Celiac disease can occur at any age and express a wide variety of signs and symptoms. A gluten-free diet is currently the only effective mode of treatment. While exclusion of gluten from the diet reverses many disease manifestations, it usually does not or is less efficient in patients with refractory celiac disease or associated autoimmune diseases. Targeted therapies to address both the nutritional and functional aspects of the disease have been devised, such as gluten-free grains and inhibition of proinflammatory cytokines. Currently, much of the promise for treating chronic and incurable diseases is centered on stem cell biology. Phase-I clinical trials using mesenchymal stem cells have demonstrated that the stem cells can be safely administered, and their effects appear to be immunomodulatory rather than regenerative. Based on previous studies, we hypothesized that allogeneic telomerase-positive stem cells that lack the genes for celiac disease could be safely administered therapeutically. Our hypothesis predicts that such stem cells would repair damaged tissues within the gastrointestinal system leading to a reversal of symptoms. In a small study (n=1) the results demonstrated a safe and effective treatment for celiac disease with a decline of deaminated gliadin peptide titer from 73 to < 1.0 throughout an eight-year time frame of allogeneic stem cell treatments.

Keywords
Adult, Stem Cell, Telomerase, Celiac Disease, Clinical, Regenerative Medicine.

Introduction
Celiac disease (e.g., Celiac sprue or nontropical sprue) is a chronic genetically-inherited gluten-sensitive immune-mediated enteropathic process primarily affecting the small intestinal mucosa [1-3]. It is the most common food-sensitive enteropathy in humans and is caused by the lack of immune tolerance (lack of oral tolerance) to gluten [4]. Celiac disease has an increased prevalence approaching 1% in the US population [5]. It occurs after ingestion of wheat gluten, or prolamins from barley and rye, in genetically susceptible individuals expressing the HLA-Class-II DQ2 (DQA*0501-DQB*0201), HLA-Class-II DQ8 (DQA*0301-DQB1*0302), and non-HLA genes [1,4,6,7,8]. Celiac disease probably has its origin in the shift from meat consumption to grain consumption in ancient times [3].

The immune response in celiac disease involves both the adaptive and innate portions of the immune system. It is generally accepted that it is a CD4(+) T-helper cell-mediated disease, in which gliadin
derived peptides, either in native form or deaminated by tissue transglutaminase-2, activate T-lymphocytes infiltrating the lamina propria. Celiac disease is characterized by the presence of anti-gliadin and anti-transglutaminase-2 antibodies, T-lymphocytic infiltration in the epithelial membrane and the lamina propria, and release of proinflammatory cytokines and other signaling proteins. Recent studies indicate that gliadin also contains peptides able to activate an innate immune response that act in concert with the adaptive immune response [1-3,9,10].

Celiac disease can occur at any age, expressing a variety of signs and symptoms [8]. It manifests itself as intestinal mucosal inflammation, villous atrophy, and crypt hyperplasia in the small intestinal mucosa, leading to intestinal malabsorption syndrome [1-3,10]. Several phenotypes of celiac disease exist [8]. Celiac disease can present with a variety of symptoms, including the typical GI abnormalities. However, celiac disease can present with non-GI symptoms involving the skin, liver, neurological system, and endocrine abnormalities such as hypothyroidism and/or diabetes mellitus [1-3,11]. Complications such as refractory celiac disease, ulcerative jejunoileitis, enteropathy associated T-cell lymphoma and small bowel adenocarcinoma occur in a minority of patients [5,8,12]. Many individuals with celiac disease may be asymptomatic [11].

The clinical presentation of celiac disease has changed during the past 30 years. Initially, diarrhea was the presenting symptom in greater than 90% of celiac disease patients before 1981. Now, diarrhea is the chief complaint in less than 40% of patients presenting with celiac disease. In contrast, the increased frequency of atypical celiac disease presentations, including iron deficient anemia, skin disorders and osteopenia, is revealed by the widespread availability of serologic testing. An association between celiac disease and autoimmune disorders, such as type 1 diabetes, autoimmune thyroiditis, Sjögren's syndrome, and systemic lupus erythematosus has been well documented, and found to be significantly higher in subjects with celiac disease as opposed to those without celiac disease [7,13-17]. To date, the available evidence suggests that a common genetic background is the main factor determining the high prevalence of the associations between autoimmune diseases and celiac disease [17]. While patients with celiac disease are at an increased risk of various autoimmune conditions, the duration of gluten exposure does not appear to be of crucial importance in the development of autoimmune diseases [13,14,18].

The availability of highly sensitive and specific serologic markers has dramatically facilitated the diagnosis of celiac disease. Tissue transglutaminase-2 immunoglobulin antibody and the endomysial immunoglobulin antibody are the most sensitive and specific serologic tests, respectively, for identifying individuals who need to undergo an intestinal biopsy [7]. Screening for immunoglobulin (Ig)A anti-tissue transglutaminase-2 (or TG2) is the first choice for celiac disease screening procedures. Anti-endomysial antibodies-IgA (EMA), on the other hand, have close to 100% specificity and a sensitivity of greater than 90%. The interaction between gliadin peptides and TG2 is responsible for the creation of unique antigenic epitopes, the TG2-created “deaminated gliadin peptides”. Deaminated gliadin peptides represent much more celiac disease-specific epitopes than native peptides, and their respective antibodies have shown promising results as serological markers for celiac disease [6]. However, the demonstration of characteristic histological abnormalities in a biopsy specimen of the small intestine remains the mainstay of diagnosis [1,3,5,11,19]. Small intestinal biopsy is still the most rigorous criterion in diagnosing this condition. However, transglutaminase, endomysial and deaminated gliadin peptide antibodies have gradually become more important from the point of view of the patient, especially in those with autoimmune diseases [8,20] as a method to detect celiac disease.

A gluten-free diet (GFD) is currently the only effective mode of treatment for celiac disease [2,3,19]. Exclusion of gluten from the diet reverses many disease manifestations, e.g., ulcerative jejunoileitis, small intestinal adenocarcinoma and T-cell lymphoma [8,12]. Such a diet is not as effective in cases of refractory celiac disease or associated autoimmune diseases [10]. Despite the proven benefits of the gluten-free diet, it can be exceedingly difficult to completely avoid gluten-containing foods, and adherence to a GFD is estimated to be about 40% to 90% effective [7,21]. Due to the many unforeseen problems associated with maintaining a gluten-free diet over the long term, new therapies addressing symptom control, reduced inflammation, and reversal of organ damage are being pursued [11].

Based on the advanced understanding of the pathogenesis of celiac disease, targeted nutritional therapies have been devised, i.e., modified flours and/or gluten-free grains (generated by genetic modification) that have been depleted of immunogenic gluten epitopes, gluten-degrading enzymes to be ingested with meals, and degradation of immunodominant gliadin peptides that resist intestinal proteases by exogenous endopeptidases. Additional therapies include decrease of intestinal permeability by blockade of the epithelial zonula occludens toxin receptor to prevent gluten entry across the epithelium, inhibition of intestinal TG2 activity by transglutaminase inhibitors, inhibition of gluten peptide presentation by HLA-DQ2 antagonists, modulation or inhibition of proinflammatory cytokines, and induction of oral tolerance to gluten [6,10].

Regenerative medicine strategies continue to be developed, which could provide treatments for incurable diseases. Stem cell biology is the current “holy grail” for regenerative medicine [22-24]. While still in its infancy, stem cell treatments have been proposed as an effective therapy for patients with severe refractory autoimmune diseases compared to conventional treatments, such as the gluten-free diet regimen for patients with refractory celiac and enteropathy-associated T-cell lymphoma [12,25,26]. Considering the ethical issues using embryonic stem cells with their propensity to form teratomas when implanted in the naive state [23,24], hematopoietic stem cells (CD34+) and mesenchymal stem cells (CD34-) are recommended to be the best proposed candidates for stem cell therapy [12,26-28]. Based on previous clinical studies
for neurodegenerative diseases [29,30], cardiovascular diseases [31], and pulmonary diseases [32], we would propose allogeneic adult-derived telomerase-positive stem cells, e.g., pluripotent stem cells (PSCs) and totipotent stem cells (TSCs), as another stem cell-based therapy for repairing damage to the gastrointestinal and immune systems in individuals with celiac disease.

Human endogenous adult-derived telomerase-positive pluripotent stem cells (PSCs) are >2 to <10 µm in size, express CD10 on their cell surface (CD10+), and lack expression for surface markers, normally found on hematopoietic stem cells (e.g., CD11b, CD14, CD19, CD34, CD45), mesenchymal stem cells (e.g., CD73, CD90, CD105, and HLA-DR), ectodermal stem cells (CD56, CD90, MHC Class-I), mesodermal stem cells (CD13, CD90, MHC Class-I), and/or endodermal stem cells (CD90, MHC Class-I) [33,34]. PSCs have essentially an unlimited proliferation potential as long as they remain undifferentiated in their native quiescent state. PSCs are normally located throughout all connective tissues within the body and represent less than 1.0% of all stem cells in the body. When differentiated in culture, a clone of PSCs derived by repetitive single cell clonogenic analysis displayed 60 discrete cell types of ectodermal, mesodermal, and endodermal origin, but not to sperm, ova, or notochord, when induced with general and specific induction agents, including exosomes from differentiated cell types. Previous studies have shown their usefulness for the regenerative treatment of individuals with Parkinson disease, myocardial infarction, and pulmonary diseases [22-24,29-33].

Human endogenous adult-derived telomerase-positive totipotent stem cells (TSCs) are 0.1 to 2 µm in size, express CD66e on their cell surface (CD66e+), and lack expression for surface markers, normally found on hematopoietic stem cells, mesenchymal stem cells, pluripotent stem cells, ectodermal stem cells, mesodermal stem cells, and/or endodermal stem cells. TSCs have essentially an unlimited proliferation potential as long as they remain undifferentiated in their native quiescent state. They are located throughout all connective tissues within the body and represent less than 0.1% of all stem cells in the body. When differentiated in culture three separate clones of TSCs, derived by repetitive single cell clonogenic analysis, displayed 66 discrete cell types of ectodermal, mesodermal, and endodermal origin, spermatogonia and notochord, when induced with general and specific induction agents, including exosomes from differentiated cell types. Previous studies have shown their usefulness for the regenerative treatment of Parkinson disease, myocardial infarction, and pulmonary diseases [22-24,29-33,35].

**Materials and Methods**

Allogeneic adult-derived telomerase-positive TSCs and PSCs were tested as a therapeutic modality in an IRB-approved study protocol and used to treat a 61-year-old male with celiac disease secondary to multiple autoimmune diseases of 57 years duration. In order of appearance the diagnosed and confirmed autoimmune diseases were Hashimoto’s thyroiditis, Sjögren’s disease, Scleroderma, Systemic Lupus Erythematosus (SLE), and Autoimmune Insulin Dependent Diabetes Mellitus. Autoimmune-associated diseases included Raynaud’s syndrome, multiple allergies, Interstitial Pulmonary Fibrosis, Atrial Fibrillation, Alopecia, and Transient Ischemic Attacks. Celiac disease of 10 years duration was diagnosed 19 years after his initial SLE diagnosis. The celiac disease assessment was conducted using annual serum antibody testing. In this test, the allergen of choice (deaminated gliadin peptide) is attached to sheep red blood cells, incubated with a sample of serum from the patient, and the amount of clumping of RBCs determined in a spectrophotometer. If no antibodies are present in the serum sample for that particular allergen, the value is <1.0 and denotes no allergy. If antibodies are present to the allergen in the serum sample, the value is greater than >1.0, with the higher the number (titer) of the antibody the more severe the allergy.

For celiac disease, the antibody titer to deaminated gliadin peptide was measured at 73 (the lab stated that their previous HIGH value for the deaminated gliadin peptide was 37) throughout a ten-year period (stage-III/IV SLE) prior to his first stem cell treatment at diagnosed two-week terminal stage-IV SLE. The SLE patient did not proceed with small intestinal biopsies for confirmation of celiac disease for fear that the procedure and procurement of the biopsy specimen would elicit a lupus flare, which would cause further damage to his organs.

The patient was treated with endogenous telomerase-positive autologous TSCs, PSCs, MesoSCs combined with telomerase-positive allogeneic TSCs and PSCs from gender-matched, ABO-matched, and/or O-negative donors, that were also absent of celiac disease, absent of autoimmune diseases, absent of deleterious genetic mutations, and absent of infectious diseases. Four donors met the above criteria, i.e., an A+ 42-year-old male (one harvest), an A+ 50-year-old male (two separate harvests), an O-negative 53-year-old male (two separate harvests), and an O-negative 80-year-old male (four separate harvests at ages 73, 75, 77, and 80).

The telomerase-positive stem cell treatment protocol for both donors and recipient consisted of ingestion of combinatorial nutraceuticals (DFRD, Macon, GA) daily for a minimum of 30 days prior to initial harvest and then throughout subsequent treatments, withdrawing 210 to 420cc’s of whole blood (based on body weight of the stem cell provider) for stem cell processing. 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. In this particular individual the combined autologous/allogeneic treatments consisted of autologous and allogeneic TSCs for intranasal delivery for neurogenic problems; autologous and allogeneic TSCs pooled, and diluted into 0.9% sterile saline for slow intravenous (IV) infusion for cardiovascular problems; autologous and allogeneic TSCs and PSCs pooled for nebulization for pulmonary problems; and autologous and allogeneic TSCs and PSCs and autologous MesoSCs pooled and diluted into 0.9% sterile saline for regular IV infusion for systemic problems, including celiac disease.
Results

For the eight years of combined autologous/allogeneic telomerase-positive stem cell treatments, the individual’s deaminated gliadin peptide titer was less than 1.0, he resumed eating a diet that included gluten, barley, and rye, and was free of any adverse symptoms of celiac disease. After cessation of the allogeneic telomerase-positive stem cells in the combined treatment protocol, approximately eight years after initial treatment, the symptoms associated with celiac disease slowly returned, his titer to deaminated gliadin peptide rose above 50 and he returned to his gluten-free diet.

Discussion

Celiac disease is a chronic genetically-based gluten-sensitive immune mediated enteropathy primarily affecting the small intestinal mucosa. It is the most common food-sensitive enteropathy in humans and is caused by the lack of immune intolerance (oral intolerance) to gluten. More specifically, the gliadins and glutenins of wheat (gluten), the prolamins and hordeins of barley, and the secalins of rye appear to precipitate immune intolerance in those that are genetically predisposed. The structural feature unique to all celiac disease proteins are sequence

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### Table 1: Informed Consent Guidelines for Telomerase-Positive Stem Cells for Clinical Therapy.

| ## | Description |
|----|-------------|
| 1  | Process for preparation for stem cell collection begins with a 30-day time period, and occurs throughout the course of treatment(s). |
| 2  | You will be required to avoid alcohol, tobacco products, vaping, and recreational drugs, because they kill telomerase-positive stem cells. |
| 3  | You will be required to avoid chemotherapeutic drugs and lidocaine (topical anesthetic) because they kill telomerase-positive stem cells. |
| 4  | You will be required to limit the intake of caffeine to not more than 95 mg per day up to two weeks before to two weeks after stem cell harvest/treatment, with NO caffeine during the 4-week harvest/treatment time period, because caffeine alters the differentiation potential of telomerase-positive stem cells. |
| 5  | You are requested to limit your intake of corticosteroids, i.e., prednisone, to zero if possible, because steroids prematurely induce telomerase-positive stem cells (TSCs and PSCs) to become mesodermal stem cells (MesoSCs). |
| 6  | You will need to consume Nutraceutical capsules daily, based on body weight, with one capsule taken for every 50 lbs body weight, i.e., 1-50-lbs = 1 capsule, 51-100-lbs = 2 capsules, 101-150-lbs = 3 capsules, 151-200-lbs = 4 capsules, etc. The formulated Nutraceuticals induce telomerase-positive stem cells to proliferate throughout all the connective tissues of your body. |
| 7  | You will need to drink plenty of fluids two weeks prior to stem cell harvest, approximately 6-8 glasses of non-alcoholic, non-cafeinated beverages daily. |
| 8  | You must abstain from any moderate to excessive physical activity 72 hours before stem cell harvest and one week after stem cell treatment. |
| 9  | You must limit any physical activity for 24 hours before to 24 hours after blood harvest/stem cell treatment. |
| 10 | If you are traveling from a distance more than a day’s travel time, the second day after you arrive is the day of rest for 24 hours before stem cell harvest. |
| 11 | Eighteen hours before your scheduled harvest you will take another supplement known as Glacial Caps. The Glacial Caps mobilize the proliferated telomerase-positive stem cells throughout the body into the blood stream. |
| 12 | On blood harvest day, an intravenous catheter will be placed in your arm. You will be given 250-ml (cc’s) of sterile normal saline through the access line. The purpose of the saline is to better hydrate you to dilate your blood vessels, allowing the blood to flow more freely. Immediately after hydration, 7 to 14 ounces (210 to 420 cc’s) of blood will be collected. |
| 13 | Donors: Because your mesodermal stem cells contain unique markers on their surface that distinguish you from everyone else and may react with the recipient’s immune system, your mesodermal stem cells will not be used. Therefore, you may or may not opt to have your mesodermal stem cells returned to you by intravenous infusion. |
| 14 | Blood may be harvested once every two months. |

Each participant with an illness that has entered the study will attempt to use their own cells to help them heal. However, the degree of illness in some participants is so great that they are not able to heal using their own cells. In this case a donor may be considered as a source for other telomerase-positive stem cells. This donor must be the same gender, have the same blood type or O-negative blood, and be relatively healthy. An initial history and physical exam will be performed on the donor by the screening physician followed by a series of basic screening labs to determine your overall health and if you have any communicable diseases to which the patient has not already been exposed. If you do, then you would be disqualified as a donor for that particular patient. If you do not have any significant health problems, then you may be considered as a donor for a given patient. The basic screening labs include kidney function tests, liver function tests, complete blood cell counts, bacterial screens, and viral screening tests including: HIV and Hepatitis. If these tests return with an abnormal result you will be notified and in the case of HIV or hepatitis, we may have to report your test result to the CDC. It is also possible that researchers will perform Genome Sequencing on your blood to determine genetic information that will help the researcher better understand how your cells may help the person who receives them. By signing below, you agree to allow your lab results to be sent to the appropriate governing body in the case of a communicable disease if it is mandated by law and you agree to allow us to perform genetic sequencing on your cells if it is determined to be useful to the study.

Table 2: How I Qualified to Be a Stem Cell Donor and What Happens to my Blood Sample.
domains rich in glutamine and proline, which accumulate in the small intestine due to their resistance to proteolytic digestion. They go on to incite a rapid innate response characterized by release of IL-15 and a drastic increase in intraepithelial lymphocytes.

The secondary adaptive response includes the binding of gluten peptides to HLA-DQ2 or HLA-DQ8 of antigen presenting cells (APCs) and the subsequent release of interferon-gamma and matrix metalloproteinases from T-cells. T-cells induce B-cells to produce IgA and IgG antibodies against gluten proteins and tissue transglutaminase. This cascade of events leads to epithelial apoptosis and subsequent intestinal mucosal injury [48].

Celiac disease can occur at any age and express a wide variety of signs and symptoms. A gluten-free diet is currently the only effective mode of treatment. While exclusion of gluten from the diet reverses many disease manifestations, it usually does not or is less efficient in patients with refractory celiac disease or associated autoimmune diseases. Targeted therapies to address both the nutritional and functional aspects of the disease have been devised, such as gluten-free grains and inhibition of proinflammatory cytokines. Currently, much of the promise for treating chronic and incurable diseases is centered on stem cell biology. Phase-I clinical trials using mesenchymal stem cells have demonstrated that the stem cells can be safely administered, and their effects appear to be immunomodulatory rather than regenerative.

Stem cell treatments represent a new therapeutic regimen in biomedical science which could in the future provide cures for diseases that up until now have been incurable, such as celiac disease [28]. Stem cell treatment is an effective therapy for patients with severe refractory autoimmune diseases compared to conventional treatments, like the ineffective gluten-free diet regimen for patients with refractory CD and enteropathy-associated T-cell lymphoma [12,25,26]. Considering the ethical issues using embryonic stem cells [23,24], hematopoietic stem cells and mesenchymal stem cells are recommended to be the best proposed candidates for stem cell therapy [12,26-28].

Hematopoietic stem cells can be used in the treatment of a number of diseases [12,26,28,36,37]. The rationale for this strategy is based on the concept of myeloablation using high-dose chemotherapy, followed by infusion of HLA-matched hematopoietic stem cells which differentiate into naïve T-cells. This regimen results in prompt remission in the treated patients [36,37].

Mesenchymal stem cells are multipotential stromal cells that can differentiate into a variety of cell types, such as myocytes, adipocytes, osteoblasts, and chondrocytes [27,38]. They can be isolated from adipose tissue, fetal tissues, muscle connective tissue, placenta and umbilical cord [27,39]. Three minimal criteria need to be met to be identified as a MSC: plastic-adherence under standard culture conditions; capability to differentiate into adipocytes (fat), osteoblasts (bone), and chondrocytes (cartilage) in vitro; expression of CD73, CD90, and CD105 cell surface markers and lack of expression of CD11b, CD14, CD19, CD34, CD45, and HLA-DR cell surface markers [27,40]. Their lack of immunogenicity makes MSCs a promising candidate for transplantation in the absence of myeloablation conditioning that is necessary for hematopoietic stem cell therapy [26,27,36,37,41]. 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, which makes them a suitable option for stem cell therapies [26,27,42]. The protective effects of MSCs are via the paracrine exertion of protective molecules like indoleamine-2,3-deoxygenase, prostaglandin E2 (PGE2), nitric oxide, and insulin-like growth factor (IGF), rather than differentiation into end-organ cells [27,43].

Based on previous studies, we hypothesize the use of an endogenous adult stem cell type that has the capability of differentiating into end-organ cells, with a subsequent loss of disease symptoms. This contrasts with the immunomodulatory effects of mesenchymal stem cells or the prerequisite of high dose chemotherapy to kill the immune system and then finding an appropriate match to allogeneic hematopoietic stem cells. The stem cell type proposed are endogenously-derived adult gender-matched and ABO-blood group-matched allogeneic telomerase-positive stem cells, specifically pluripotent stem cells and totipotent stem cells. Both stem cells have been shown in culture to differentiate into cells of the gastrointestinal system, e.g., epithelial lining cells, cells within the lamina propria, smooth muscle cells, cells of the submucosa, blood vessels, nerve ganglia, nerve cells, nerve fibers, and connective tissue cells, as well as cells of the immune system [22,24,29,33,35].

We chose not to use allogeneic telomerase-positive mesodermal stem cells (MesoSCs) for treatment because these cells express MHC Class-I cell surface markers that distinguish self from non-self. It was our fear that allogeneic MesoSCs, even from a gender-matched/ABO blood group-matched individual would elicit a graft versus host disease (GVHD) response which would be detrimental either to the donor cells or to the recipient [44,45]. Therefore, the stem cells utilized for these treatments were a combination of telomerase-positive allogeneic TSCs and PSCs and telomerase-positive autologous TSCs, PSCs, and MesoSCs.

Telomerase is an enzyme that adds a telomere to the end of each chromosome during cell division to maintain an essentially unlimited proliferation potential [46]. Once the telomerase enzyme is lost due to differentiation of the cell, it assumes a biological clock of 70 population doublings before pre-programmed senescence and cell death occurs [47].

We utilized four separate donors for the combined allogeneic/autologous telomerase-positive 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 80-year-old male (four separate harvests).
Telomerase-negative mesenchymal stem cells have a defined biological clock of 50-70 population doublings before programmed senescence and cell death [45], with their biological clock starting at birth. Therefore, to get the most cell doublings per stem cell it has been proposed to use “as young as possible” mesenchymal stem cells, i.e., derived from umbilical cords, newborns, or young adults.

In contrast, our “best” donor was a healthy 80-year-old male, at time of last harvest. Being telomerase-positive, his stem cells have an unlimited proliferation potential if they remain undifferentiated. Once they begin to differentiate and lose the telomerase enzyme, they assume all the characteristics of telomerase-negative stem cells with a biological clock beginning at 70 population doublings before the cells undergo pre-programmed senescence and die.

Of the nine telomerase-positive stem cell treatments attempted including the use of allogeneic stem cells, eight treatments were successful and one treatment did not work. The one combined autologous/allogeneic treatment that did not work was due to a serious ankle/foot injury that occurred to the patient two weeks before the scheduled stem cell transplant. Due to the scheduling logistics of having the physician (in-state), isolator (out-of-state), patient (out-of-state), and donors (in-state and out-of-state), present on the same day and same time, the treatment went on as previously scheduled. The reason for failure, however, was that all the telomerase-positive stem cells (both autologous and allogeneic) were directed by his body to treat the previous ankle/foot injury, which admittedly was life threatening, in less than a week with no subsequent scarring. In contrast, none of the individual’s ongoing problems and directed treatments, i.e., neurogenic (TSC - intranasal), cardiovascular (TSC - slow IV), pulmonary (TSC and PSC - nebulized), or systemic (TSC, PSC, and autologous MesO SCs - regular IV) showed any decline in their problem-associated symptoms. This led us to conclude that if an individual has a life-threatening condition, that that condition will be repaired first no matter where the activated telomerase-positive stem cells are placed within the body.

Conclusion
The results from this study, albeit with a very small sample size (n=1) demonstrated a loss of antibodies to the deaminated gliadin peptide throughout a ten-year titer average of 73 to a titer of less than 1.0 during an eight-year time frame. This time frame coincided exactly with their allogeneic telomerase-positive stem cell treatments. During that eight-year time frame the individual ate a normal gluten-containing diet with no adverse side effects. Approximately one year after the allogeneic transplants stopped, the individual slowly resumed signs and symptoms of severe celiac disease, his gliadin titer rose above 10, and he is currently on a gluten-free diet. We hypothesize that continued treatments with telomerase-positive stem cells from compatible allogeneic donors absent of celiac disease should continue to rescue this individual from the ravages of his autoimmune diseases, including celiac disease.

To increase our sample size and verify the capabilities of the telomerase-positive stem cells as an interventional biological therapy for celiac disease, we propose the following Phase-II randomized double-blinded placebo-controlled studies. We propose using an expanded population of individuals diagnosed with very severe celiac disease (deaminated gliadin peptide titer above 50) and comparing telomerase-positive allogeneic TSCs and PSCs to telomerase-negative allogeneic mesenchymal stem cells (MSCs) to determine which population of allogeneic stem cells, TSCs/PSCs versus MSCs, is better suited to repair gastrointestinal and immune tissues and reverse the symptoms of celiac disease.

References
1. Cardenas A, Kelly CP. Celiac sprue. Semin Gastrointest Dis. 2002; 13: 232-244.
2. Briani C, Samaroo D, Alaedini A. Celiac disease: from gluten to autoimmunity. Autoimmun Rev. 2008; 7: 644-650.
3. Freeman HJ. Celiac disease: a disorder emerging from antiquity, its evolving classification and risk, and potential for new treatment paradigms. Gut Liver. 2015; 90: 28-27.
4. Rossi M, Maurano F, Luongo D. Immunomodulatory strategies for celiac disease. Int Rev Immunol. 2005; 24: 479-499.
5. Al-Bawardy B, Codipilly DC, Rubio-Tapia A, et al. Celiac disease: a clinical review. Abdom Radiol (NY). 2017; 42: 351-360.
6. Setty M, Hormaza L, Guandalini S. Celiac disease: risk assessment, diagnosis, and monitoring. Mol Diagn Ther. 2008; 12: 289-298.
7. Nadhem ON, Azeez G, Smalligan RD, et al. Review and practice guidelines for celiac disease in 2014. Postgrad Med. 2015; 127: 259-265.
8. Caio G, Volta U, Sapone A, et al. Celiac disease: a comprehensive review. BMC Med. 2019; 17: 142.
9. Giangani C, Auricchio S, Troncone R. Adaptive and innate immune responses in celiac disease. Immunol Lett. 2005; 99: 141-145.
10. Schuppan D, Junker Y, Barisani D. Celiac disease: from pathogenesis to novel therapies. Gastroenterology. 2009; 137: 1912-1933.
11. Rubio-Tapia A, Hill ID, Kelly CP, et al. American College of Gastroenterology clinical guidelines: diagnosis and management of celiac disease. Am J Gastroenterol. 2013; 108: 656-676.
12. Ondreika A, Jagadeesh D. Enteropathy-associated T-cell lymphoma. Curr Hematol Malig Rep. 2016; 11: 504-513.
13. Satenga-Guidetti C, Solero E, Scaglione N, et al. Duration of gluten exposure in adult coeliac disease does not correlate with risk for autoimmune disorders. Gut 2001; 49: 502-505.
14. Viljamaa M, Kaukinen K, Huhtala H, et al. Coeliac disease, autoimmune diseases and gluten exposure. Scand J Gastroenterol. 2005; 40: 437-443.
15. Mirza N, Bonilla E, Phillips PE. Celiac disease in a patient with systemic lupus erythematosus: a case report and review of the literature. Clin Rheumatol. 2007; 26: 827-828.
16. Iqbal T, Zaidi MA, Wells GA, et al. Celiac disease arthropathy and autoimmunity study. J Gastroenterol Hepatol. 2013; 28:
17. Diamanti A, Capriati T, Bizzarri C, et al. Autoimmune diseases and celiac disease which came first: genotype or gluten? Expert Rev Clin Immunol. 2016; 12: 67-77.

18. Ouaka-Kchaou A, Ennaifer R, Elloumi H, et al., Autoimmune diseases in coeliac disease: effect of gluten exposure. Therap Adv Gastroenterol. 2008; 1: 169-172.

19. Shannahen S, Leffler DA. Diagnosis and updates in celiac disease. Gastrointest Endosc Clin N Am. 2017; 27: 79-92.

20. Sayed SK, Imam HM, Mabran AM, et al. Diagnostic utility of deaminated gliadin peptide antibody in celiac disease compared to anti-tissue transglutaminase and IgA-endomysium antibodies. Egypt J Immunol. 2012; 19: 41-52.

21. Abu-Janb N, Jaana M. Facilitators and barriers to adherence to gluten-free diet among adults with celiac disease: a systemic review. J Hum Nutr Diet. 2020.

22. Young HE, Duplaa C, Romero-Ramos M, et al. Adult reserve stem cells and their potential for tissue engineering. Cell Biochem Biophys. 2004; 40: 1-80.

23. Young HE, Speight MO, Black AC Jr. Functional Cells, Maintenance Cells, and Healing Cells. J Stem Cell Res. 2017; 1: 003: 1-4.

24. Young HE, Black AC. Pluripotent Stem Cells, Endogenous versus Reprogrammed, a Review. MOJ Orthop Rheumatol. 2014; 1: 72-90.

25. Biagi F, Gobbi P, Marchese A, et al. Low incidence but poor prognosis of complicated coeliac disease: a retrospective multicentre study. Dig Liv Dis. 2014; 46: 227-230.

26. Ciccocioppo R, Canegmi GC, Roselli EA, et al. Are stem cells a potential therapeutic tool in coeliac disease. Cell Mol Life Sci. 2015; 72: 1317-1329.

27. Moheb-Alian A, Forouzesh F, Rostami-Nejad M et al. Mesenchymal stem cells as potential therapeutic approaches in celiac disease. Gastroenterol Hepatol Bed Bench. 2016; 9: S1-S7.

28. Iacob R, Sirbu-Boeti P, Iacob S, et al. Stem cell therapies for gastrointestinal and liver diseases. Chirurgia (Bucur). 2009; 104: 131-140.

29. Young HE, Hyer L, Black AC Jr, et al. Treating Parkinson disease with adult stem cells. J Neurol Disorders. 2013; 2: 1.

30. Young HE, Hyer L, Black AC Jr, Robinson JS Jr. Adult stem cells: from bench-top to bedside. In: Tissue Regeneration: Where Nanostructure Meets Biology, 3DBiotech, North Brunswick, NJ. 2013; 1: 1-60.

31. Young HE, Limnios JJ, Lochner F, et al. Adult healing cells and cardiovascular disease: From bench top to bedside. J Stem Cell Res. 2017; 1: 1-8.

32. Young HE, Black GF, Coleman JA, Hawkins KC, Black Jr AC. Pulmonary diseases and adult healing cells: from bench top to bedside. J Stem Cell Res. 2017; 1: 1-9.

33. Young HE and Black Jr AC. Naturally occurring adult pluripotent stem cells. In: Stem Cells: From Biology to Therapy, Advances in Molecular Biology and Medicine. 1st Ed, R.A. Meyers, Ed, WILEY-BLACKWELL-VCH Verlag GmbH & Co. KGaA. 2013; 3: 63-93.

34. Young HE, Steele T, Bray RA, et al. Human progenitor and pluripotent cells display cell surface cluster differentiation markers CD10, CD13, CD56, CD90 and MHC Class-I. Proc Soc Exp Biol Med. 1999; 221: 63-71.

35. Young HE, Black AC Jr. Adult-derived stem cells. Minerva Biotechnologica Cancer Gene Mechanisms and Gene Therapy Reviews 2005; 17: 55-63.

36. 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: 77-89.

37. Al-Toma A, Visser OJ, van Roessel HM, et al. Autologous hematopoietic stem cell transplantation in refractory celiac disease with aberrant T cells. Blood. 2007; 109: 2243-2249.

38. Ding DC, Shyu WC, Lin SZ. Mesenchymal stem cells. Cell Transplant. 2011; 20: 5-14.

39. Charbord P. Bone mesenchymal stem cells: historical overview and concepts. Hum Gene Ther. 2010; 21: 1045-1056.

40. Dominici M, Le Blanc K, Mueller I, et al. Minimal criteria for defining multipotent mesenchymal stromal cells. The International Society for Cellular Therapy position statement. Cytotherapy. 2006; 8: 315-317.

41. Barry FP, Murphy JM, English K, et al. Immunogenicity of adult mesenchymal stem cells: lessons from the fetal allograft. Stem Cells Dev. 2005; 14: 252-265.

42. Gonzalez MA, Gonzalez-Rey E, Rico L, et al. Adipose-derived mesenchymal stem cells alleviate experimental colitis by inhibiting inflammatory and autoimmune responses. Gastroenterology. 2009; 136: 978-989.

43. Siegel G, Schafer R, Dazzi F. The immunosuppressive properties of mesenchymal stem cells. Transplantation. 2009; 87: S45-S49.

44. Abbas AK, Lichtman AH, Pillai S. In: Cellular and Molecular Immunology. Elsevier, Saunders, Chap. 6, 2012.

45. Kumar V, Abbas AK, Fausto M, et al. In: Robbins and Cotran Pathologic Basis of Disease. Elsevier, Saunders. 2010; 226-230.

46. Zvereva MI, Shcherbakova DM, Dontsova OA. Telomerase: structure, functions, and activity regulation. Biochemistry (Mosc). 2010; 75: 1563-1583.

47. Hayflick L, Moorehead PS. The serial cultivation of human diploid cell strains. Exp Cell Res 1961; 25: 585-621.

48. Weiser H, et al. The Biochemical Basis of Celiac Disease, Cereal Chemistry. 2008; 85.