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# Allogeneic and Autologous Telomerase-Positive Stem Cells as a Potential Treatment for Systemic Lupus Erythematosus

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## ABSTRACT

*Systemic lupus erythematosus (SLE) is a chronic incurable and potentially fatal autoimmune disease. SLE manifests itself with the production of autoantibodies to partially digested nuclear components, cells, and non-cellular material. With any type of tissue insult, there is a release of material from damaged tissues which initiates a cascade of events that perpetuate a lupus flare/crisis, resulting in replacement of functional tissue with non-functional scar tissue in all organs of the body. Current pharmacological interventions use immunosuppressive therapy, cytotoxic agents, and/or biologics to halt the progression of SLE. Studies are ongoing to prove the utility of stem cells to cure people with chronic diseases. Myeloablation followed with HLA-matched hematopoietic stem cells demonstrate its ability to halt the progression of SLE. Mesenchymal stem cells demonstrate an immunomodulatory effect on the immune system, slowing the progression of SLE. Neither stem cell treatment has shown an increase in systemic organ functioning. We hypothesize that telomerase-positive stem cells would halt progression of disease and increase systemic organ functioning. A 61-year-old male was diagnosed as two-week terminal stage-IV SLE, with systemic organs functioning at or below 25%. He was treated with multiple autologous and allogeneic telomerase-positive stem cell transplants. He is still alive after 9+ years and his organs are functioning at or near 70%.*

## Keywords

Adult, Stem Cell, Telomerase, Systemic lupus erythematosus, SLE, Regenerative Medicine.

## Introduction

Systemic lupus erythematosus (SLE) is a chronic incurable and potentially fatal autoimmune disease. It manifests itself with the production of autoantibodies to partially digested nuclear components, cells, and non-cellular material. With any type of tissue insult, there is a release of material from damaged tissues. This begins the cascade of events that perpetuates a lupus flare/crisis. With the release of material from damaged tissue there is an influx of immune cells to the area of tissue insult, partial degradation of released material, binding of autoantibodies to antigens on the partially degraded material, complement binding to antigen-antibody complexes, circulation of complexes of antigen-antibody-complement throughout the vasculature, entrapment of the antigen-antibody-complement complexes within small diameter capillary beds that can occur within the limbs and various organs throughout the body. This causes further tissue destruction, release of damaged tissue materials, and the lupus flare/crisis cycle perpetuates itself. Once the immune system has "burned itself out", i.e., temporarily depleted itself of neutrophils, macrophages, NK-cells, mast cells, antigen-presenting cells, eosinophils, and/or

basophils, autoantibodies and complement, the lupus flare/crisis dissipates, leaving focal areas of tissue destruction in need of repair. The repair process occurs with a proliferation of fibroblasts and deposition of non-functional scar tissue in areas previously occupied by functional parenchyma. The replacement of functional tissue with non-functional scar tissue leads to an incremental decrease in organ function with each successive lupus flare/crisis. Systemic lupus erythematosus does not directly kill the individual. Rather, when the incremental replacement of functional tissue with scar tissue exceeds the organ's ability to function, it ceases to function. Death of the individual occurs when multiple vital organ systems, e.g., heart, lungs, brain, spinal cord, peripheral nervous system, gastrointestinal system, liver, kidneys, endocrine organs, etc., cease to function.

The clinical management of systemic lupus erythematosus is tenuous and multifaceted. This is due in part to ongoing multiple disease manifestations, lack of universally accepted measures of the disease, and lack of safe and effective targeted therapies [1]. Observational studies have a prominence in SLE with observations being a source of vital information for various therapeutic modalities with respect to predicted diagnoses, proposed outcomes, effectiveness of treatments, and potential adverse side effects [2]. Therefore, the best treatment options depend on a multidisciplinary and collaborative approach to patient care [3]. Unfortunately, despite the improvement in the management of SLE due to basic science, pharmacological, and/or technological developments, SLE remains a disease that over the years produces irreparable damage to patients' organs [4].

Individual organs and organ systems irreparably damaged in SLE patients include the peripheral and central nervous systems (polyneuropathies, multiple mononeuronpathies, sensory deficits, neuropathic pain, motor deficits, small-fiber peripheral neuropathies, dorsal root ganglion loss, cranial neuropathies, central nervous system neuropathies) [5-8], headaches (migraines, cluster headaches, intracranial hypertension) [9], lung (idiopathic pulmonary fibrosis, pleuritis, inflammation of the pleural linings) [10-20], heart (pericarditis, coronary artery disease, cardiomyocyte necrosis, cardiomyopathies, cardiac arrythmias) [21,22], gastrointestinal system (ulcerations, vasculitis, esophageal dysmotility, heartburn, dysphagia, celiac disease) [23], pancreas (pancreatitis, diabetes mellitus) [23], liver (hepatitis, liver sclerosis) [23], kidney (nephritis, end stage renal disease) [24], bone (osteoporosis, secondary bone fractures) [4], and skin (butterfly rash with erythematous macules, telangiectasia or papulosquamous lesions, facial edema, psoriasiform lesions, discoid lesions, facial lupus profundus, scarring alopecia, chronic chilblain lupus, photosensitivity, urticaria, erythema, Raynaud's phenomenon, vasculitis), etc. [25].

Current therapeutic interventions for patients with a diagnosis of SLE are dependent on particular symptom manifestations and potential conflicting side effects. The pharmacological approach includes the use of immunosuppressive therapy, cytotoxic agents, and biologics, such as glucocorticoidsteroids, hydroxychloroquine, mycophenolate mofetil, azathioprine, cyclophosphamide, methotrexate, rituximab and belimumab [1-3,6,20,23]. Potential adverse side effects of these pharmacological agents include peripheral edema, hyperglycemia, hypertension, tachycardia, increase in appetite, weight gain, increase risk of ulcers, gastritis, osteoporosis, brittle bones, bone fractures, increased levels of cholesterol and triglycerides, cataracts, glaucoma, blurred vision, thinning of skin, easy bruising, insomnia, mood swings, depression, irritability, anxiety, muscle weakness, increased growth of body hair, acne, and increased susceptibility to infections (glucocorticoids); alopecia, migraines, dizziness, nervousness, irritability, numbness, tingling, muscle weakness, skin rashes, itching, stomach cramps, nausea, vomiting, diarrhea, chest pain, cardiomyopathy, very slow heart rate, weak pulse, tachycardia, and congestive heart failure (hydroxychloroquine); migraines, dizziness, drowsiness, lightheadedness, pain, tremors, weakness, paresthesia, indigestion, stomach pain, nausea, vomiting, constipation, diarrhea, melena, fever, heart arrhythmia, hypotension, peripheral edema, rash, and itching (mycophenolate mofetil); skin rash, dizziness, fatigue, abdominal pain, nausea, vomiting, diarrhea, hepatotoxicity, and cloudy urine (azathioprine); alopecia, poor appetite, nausea, vomiting, diarrhea, bloody stools, anemia, discoloration of skin, a wound that will not heal, discoloration of nails, joint pain, muscle weakness, muscle spasms, chest pain, irregular heartbeat, trouble breathing, missed menstrual periods, loss of fertility, mouth sores, bladder irritation, hemorrhagic cystitis, lower the body's ability to fight, and kills immune system (cyclophosphamide); alopecia, tiredness, dizziness, muscle weakness, muscle cramps, feeling sick, nausea, vomiting, diarrhea, anemia, migraines, lung lesions, dry cough, shortness of breath, pleural effusion, chest pain, tachycardia, heartbeat that does not feel normal, life threatening skin reactions: red, swollen, blistered, peeling skin, rash, fevers, chills, red or irritated eyes, ulcerative stomatitis (mouth ulcers), throat ulcers, nose ulcers, eye ulcers, increased risks of serious infections leading to death, malignant lymphomas, end stage kidney disease, ascites fluid, trouble passing urine, end stage liver fibrosis, liver cirrhosis, can seriously harm or end a pregnancy, decreased fertility, and kills immune system (methotrexate); black tarry stools, bleeding gums, bloating or swelling in face, arms, hands, lower legs, and feet, blood in urine, blood in stools, body aches and pains, burning or stinging skin sensations, difficulty breathing, trouble breathing with exertion, noisy breathing, sneezing, cough, dry mouth, sore throat, stuffy or runny nose, ulcers in mouth and on lips, flushed dry skin, ear congestion, fever, blurred vision, sweating, dizziness, fainting, lightheadedness, chills, confusion, fruit-like breath odor, migraines, urticaria, itching, rash, increased hunger, polyuria, lower back pain, flank pain, nausea, pain and tenderness around eyes and cheekbones, painful blisters on lips, nose, eyes, and genitalia, painful or difficult urination, pale skin, pinpoint red spots on skin, pounding in ears, seizures, slow heartbeat, irregular heartbeat, tachycardia, swelling of tongue and throat, swollen glands, tingling of hands and feet, unusual bleeding or bruising, unusual weight gain or loss, blistering, peeling or loosening of skin, systemic blistering, burning, crawling, itching, numbness, prickling, "pins and needles" or tingling sensations, decreased frequency and amount of urine, joint and muscle pain,

red and swollen joints, difficulty with ambulation, discouragement, depression, irritability, trouble concentrating, and insomnia (rituximab); and allergic hypersensitivity reactions, itching, swelling of face, lips, mouth, tongue, throat, arms, legs, low blood pressure, nausea, diarrhea, fever, night sweats, dizziness, fainting, unusual tiredness, unexplained weight loss, swollen glands, unusual lumps or growths, sore throat, runny or stuffy nose, cough, sneezing, bronchitis, wheezing, chest tightness, trouble breathing, pain, itching, redness, swelling at injection site, pain in arms and legs, migraines, depression, anxiety, thoughts of suicide, thoughts of hurting yourself, thoughts of hurting others, sweating, life threatening infections, heart problems, chest pain, left arm pain, left jaw pain, insomnia, urinary tract infections, and anemia (belimumab) [26-33]. The above adverse side effects for these pharmacological agents are considered minor, inconsequential, and acceptable in the treatment of autoimmune diseases, such as SLE.

Alternatively, treatments with stem cells represent a new therapeutic approach in regenerative medicine. Stem cell therapy has been hypothesized as an effective treatment modality for patients with incurable severe refractory autoimmune diseases, such as systemic lupus erythematosus, compared to conventional pharmacological treatments [34-37]. Considering the ethical issues using embryonic stem cells or induced pluripotent stem cells with their propensity to form teratomas when implanted in their naïve state [24], CD34+ hematopoietic stem cells and CD34- mesenchymal stem cells have been proposed to be the best candidates for stem cell therapy [34-38].

Hematopoietic stem cell (HSC) transplantation has been shown to ameliorate a variety of non-malignant diseases, such as inherent defects of hematopoiesis, metabolic diseases and severe autoimmune diseases [34,36,37,39,40]. The rationale for this strategy is based on the concept of myeloablation of the immune system using high-dose chemotherapy. This is followed by infusion of HLA-matched bone marrow. The infused CD34+ HLA-matched HSCs differentiate into naïve T-cells. This regimen results in prompt cessation of the manifestations of SLE in treated patients [39,40]. Unfortunately, there is no resulting gain of function of any organ or organ system that had been previously damaged by SLE-associated flares/crises, except the immune system.

Mesenchymal stem cells (MSCs) are multipotent stromal cells that can differentiate into a variety of cell types, such as adipocytes, osteoblasts, and chondrocytes [38,41]. They can be isolated from adipose tissue, bone marrow, muscle connective tissue, fetal tissues, umbilical cord and placenta [38,42]. Four criteria need to be met for a cell to be identified as a mesenchymal stem cell. These criteria are adherence to a plastic substratum under standard culture conditions; capability to differentiate into adipocytes (fat), osteoblasts (bone), and chondrocytes (cartilage) in culture; expression of cluster of differentiation cell surface markers CD73, CD90, and CD105; and lack of expression of cluster of differentiation cell surface markers CD11b, CD14, CD19, CD34, CD45, and HLA-DR [38,43]. The lack of HLA-DR cell surface markers makes CD34- MSCs promising as candidates for transplantation in the absence of the myeloablation conditioning that is necessary for hematopoietic stem cell therapy [36,38-40,44]. Clinical studies have shown that MSCs have a strong modulatory effect on all immune cells, e.g., Natural Killer (NK-) cells, intraepithelial lymphocytes, antigen-presenting cells, B-cell lymphocytes, T-Reg (regulatory) cells, and T-cell responses, making them a suitable option for stem cell therapies for autoimmune diseases [36,38,45].The protective effects of MSCs are associated with the paracrine secretion of protective molecules, e.g., nitric oxide, insulin-like growth factor (IGF), indolemine-2,3-deoxygenase, and prostaglandin E2 (PGE2), within exosome secretory vesicles rather than their differentiation into end-organ functioning cells [38,46]. Unfortunately, while MSC transplantation slows the progression of SLE, it has not shown any signs of regain of function of any organ or organ system damaged by SLE-associated flares.

We propose the use of an alternative group of endogenous adult-derived stem cells, rather than pharmacological therapeutics, myeloablation followed by HLA-matched bone marrow transplant, or mesenchymal stem cell transplantation, as a treatment modality for systemic lupus erythematosus. We have extensively characterized this particular group of stem cells [47]. Collectively, their characteristics include the presence of the telomerase enzyme when the stem cells are in their native undifferentiated state within the connective tissues of an individual; loss of the telomerase enzyme during their subsequent differentiation; induced differentiation into 66 discrete cell types of the body, including spermatogonia and notochord, in culture [48]; and formation of functional cells in culture, e.g., neurons secreting neurotransmitters [49], contracting cardiomyocytes regulated by application of propranolol and isoproterenol [50], and induced pancreatic islets secreting insulin in response to a glucose challenge [51]. We tested these stem cells for ability to regenerate/repair the appropriate damaged tissues in animal models of induced-Parkinson disease [52], induced-traumatic brain injury [53], induced-myocardial infarction [54], and induced-lung fibrosis [55]. And in our human clinical studies we have shown increases in organ functioning in individuals treated with naïve telomerase-positive stem cells for Parkinson disease [56], myocardial infarction [57], idiopathic pulmonary fibrosis [55,58], and chronic obstructive pulmonary disease [55]. Based on those studies, we hypothesize that adult-derived telomerase-positive stem cells, e.g., totipotent stem cells (TSCs), pluripotent stem cells (PSCs), and mesodermal stem cells (MesoSCs), would collectively slow the progression of SLE and improve functioning in the damaged organs.

## Methods and Materials

Autologous and allogeneic adult-derived telomerase-positive stem cells (TSCs, PSCs, and MesoSCs) were tested as a therapeutic regimen in an IRB-approved study protocol for a 61-year-old male with systemic lupus erythematosus (SLE) of 31 years duration. Additional autoimmune diseases diagnosed and confirmed in this individual were Hashimoto's thyroiditis, Sjogren's disease, Scleroderma, and Autoimmune Insulin Dependent Diabetes Mellitus. Autoimmune-associated diseases included Alopecia,

Raynaud's syndrome, multiple severe allergies, Idiopathic Pulmonary Fibrosis, Celiac Disease, Atrial Fibrillation, and Transient Ischemic Attacks [59].

Disease assessments were assessed using annual serum antibody testing for allergens. If no antibodies are present in the serum sample for that particular allergen, the value is <1.0. If antibodies are present to the allergen in the serum sample, the value is >1.0, with the higher the titer the more severe disease. Allergens associated with his autoimmune diseases were all at or above a titer of 10. For example, his initial antibody titer for deaminated gliadin peptide (allergen for celiac disease) was 73 [59].

At age 30, the individual was diagnosed as Stage-I SLE, genetically inherited along his maternal germ line (i.e., great-great grandmother, to great grandmother, to grandmother, to mother, to son). Progressing from stage-I SLE (age 30) to stage-IV SLE (age 61) he stated that he tried every prescribed AMA-approved treatment for SLE recommended by his rheumatologists, but the treatments either did nothing or accelerated the progression of his diseases. Since past pharmacological treatments did not perform as expected, an alternate experimental therapy was attempted, i.e., the use of autologous and allogeneic telomerase-positive stem cells.

Recipients and donors were mandated to follow the informed consent guidelines for telomerase-positive stem cells for clinical therapy [58,59]. 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 avoidance of alcohol, tobacco products, vaping, recreational drugs, lidocaine, and chemotherapeutic agents because they kill telomerase-positive stem cells; limit use of caffeine and corticosteroids because they alter the differentiative capabilities of telomerase-positive stem cells; ingestion of combinatorial nutraceuticals (DFRD, Macon, GA) daily for a minimum of 30 days prior to initial harvest and then throughout subsequent treatments of recipient (and donor harvests) to increase proliferation of telomerase-positive stem cells within the person's own connective tissues, making the person their own bioreactor for stem cell proliferation; drink plenty of fluids two weeks before stem cell harvest; limit moderate to excessive exercising during a two-week window around stem cell harvest/treatment to maximize directed repair responses; and to ingest glacial caps (DFRD) 18 hours before stem cell harvest to mobilize stem cells into the blood stream. Donors were screened for gender, ABO-blood group, infectious diseases, genes for autoimmune diseases, and genes for any other deleterious genetic mutations. Donors were also given the option to have their activated mesodermal stem cells returned to them.

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, segregated into individual populations of TSCs, PSCs, and MesoSCs, and activated [58,59]. Allogeneic mesodermal stem cells from donors were not used due to their expression of self-recognition MHC Class-I molecules on their cell surface [47]. Since MHC Class-I molecules might induce a graft versus host response [60,61], it was felt that it was too great a risk for potential detriment to the recipient. Neither TSCs or PSCs display either MHC Class-I or HLA-DR molecules on their cell surface [62] and were utilized in the treatment protocol from the allogeneic donors.

Just before his first treatment with autologous telomerase-positive stem cells the individual was diagnosed as two-week terminal stage-IV SLE with his organs functioning at or less than 25%, after having already lost two organ systems. The individual was on 64 mg of hydromorphone every four hours for intense neuropathic pain, he demonstrated brain fog, his spinal rootlets L1 to S4 were attached to his spine with scar tissue, he exhibited bilateral sciatica, polyarthralgia, skeletal muscle cramping, spasms and twitching, generalized muscle aches and pains, he was experiencing almost continuous cluster headaches alternating with occasional migraines, severe fatigue, systemic urticaria, mastocytosis, "red leopard spots" (IgG reactivity to IgM's, with IgG titer > 50), pericarditis, cardiac arrythmias, cardiovascular disease (<25% cardiac output), bilateral pleuritis, painful breathing, difficulty breathing (lung function 25% FEV1), anemia, recurrent low grade fever, pain sensitivity to touch/pressure, insomnia, narcolepsy, hepatitis, jaundice, nephritis, pancreatitis (antibodies to beta-cells, titer > 50), hyperglycemia (glucose > 800 IU/dL), mouth ulcers, nose ulcers, fever, chills, night sweats, dry eyes, dry 'alligator' skin, gastritis, nausea, vomiting, abdominal pain, alternating constipation and diarrhea, photosensitivity, increase in number and severity of allergies (antibody titers >50; deaminated gliadin peptide titer 73), cold insensitivity, vasculitis, enlarged lymph nodes, alopecia, complete absence of hair below his clavicles, sparse white hair on his head, anti-nuclear antibodies (ANA) titer >50, etc., and in his own words "basically a living hell".

During the nine years since his first (autologous) stem cell treatment, the SLE participant has undergone 20 additional autologous stem cell procedures and received telomerase-positive allogeneic TSCs and PSCs on nine separate occasions, i.e., once from the 42-year-old A-positive male, twice from a 53-year-old O-negative male, twice from a 50-year-old A-positive male, and four times, age at time of donation of 73, 75, 77, and 80-year-old O-negative male. The symptoms expressed by the SLE recipient at the particular time of treatment dictated the particular directed treatment regimen used with the telomerase-positive stem cells. For example, autologous and allogeneic TSCs only for intranasal infusion for neurogenic/central and peripheral nervous system issues; autologous and allogeneic TSCs only for slow intravenous infusion using the Thebesian venous system for cardiovascular problems; allogeneic and autologous TSCs and PSCs for nebulization for breathing problems due to his diagnosis of idiopathic pulmonary fibrosis; and allogeneic and autologous TSCs and PSCs and autologous MesoSCs diluted in 0.9% sterile saline for regular intravenous infusion for systemic and associated autoimmune issues, including SLE, Hashimoto's thyroiditis, Sjogren's disease, Scleroderma, multiple allergies, Celiac Disease, Atrial Fibrillation, Transient

Ischemic Attacks, hepatitis, pancreatitis, nephritis, etc.

## Results

His first treatment used his own autologous telomerase-positive stem cells, i.e., TSCs by intranasal infusion and PSCs and MesoSCs by regular IV infusion. That treatment proved life-saving with a loss of the neuropathic pain (by one week post-transplant), loss of need for morphine, loss of brain fog, loss of bilateral sciatica, loss of cluster headaches, loss of systemic pain and sensitivity, and functional stasis in his remaining viable organs (heart: 25% cardiac output; lungs: 25% FEV1) (by one month post-transplant).

Unfortunately, due to having an inherited genetic defect for SLE, the individual reverted in just over a month's time frame and a second telomerase-positive stem cell treatment was performed. This time the treatment used allogeneic telomerase-positive TSCs and PSCs from a gender-matched (42-year-old male) with A+ blood group-matched donor that did not have a family history of SLE and absent of infectious diseases and deleterious genetic mutations. Protocol used was TSCs intranasal for CNS issues, TSCs slow IV infusion for heart, TSCs and PSCs nebulized for lung, and TSCs and PSCs systemically for autoimmune issues. Results from his second telomerase-positive stem cell treatment (and first allogeneic treatment) demonstrated a further decline in autoimmune-related CNS issues, an increase in heart function (cardiac output of 40%), an increase in lung function (FEV1 > 30%), and a further decrease in autoimmune-related systemic issues.

The telomerase-positive stem cells for his third (2nd allogeneic) treatment were derived from a gender-matched (male) and O-negative donor (at time of 1st donation, age 72) with a family history absent of SLE or any other autoimmune disorders, absent of infectious diseases, and absent of deleterious genetic mutations. Protocol used was TSCs intranasal for CNS issues, TSCs slow IV infusion for heart, TSCs and PSCs nebulized for lungs, and TSCs and PSCs systemically for autoimmune and other organ issues. Results from his third telomerase-positive (and second allogeneic) stem cell treatment demonstrated a loss of CNS issues, an increase in heart function to nearly 70% cardiac output, an increase in lung function to nearly 70% FEV1, a decrease in autoimmune issues, and increases in remaining organs, with functioning at or above 50%.

Since his third telomerase-positive stem cell treatment he has had an additional 19 autologous stem cell treatments (20 total) and seven allogeneic telomerase-positive stem cell treatments (9 total), for a total of 29 treatments thus far. Currently, his remaining organs are functioning at or above 70% of normal, he has greatly reduced neurogenic symptoms, reduced pulmonary symptoms, and reduced or absent SLE-related symptoms.

## Discussion

Stem cells are being examined as the "holy grail" for regenerative medicine as the preferred treatment for chronic and/or terminal diseases and for diseases with no known cure [50,58,59,62]. With respect to systemic lupus erythematosus, which is a chronic and sometimes fatal disease, hematopoietic stem cells and mesenchymal stem cells have been proposed as the best candidates for therapeutic regenerative medicine [34,36-38].

Since hematopoietic stem cells contain both MHC Class-I and HLA-DR cell surface markers that an intact immune system can use to recognize self from non-self [60], the direct transplantation of HSCs into individuals with an intact immune system should not be attempted. This is due to a graft versus host disease (GvHD) response that could either kill the graft or kill the recipient [61]. Therefore, myeloablation is performed to destroy the recipient's immune system before any attempt is made to transplant donor HLA-matched HSCs. For those individuals that survive the chemotherapy necessary to kill their immune system (about 75%), another 25% or so pass away due to inability of finding a compatible HLA-matched donor for hematopoietic stem cell replacement therapy. Of the remaining 50% of the surviving individuals, the myeloablation therapy/HLA-matched bone marrow transplant does stop the progression of SLE and it does restore an intact donor immune system to the individual. However, it does little to nothing with respect to restoring function in other organs compromised by SLE flares.

Clinical trials have demonstrated immunomodulatory effects of mesenchymal stem cell in the treatment of SLE. Exosomes containing protective molecules are secreted from the transfused mesenchymal stem cells to slow the progression of the disease [63,64]. As with myeloablation followed by HLA-bone marrow transplant, mesenchymal stem cells do little to nothing to restore function in organs compromised by SLE flares.

Both hematopoietic stem cells and mesenchymal stem cells are telomerase-negative [62,65] and therefore have a limited doubling life-span before pre-programmed cell senescence and cell death occurs [66]. Therefore, to get the most cell doublings per stem cell it has been proposed to use "as young as possible" telomerase-negative stem cells. These "young" stem cells can be obtained from umbilical cords, placentas, amnions, newborns, or young adults.

In contrast, our "best" donor was a healthy O-negative individual that donated his telomerase-positive stem cells at ages 72, 75, 77, and 80-years of age. Being telomerase-positive, his stem cells had an unlimited proliferation potential as long as they remained undifferentiated [67]. This is the native naïve state of the telomerase-positive stem cells within the connective tissues. Once the telomerase-positive stem cells begin to differentiate, they lose the telomerase enzyme and assume all the characteristics of telomerase-negative stem cells with a biological clock, starting at zero with the potential of 70 population doublings before the cells senesce and die [48,65].

Therefore, no matter the age of the donor of telomerase-positive stem cells, the donor will be providing stem cells with essentially

unlimited proliferation potential until differentiation begins. We utilized four separate donors for the combined autologous and/or allogeneic stem cell transplants. Telomerase-positive TSCs and PSCs were isolated from an A-positive 42-year-old male (one harvest), an A-positive 50-year-old male (two separate harvests), an O-negative 53-year-old male (two separate harvests), and an O-negative 72 to 80-year-old male (four separate harvests). We did not use mesodermal stem cells from any of the allogeneic donors. Mesodermal stem cells contain MHC Class-I markers that can be recognized as self vs non-self and induce a graft versus host disease response [60,61]. Therefore, to prevent GvHD response that might kill the recipient, these cells were not used for treating the recipient, but returned to the donor.

As noted in the Results section, treatment with adult endogenously-derived, both autologous and allogeneic, telomerase-positive stem cells rescued a two-week terminal stage-IV patient from death. To date at nine years and counting, he has had 29 telomerase-positive stem cell treatments (20 autologous and 9 allogeneic). The telomerase-positive stem cell treatments have worked to reduce autoimmune related symptoms, reduce CNS issues, and demonstrated a gain of function in all remaining viable organs [58,59,69,70]. Since he is still alive, and even though this is a small study sample (n=1), this suggests both the safety and efficacy of using telomerase-positive stem cells to rescue individuals with SLE having multiple organs with decreased function.

While the allogeneic treatments proved successful in both forestalling SLE disease progression and increasing systemic organ functioning, the treatments did bring to light some rather unique, peculiar and unforeseen side effects. These side effects were an appearance of hair follicles, both above and below his clavicles in the same locations as those of the donors; a change in the hair pattern and hair color of the recipient to that of the donors; personality transfer from donors to recipient; an apparent permanent loss in the majority of his previous allergies; transient loss of an allergy to deaminated gliadin peptide, but only during treatment period with allogeneic stem cells; gain in an allergy expressed by one of the donors; and gain of food preferences expressed by one of the donors.

The appearance of donor-specific traits, e.g., hair follicles, hair pattern, hair color, and personality, was seen in the recipient following transplants of allogeneic TSCs by their intranasal delivery. His first allogeneic transplant was from a 42-year-old A+ male that had auburn-colored hair and a nasty/aggressive personality. Those traits were expressed in the recipient approximately one month after treatment with donor allogeneic stem cells, giving him a fuller head of auburn-colored hair and the personality of the donor. His second allogeneic stem cell transplant was from a then 72-year-old O-negative male with black hair and a mellow/laid back personality. Those particular donor-specific traits were expressed in the recipient about a month after treatment. The SLE patient received two allogeneic telomerase-positive stem cell treatments from a 53-year old O-negative male with black hair and an aggressive/caring personality. As was seen previously, those particular donor's traits were transferred to the recipient. His second allogeneic donor, original age of donation at 72-years of age, contributed stem cells a second time, at age 75. While both the 53-year-old O-negative donor and the 75-year-old O-negative donor had black hair, their respective personalities were different and the patient reverted more to the mellow/laid back personality of the 75-year-old donor. The SLE recipient received an allogeneic stem cell treatment from both a 50-year-old A+ male with sandy-brown hair with a kind/caring personality and from the then 77-year-old O-negative donor. Even though the stem cell treatments included TSCs by intranasal infusion, there were no visible changes in hair color, personality traits, or a decrease in any SLE symptoms, e.g., neurogenic, cardiovascular, pulmonary, or systemic. However, a life-threatening open injury on the recipient's ankle/foot healed in less than a week after his combined autologous/allogeneic stem cell treatment, with no scarring at the wound site. About three months later he received another stem cell transplant from the 50-year-old sandy-brown hair-colored donor with the kind/caring personality. In this case, the donor's traits transferred to the recipient as well as a decrease in SLE symptoms, e.g., neurogenic, cardiovascular, pulmonary, or systemic. His last allogeneic treatment came from the then 80-year-old O-negative male with black hair and the mellow/laid back personality. As before, hair color, personality traits, and a decline in SLE-related symptoms and increases in organ functions appeared in the recipient. Based on results from an ongoing clinical study of chronic obstructive pulmonary disease [69] where treatment with allogeneic stem cells was by nebulization and intravenous (IV) infusion, it was noted there was no transfer of personality traits from the donors to the recipient. Results from that study combined with results from the current study, suggest that only when the intranasal route of TSC infusion to bypass the blood-brain barrier for the treatment neurogenic problems was used with allogeneic TSCs, was there a change of personality transfer from the donor to the recipient.

However, as eluded to above with the ankle/foot injury, when the TSCs were infused intranasally, the transfer of hair pattern, hair color, and personality did not occur 100% of the time. The treatment protocol in this instance utilized stem cells from the recipient as well as from two separate donors (50-year-old and 77-year-old). This was performed to maximize stem cell numbers for a reduction of SLE manifestations and increase functioning in his organs impacted by continuing SLE-induced replacement of functional tissue with non-functional scar tissue. Pooled autologous and allogeneic TSCs were used for an intranasal infusion to bypass the blood-brain barrier for neurogenic issues, pooled autologous and allogeneic TSCs were used for a slow intravenous infusion via the Thebesian venous system for cardiac issues, pooled autologous and allogeneic TSCs and PSCs were nebulized for lung issues, and pooled autologous and allogeneic TSCs and PSCs and autologous MesoSCs were infused through the median cubital vein by a regular intravenous infusion for systemic issues [58,59,69,70]. Utilizing the treatment regimen described above, we had expected a see a reduction in SLE symptoms and an increase in organ functioning. Unfortunately, or fortunately, that did not occur. Instead, all the activated stem cells specifically directed to the brain, spinal cord,

lungs, heart, gastrointestinal system, and kidneys, ended up at the open ankle/foot injury. The open wound was repaired it in less than a week, with an epidermal covering of pristine skin and no apparent scar tissue. Apparently, the recipient's body sensed that the open ankle/foot injury was more life-threatening to the recipient's further existence than the current SLE manifestations and directed the activated stem cells infused at other distant sites to mobilize to that area and repair the open wound.

We have seen this phenomenon occur in other individuals with other diseases treated with the telomerase-positive stem cells. Our first Parkinson patient was treated with telomerase-positive stem cells. His Parkinson disease symptoms stabilized and remained in stasis even after two additional stem cell treatments. Unbeknownst to us, the individual had experienced a massive myocardial infarction six years previously that had left his cardiac output at 25%. By six months after the first of the two additional stem cell transplants that did not help his Parkinson disease, his cardiac output rose to 35%. And six months after the second stem cell treatment his cardiac output rose to 45% [57]. Our first traumatic spinal cord injury patient treated had been in a car accident 10 years previously that had completely transected their spinal cord at the level of T12. They had lost sensation and function in all organs below T12, e.g., bladder, bowel, and ambulation. Their expressed goal was to walk unassisted. After two stem cell treatments, there was a complete restoration of bladder and bowel functions, but no walking assisted or unassisted. In both instances, their bodies apparently viewed heart function and bladder/bowel function more important for quality of life for the individuals than the particular entities in which we were using directed treatments to restore function, e.g., Parkinson disease and ambulation.

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 remaining. And 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.

While the SLE individual has retained his long-standing allergies to penicillin, shellfish, contrast dye, tobacco smoke, and chocolate, he has apparently and permanently lost his allergies to grasses, pollens, mold, polyester, wool, nylon, latex, chicken, turkey, duck, eggs, milk, cheeses, yogurt, cooked vegetables, spices, and MSG, with antibody titers less than 1.0. He had a transitory loss of an allergy to deaminated gliadin peptide, titer reduction from 73 to less than 1.0 during the time period of his allogeneic transplants. During this time period he could eat gluten containing foods without any adverse side effects. However, with cessation of the allogeneic transplants, his deaminated gliadin peptide titer began to rise, currently above 50, and he is again on a gluten-free diet [59]. Interestingly, he has gained an allergy to soy protein, one expressed by the O-negative male that donated stem cells four times. We also noted that he has gained food preferences to that of the same O-negative male that donated stem cells four times, e.g., cooked asparagus in garlic sauce, pimento cheese, and blue cheese, three foods that the recipient either refused to eat or could not eat due to allergies, since 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.

We would hypothesize that as cells of the immune system are depleted during lupus flares/crises that the telomerase-positive allogeneic stem cells replace genetically defective immune cells with cells containing the full complement of enzymes and function as they would in a normal non-SLE individual. In addition, activated telomerase-positive stem cells either repair/replace non-functional scar tissue and/or regenerate new functional organ parenchyma, as seen with the increase in organ function in this individual, from at or below 25% to about 70%, over a period of nine years and counting. We have seen a similar phenomenon of increase in organ functioning after application of telomerase-positive adult-derived stem cells in multiple individuals with neurodegenerative diseases, traumatic brain injuries, traumatic spinal cord injuries, cardiovascular disease, pulmonary diseases, and systemic diseases in our current and ongoing human clinical studies [52,55-59,69,70].

We hypothesize the use of endogenous adult-derived telomerase-positive stem cells, rather than pharmacological therapeutics with their associated adverse side effects, myeloablation followed by HLA-matched bone marrow transplant, or mesenchymal stem cell transplantation, as a treatment modality for systemic lupus erythematosus. The telomerase-positive stem cells have shown the ability differentiate in culture demonstrating phenotypic expression markers for functioning parenchyma [47]. In animal models of disease, a genomically-labeled clone derived by repetitive single cell clonogenic analysis was shown to replace dopaminergic neurons in induced Parkinson disease [52]; pyramidal neurons, interneurons, glial cells, and capillaries after brain trauma [53]; cardiomyocytes, cardiac skeleton, and vasculature after induced myocardial infarction [54]; and regeneration of alveolar sacs, alveolar ducts, vasculature, and bronchioles in a chemotherapy-induced lung fibrosis model [55]. In our ongoing human clinical studies the transplantation of autologous and/or allogeneic telomerase-positive stem cells stabilized and reduced Parkinsonian symptoms in 75% of the population treated [56]; increased cardiac output in all of the patients treated [57,70]; increased FEV1's (forced expiratory volume in one second) in Gold-4 idiopathic pulmonary patients with initial FEV1's of less than 30% (14% and 25%, respectively) [58]; and increased FEV1's in Gold-3 chronic obstructive pulmonary patients with initial FEV1's less than 49% (30%, respectively) [69].

To increase our sample size and verify the capabilities of the telomerase-positive stem cells as an interventional biological therapy for systemic lupus erythematosus, we propose the following Phase-II randomized double-blinded placebo-controlled studies. We propose using an expanded population of individuals diagnosed with severe SLE with systemic organs functioning at or

below 50%. Then compare the safety and efficacy of telomerase-positive allogeneic TSCs and PSCs to telomerase-negative allogeneic mesenchymal stem cells (MSCs) to determine which population, TSCs/PSCs versus MSCs, is better suited to slow the progression of the disease and repair/restore organ functions in individuals with systemic lupus erythematosus.

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