worsening of symptoms, which in time, results in a loss of visual acuity in the central area of vision. Macular degeneration does not result in complete blindness, because peripheral vision remains. However, loss of central vision can make it difficult to perform daily activities, such as reading,

driving, recognizing faces, etc. There are two forms of macular degeneration, wet and dry. Wet macular degeneration occurs in about 20% of the cases and can be treated pharmacologically. Dry macular degeneration occurs in about 80% of all cases and there is no known treatment or cure for this disorder. Currently, stem cells are the Holy Grail for regenerative medicine for diseases and/or disorders with no known cure. Three types of stem cells have been proposed to treat individuals with macular degeneration, e.g., mesenchymal stem cells, embryonic stem cells, induced pluripotent stem cells. Mesenchymal stem cell therapy utilizes exosome-based secretory vesicles to slow the progression of the disease. There are several issues with respect to using embryonic stem cells to treat this disorder, e.g., ethical, moral, teratoma formation, and transplanting allogeneic cells with subsequent immunosuppressant use and its associated comorbidities. Induced pluripotent stem cells have been proposed to circumvent any ethical and moral issues with embryonic stem cells. In addition, if the iPSCs are pre-induced to form differentiated cell types, then teratoma formation is a non-issue.

We offer a fourth possibility for treating macular degeneration, endogenous adult-derived totipotent stem cells. They offer all the positives of IPSCs without the negatives. Autologous TSCs were used to treat four individuals with macular degeneration that had lost central vision acuity. Following their second TSC treatment using a non-invasive intranasal route, central vision acuity was restored in two patients. The remaining two patients did not respond to treatment for macular degeneration. One had comorbidity to the heart that was repaired instead, increasing their cardiac output by 5% after each stem cell treatment. The other individual was non-compliant to defined guidelines for optimized TSC transplants. Therefore, autologous TSCs proved to be both safe and effective (50%) at restoring central vision acuity in individuals with age-related macular degeneration.

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