ABSTRACT

Chronic inflammatory demyelinating polyneuropathy, e.g., chronic inflammatory demyelinating polyradiculoneuropathy (CIDP), is a rare autoimmune mediated peripheral neuropathy. CIDP is defined as symptomology of greater than two months duration and electro diagnostic evidence of peripheral nerve demyelination. The estimated overall prevalence of CIDP is 4.8 to 8.9 cases per 100,000 people. Symptomology includes motor, sensory, and autonomic involvement resulting in symmetrical proximal and distal muscle weakness, loss of strength, areflexia of greater than eight weeks duration, numbness, weakness, sensory ataxia, paresthesia, decreased peripheral temperature, and gait disorder. As CIDP progresses there is axonal loss within mixed peripheral nerves secondary to demyelination, which is associated with a poor prognosis. Autoantibodies identified for CIDP thus far include contactin-1 (CNTN1), contactin-associated protein-1 (Caspr1), contactin-2 (CNTN2), neurofascin-155 (Nfasc-155), neurofascin-140/186 (Nfasc-140/186), L1, gliomedin, and vinculin. Another marker of CIDP is sphingomyelin protein in the cerebral spinal fluid. Potential treatment options for CIDP are first-line therapies, such as corticosteroids, plasma exchange, and/or immunoglobulins. If patients are refractory to first-line treatments to halt progression of the disease, then second-line therapies, such as chemotherapeutic drugs, immunosuppressive drugs, and/or immunomodulatory drugs, are utilized. Lastly, if first- and second-line therapies fail, novel unconventional therapies have been utilized, such as high-dose cyclophosphamide to eradicate a defective immune system containing CIDP-associated autoantibodies to nodal and paranodal proteins. This is then followed with either autologous or HLA-matched allogeneic hematopoietic stem cell transplantation (HSCT) with the intent to replace the defective immune system with a normal immune system absent of CIDP-associated autoantibodies. Whatever therapeutic treatment regimen(s) is/are utilized, maintenance treatments are required for years to maintain stasis in individuals with CIDP. Unfortunately, while first-line, second-line, and/or HSCT treatments may halt the progression of the CIDP and maintain individuals in stasis, they do little to restore neurophysiological function to the individual. We proposed an alternative unconventional therapy to treat CIDP, the use of adult autologous adult telomerase positive stem cells to halt progression of the disease and restore (neuro-) physiological function to the tissues. This hypothesis was based on previous clinical studies utilizing telomerase positive stem cells with Parkinson disease, Alzheimer’s disease, age-related dry macular degeneration, traumatic blindness, traumatic spinal cord injury, myocardial infarction, chronic obstructive pulmonary disease, idiopathic pulmonary fibrosis, celiac disease, systemic lupus erythematosus, and osteoarthritis. Within this small cohort (n=3) clinical study, there were no adverse events reported for any participant treated. While there was no direct proof that the autologous telomerase positive stem cells contributed to the results seen in two of these participants, there was indirect proof for restoration of neurophysiological functions. This was demonstrated with respect to return of motor, sensory, and autonomic functions, e.g., increased strength, return of sensory input, return of reflexes, loss of numbness, increased blood flow, normal body temperature in extremities, and normal gait. Indirectly, this suggested that autologous telomerase positive stem cells are safe and demonstrate a 66% efficacy with respect to halting progression of chronic inflammatory demyelinating polyneuropathy and restoration of neurophysiological functions.
Keywords
Telomerase, Positive, Stem Cells, Totipotent, Pluripotent, Mesodermal, CIDP, Nodal, Paranodal, Autoantibodies, Corticosteroids, Plasmapheresis, IVIg, Chemotherapeutic Drugs, Immunosuppressive Drugs, Immunomodulatory Drugs, HSCT, Neurophysiology.

Introduction
First described almost 50 years ago, chronic inflammatory demyelinating polyneuropathy (e.g., chronic inflammatory demyelinating polyradiculoneuropathy, CIDP) is a rare autoimmune mediated peripheral neuropathy. According to the European Federation of Neurological Societies/Peripheral Nerve Society criteria, CIDP is defined by a clinical presentation of greater than two months duration and electro diagnostic evidence of peripheral nerve demyelination [1-5]. CIDP has an estimated incidence of 0.7 to 1.6 cases per 100,000 persons per year. The overall prevalence is 4.8 to 8.9 cases per 100,000 persons [3]. It was initially described in 1975 as a chronic inflammatory demyelinating polyradiculoneuropathy, but cases consistent with CIDP were described as early as 1958 [6,7]. More than half of the people affected with CIDP cannot walk unaided when symptoms are at their zenith. CIDP has a variable progression that can be relapsing-remitting, stepwise progressive, or gradually progressive [6]. CIDP may or may not respond to current conventional first-line or second-line treatments or novel unconventional treatments, and is dependent on the clinical course of the disease [8].

There are several forms of inflammatory demyelinating polyneuropathy (IPD), dependent on their duration of activity, e.g., acute inflammatory demyelinating polyneuropathy (AIDP) versus acute-onset chronic inflammatory demyelinating polyneuropathy (CIDP). Both IPDs present with similar symptomology during the early stages of disease progression (up to eight weeks), but differ as CIDP progresses beyond eight weeks duration. Similarities during first eight weeks include human immunodeficiency virus status; presence of autoimmunity disorders; presence of oncogenic diseases; cranial, motor, and autonomic nerve involvements; hospital admissions; and mortality rates. However, AIDP patients showed an increase in proinflammatory disturbances, sensory ataxia, and treatment success when corticosteroids were combined with intravenous immunoglobulins (IVIg) [11].

There are several clinical types of CIDP that can be described as either “typical CIDP” or “atypical CIDP” [1,12]. Typical CIDP is the most common form and is characterized by symmetrical proximal and distal muscle weakness predominantly effecting motor fibers. Demyelination predominantly affects distal nerve terminals and nerve roots, where the blood-nerve barrier is anatomically deficient, which suggests an antibody-mediated demyelination of the nerve [1]. Atypical CIDP affects both motor and sensory fibers of a mixed nerve. It is characterized by multifocal demyelination of nerve trunks, resulting in asymmetrical polyneuropathy. In atypical CIDP, cellular immunity is likely to be involved in the breakdown of the blood-nerve barrier at the site of the conduction blocks [1]. The therapeutic treatment of CIDP is dependent on the form of CIPD expressed in the individual, whether it is either typical CIDP or atypical CIDP [1].

The signs and symptoms of CIDP can be confused with other neurological diseases, such as Guillain-Barre syndrome (GBS), and in non-GBS that may mimic its symptoms, such as genetic neuropathy, diabetic neuropathy, and chronic idiopathic axonal polyneuropathy. Electrophysiological misinterpretations led to non-GBS diagnoses due to the following. 1) Diagnosis of CIDP is challenging, some patients with severe early axonal damage do not fully fit the criteria for CIPD. 2) There is a heterogeneous slowing of nerve conduction. 3) Objective and reliable tools to monitor progression of CIDP are lacking. 4) In CIDP there are sensory and motor symptoms in proximal and distal segments of multiple limbs with areflexia of more than eight weeks duration. 5) In non-GBS there are sensory and motor symptoms in intermediate segments of one or more limbs with areflexia of less than eight weeks duration. 6) ~25% of patients do not respond to the first-line therapies for CIDP, including IVIg. 7) ~15% of patients do not respond to either first-line or second-line treatment therapies for CIDP. And 8) recognition of these patients is difficult and further treatment is based solely on observational studies [13,14].

In CIDP, humoral and cellular components of a person’s immune system attack myelin on large peripheral nerve fibers that lead to demyelination. General demyelination is expressed as slowed conduction velocities, temporal dispersion, and conduction block, and as segmental demyelination, it is expressed as onion bulb formation and endoneurial inflammatory infiltrates. These manifestations result in numbness, weakness, sensory ataxia, areflexia, and paresthesia. As the disease progresses, axonal loss occurs secondary to demyelination and is associated with a poor prognosis [6,15,16].

No single autoantibody has been identified as a biomarker for Schwann cell Para nodal and nodal proteins associated with CIDP. Autoantibodies identified for CIDP thus far include contactin-1 (CNTN1), contactin-associated protein-1 (Caspr1), contactin-2 (CNTN2), neurofascin-155 (Nfasc-155), neurofascin-140/186(Nfasc-140/186), LM1, gliomedin, and vinculin. Individuals expressing these autoantibodies are considered seropositive for CIDP [17-26]. Other biomarkers for CIDP are the presence of sphyngomyelin in cerebral spinal fluid [27]. Some of the autoantibodies may have diagnostic significance, while others may predict response of an individual to immunomodulation drugs. For example, contactin-1 autoantibodies have been associated with later onset of CIDP and a more aggressive progression of the disease [28,29].

Therapeutic Treatment Options for CIDP
Potential treatment options explored for CIDP are first-line therapies, such as corticosteroids (e.g., prednisone, methylprednisolone, dexamethasone (oral, intravenous, intramuscular, or subcutaneous – pulse or continuous dosing)), plasma exchange (PE, plasmapheresis with immune adsorption), and/or immunoglobulins (delivered by subcutaneous or
intravenous infusion). Second-line therapies utilized are chemotherapeutic drugs (e.g., cyclophosphamide, methotrexate), immunosuppressive drugs (e.g., interferon-alpha (IFN-α), INF-β1a, azathioprine, mycophenolate mofetil, fingolimod, bortezomib), and/or immunomodulatory monoclonal antibodies (e.g., rituximab, eculizumab, natalizumab, alemtuzumab). Lastly, novel unconventional therapies have been utilized, such as autologous or HLA-matched allogeneic hematopoietic stem cell transplantation (HSCT) following high-dose cyclophosphamide to eradicate the defective immune system [3,6,26,30-42].

First-Line Therapies for CIDP
Corticosteroids, e.g., prednisone, methylprednisolone, dexamethasone (oral, intravenous, intramuscular, or subcutaneous – pulse or continuous dosing) are used to inhibit the activity of phospholipases following tissue damage. Phospholipases are endogenous enzymes that convert damaged cell membrane phospholipids to form arachidonic acid. Arachidonic acid is the rate-limiting precursor in the formation of promoters of inflammation, e.g., prostaglandins, prostacyclins, thromboxanes, leukotrienes, hydroxyeicosatetraenoic acid (HETE), and hydroxyperoxyeicosatetraenoic acid (HPETE). Corticosteroids also act by reducing the transcription of genes encoding cyclooxygenase-2 (COX-2), phospholipase A2, and proinflammatory cytokines, such as interleukin-1 (IL-1), tumor necrosis factor (TNF), and nitric oxide synthase (iNOS) [43].

Plasma exchange is an option for treatment of autoimmune-generated neuropathies, such as CIDP. Frequent plasmapheresis combined with immune adsorption prolongs the reduction of autoantibodies to Schwann cell nodal and para nodal proteins, which may be required for effective long-term treatment [44-47].

Intravenous immunoglobulins are the cornerstone for the treatment of CIDP and are generally well tolerated. However, numerous adverse reactions ranging from mild to severe have been reported [32]. In the United States, 87% of responding community neurologists cited criteria other than those in the European Federation of Neurological Societies/Peripheral Nerve Society guidelines for the treatment of CIDP. Intravenous immunoglobulin is the preferred treatment of choice for patients with CIDP. These additional criteria included variations in disease course, lack of biomarkers, variability in treatment approaches regarding beginning dose of IVIg, length of IVIg therapy, outcome measures, fear of deterioration after stopping long term IVIg treatment and protocols for weaning off IVIg therapy. The finding that ~50% of community neurologists endorsed electro diagnostic criteria that did not support a CIDP diagnosis, indicated difficulties in relying heavily on neurophysiological findings. More education on CIDP diagnosis and treatment, and a clear and clinically focused guideline would enhance best practices, particularly in the current climate of multiple guidelines and increased information [48-51].

Predominant autoantibody isotypes to Schwann cell para nodal and nodal proteins were immunoglobulin-G4 (IgG4), IgG3, and IgG1. Patients that were seropositive for autoantibody isotypes IgG3 and IgG1 proved responsive to first-line IVIg treatments [52].

Second-Line Therapies for CIDP
In contrast, individuals with IgG4 autoantibody-associated CIDP included symptomology of onset before age 30, severe neuropathy, areflexia, subacute onset, sensory ataxia, tremor (e.g., high amplitude, low frequency, postural, and intention), and demonstrated a poor response to first-line treatments, such as IVIg. This suggested the possibility of responsiveness to second-line treatments. Chemotherapeutic high-dose cyclophosphamide can be given to refractory CIDP patients with disease persistence after standard first-line therapies and, dependent on the individual patient, may have a response that lasts over three years, with long-term remission of the disease [52]. Chemotherapeutic treatment with cyclophosphamide and methotrexate, and immunotherapeutic treatment with rituximab proved effective in IVIg-resistant IgG4 seropositive CIDP individuals. Therefore, testing for autoantibody IgG isotype should ultimately be a part of diagnostic workup to guide subsequent treatments [21,28,29].

Various associations have been shown between autoantibodies and CIDP clinical presentations. For example, anti-contactin-1 and anti-neurofascin-155 are the first pathogenic autoantibodies associated with CIDP; anti-neurofascin-155 has been associated with tremors, ataxia, and poor response to IVIg; anti-contactin-1 has been associated with nephrotic syndrome; complement-fixing IgG3 antibodies targeting para nodal proteins have been associated with acute-onset CIDP; and IgG3 antibodies are used to select CIDP patients for rituximab treatment [53].

CIDP has a variable course and treatment response. A few patients experience a cure or remission (stasis), whereas a majority of CIDP patients treated with first-line and second-line therapeutics continues progression of the disease despite treatment prognosis [3,6,54,55]. Reasons for therapeutic failure in patients with CIDP are alternative diagnoses and inadequate therapies. Certain electrophysiological features and clinical tests, e.g., CSF sphyngomyelin, specific autoantibodies to para nodal proteins, and immunoglobulin isolates, help identify true CIDP versus other neurological diseases that mimic its symptoms. Once true CIDP is confirmed, optimization of therapeutic treatments may result in consistent improvement [56]. The symptomology of pain, intermediate rather than proximal or distal electrophysiological findings, systemic rather than limb-based symptoms, and/or monoclonal serum protein rather than sphyngomyelin in the cerebral spinal fluid, should raise suspicion for alternative diseases that mimic CIDP with potential adverse outcomes if given first-line and second-line CIDP therapeutics to halt progression of their disease [57].

Maintenance treatments are required for years and must be carefully regulated to prevent under-treatment or overtreatment. Patients who do not improve, or insufficiently improve following treatment, usually have immunoglobulin G4 antibodies to node of
CIDP, utilizing adult autologous telomerase positive stem cells, to take an alternative novel therapeutic approach to the treatment of a restoration of function to the individual. In that respect, we have progression of CIDP. None of these therapeutic treatments offers Unfortunately, currently the first-line, second-line, and/or immunomodulatory pretreatment regimens to eradicate a defective hematopoietic stem cell transplantation therapy still involves risks to the patient, due to latent induced comorbidities caused by high-dose intravenous chemotherapeutic, thymoglobulin, and intravenous rituximab (antibody to CD20, most or all B-cells) [62].

Hematopoietic stem cell transplantation is a novel unconventional therapy that provides the possibility for CIDP remission (stasis). Clinical symptomology with electrophysiological evidence shows that a majority of patients utilizing this therapy improve. However, hematopoietic stem cell transplantation therapy still involves risks to the patient, due to latent induced comorbidities caused by high-dose intravenous chemotherapeutic, thymoglobulin, and immunomodulatory pretreatment regimens to eradicate a defective immune system before HSC transplantation therapy can occur [63].

Unfortunately, currently the first-line, second-line, and/or hematopoietic stem cell transplantation therapies only slow or halt progression of CIDP. None of these therapeutic treatments offers a restoration of function to the individual. In that respect, we have taken an alternative novel therapeutic approach to the treatment of CIDP, utilizing adult autologous telomerase positive stem cells, to regenerate/restore myelinated mixed nerves within the extremities to restore neurophysiological function. This therapy is based on the ability of these adult derived telomerase positive stem cells to migrate to damaged tissues within the body and repair the damage to the appropriate level to restore function to the damaged organ/tissues. Safety and efficacy of using telomerase positive stem cells for restoration of function has been shown in previous clinical studies for Parkinson disease [64-66], Alzheimer’s disease [67], age-related dry macular degeneration [68], traumatic blindness [69], traumatic spinal cord injury [70], myocardial infarction [71,72], chronic obstructive pulmonary disease [73,74], idiopathic pulmonary fibrosis [74,75], celiac disease [76], systemic lupus erythematosus [77], and osteoarthritis [78] (Table 1).

In this small cohort clinical study (n=3), three patients refractory to established CIDP therapies were treated with their own autologous adult-derived telomerase positive totipotent stem cells, pluripotent stem cells, and mesodermal stem cells. Totipotent stem cells were given by intranasal topical application, while pluripotent stem cells and mesodermal stem cells were delivered by intravenous infusion. Results post-transplant demonstrated that two of the three persons treated regained proprioceptive (balance) and sensory and motor functions to their extremities during their respective time-period(s) of treatment. The individual that demonstrated no change in their symptomology did not follow informed consent guidelines throughout their treatments. Since no adverse reactions were reported from any participant, treatment with adult autologous telomerase positive stem cells proved to be both safe and 66% efficacious in restoring neurophysiological functions in participants with diagnosed chronic inflammatory demyelinating polyneuropathy.

Materials and Methods
Autologous adult telomerase positive stem cells, e.g., totipotent stem cells, pluripotent stem cells, and mesodermal stem cells, were utilized in an IRB-approved study protocol for neurodegenerative diseases. Inclusion criteria were any female or male, aged 18 to 120, with diagnosed chronic inflammatory demyelinating polyneuropathy or chronic demyelinating polyradiculoneuropathy (CIDP). In addition, participants in this study were diagnosed as being refractory to established CIDP therapeutic treatments.

Participants were mandated to follow the informed consent guidelines for clinical therapy [79]. Informed consent guidelines consisted of a defined protocol to maximize the number of telomerase-positive stem cells for harvest and subsequent repair of the tissues. These included avoidance of alcohol, tobacco products, vaping, recreational drugs, lidocaine, and chemotherapy agents because they kill telomerase-positive stem cells; limit use of caffeine because it prevents differentiation of telomerase-positive stem cells; limit the use of corticosteroids because they prematurely induce a commitment of TSCs and PSCs into the mesodermal lineage. Participants were instructed to ingest combinatorial nutraceuticals (CN) (DFRD, Macon, GA) daily for a minimum of 30 days prior to initial harvest and then throughout subsequent treatments to increase proliferation of telomerase-
positive stem cells within the person’s own connective tissues, thus making the person their own sterile bioreactor for telomerase positive stem cell proliferation. Participants were to drink plenty of aqueous-based fluids two weeks before stem cell harvest to remain hydrated to ease blood removal at harvest. Moderate to excessive exercising was excluded during a two-week window around stem cell harvest/treatment to maximize directed repair responses. And 18 hours before stem cell harvest two glacial caps (GC, DFRD) were ingested to induce reverse diapedesis of the telomerase-positive stem cells into the blood stream [64-78].

Harvesting of 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 elements utilizing ‘FDA-mandated minimal manipulative procedures’, utilizing gravity/zeta potential and differential density gradient centrifugation with serum, sterile saline and sterile distilled water gradients. The stem cells were segregated into individual populations of TSCs, PSCs, and MesoSCs, and activated [64-78].

Autologous TSCs were given by intranasal topical application for neurogenic treatment. The cells were concentrated in 0.5cc’s of liquid and split into two equal populations of 0.25cc’s each. The recipient was instructed to wash the mucus from their nostrils with 0.65% sterile saline, after which they were placed into the reversed Trendelenburg position (Fig. 1). Each nostril received an aliquot of 0.25cc’s concentrated TSCs, place dropwise onto the olfactory epithelium in the superior meatus of the nose. The recipient remained in the reverse Trendelenburg position for five minutes, and then placed in the upright position. Pooled autologous PSCs and MesoSCs were diluted in 250cc’s of normal sterile heparin/saline for regular intravenous infusion into an accessible vein, preferably the median cubital vein [64-78].

### Results

Before receiving telomerase-positive stem cell treatment, all participants exhibited symptomology suggestive of CIDP, e.g., areflexia of greater than 8 weeks duration; decrease in strength; symmetrical proximal and distal muscle weakness leading to a decrease in strength; coldness of their extremities (autonomic temperature instability). Sensory loss in the extremities eliciting numbness, sensory ataxia, and paresthesia; and loss of proprioception leading to unstable balance when standing or ambulating (gait disorder). Participants were also refractory to established CIDP therapeutic treatments.

Results following their first autologous telomerase positive stem cell transplant demonstrated that two of the three persons

### Table 1: Results from IRB-Approved Clinical Study Protocols of Fresh Isolate Telomerase Positive Stem Cell Technologies.

| Ref # | Clinical Trial                  | Sample Size, n= | Adverse Events | Description                                                                 | Efficacy |
|-------|---------------------------------|----------------|---------------|----------------------------------------------------------------------------|----------|
| 64-66 | Parkinson’s Disease             | 12             | None          | 10/12 showed reversal of symptoms 1st month after treatment. At 7 & 14-months post-treatment 2/12 regressed at slower rate than before treatments began; 4/12 remained in stasis; 4/12 normal or near normal. 2/10 – no response, did not follow informed consent guidelines | 66%      |
| 67    | Alzheimer’s Disease             | 4              | None          | 2/4 participants completely reversed symptoms. 2/4 – no response, did not follow informed consent guidelines | 50%      |
| 68    | Age-Related Dry Macular Degeneration | 4  | None          | 2/4 participants completely reversed symptoms. 2/4 – no response, did not follow informed consent guidelines | 50%      |
| 69    | Traumatic Blindness             | 1              | None          | From completely blind to shades of black and gray (partial restoration of ‘night’ vision) after two treatments. | 100%     |
| 70    | Traumatic Spinal Cord Injury    | 1              | None          | From complete paraplegia from T12 and below, to regain of bladder/bowel function after two treatments. | 100%     |
| 71, 72| Cardiovascular Disease          | 2              | None          | One participant had myocardial infarction six years prior to treatment initiation. 1st treatment raised cardiac output from <25% to 35%; 2nd treatment from 35% to 45%; Other participant raised cardiac output from <25% to ~70% | 100%     |
| 72    | Cardiovascular Disease with CN-SP only | 1  | None          | One participant with <10% cardiac output and walk <10 ft. Ingested CN-SP only. Within 6 months, cardiac output raised to 35%. ~6 more months, cardiac output >45% & 9-holes of golf. | 100%     |
| 73, 74| Chronic Obstructive Pulmonary Disease | 51 | None          | 48 participants demonstrated increase in lung function, one participant for 8+ years. Three participants showed no effect to treatment, but did not follow informed consent guidelines | 94%      |
| 74, 75| Idiopathic Pulmonary Fibrosis   | 2              | None          | Increased pulmonary function in one participant from 14% to 27%, and then stabilized at 25% for 8+ years. In other participant from <25% to ~70% for almost 10+ years | 100%     |
| 76    | Celiac Disease                  | 1              | None          | Completely reversed symptoms of celiac disease, went from 1:73 titer to 1:<1 titer during treatment period. Reverted when treatments stopped | 100%     |
| 77    | Systemic Lupus                  | 1              | None          | Two-week terminal, increased organ functioning from less than 25% to ~80%, 9+ years | 100%     |
| 78    | Osteoarthritis                  | 6              | None          | Decreased pain, increased ambulation | 100%     |

| #6 | Safe      | Average Efficacy | 87% |

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treated ceased the progression of their CIDP for up to six months following treatment. For every autologous telomerase positive stem cell transplant thereafter, these two participants regained proprioceptive (balance) and autonomic, sensory, and motor functions to their extremities for four to six months following each treatment, during their respective time-period(s) of treatments. The individual that demonstrated no change in their symptomology did not follow informed consent guidelines throughout their respective time period of treatments.

No adverse reactions were reported from any participant in the trial. Treatment with adult autologous telomerase positive stem cells proved to be both safe and 66% efficacious in restoring neurophysiological function in participants with diagnosed chronic inflammatory demyelinating polyneuropathy.

**Discussion**

**Progressional Therapeutic Treatment Options for CIDP**

The primary goal for therapy in patients with autoimmune neuropathology’s, e.g., Guillain-Barr syndrome (GBS) and chronic inflammatory demyelinating polyneuropathy (CIDP) is improvements in strength, function, gait disorder, autonomic instability, pain, and sensory loss. Patients with very mild symptomology that does not interfere with daily activities can be observed without treatment. Once deterioration begins that interferes with daily living, first-line treatments can be employed to slow or halt the progression of the disease. These interventions include corticosteroids, plasma exchange, and/or intravenous/subcutaneous immunoglobulin. If first-line treatments fail to elicit the desired response, then second-line therapies are utilized, such as chemotherapeutics, immunosuppressive drugs, and/or immunomodulatory drugs. The majority of CIDP patients require long-term therapy to maintain a positive response (halting progression of their disease with continued stasis) and to prevent a relapse of the disease. If both first-line and second-line therapies are ineffective at halting progression of the disease, then novel therapies are employed to halt progression of CIDP. One such novel therapy is hematopoietic stem cell transplantation (HSCT) following high-dose chemotherapy. In this novel therapy, the defective immune system is eradicated with high-dose chemotherapy, followed by HSCT to replace the defective immune system containing autoantibodies with a normal functioning immune system, without autoantibodies [80-82].

Unfortunately, first-line CIDP treatments utilizing corticosteroids, plasmapheresis, and immunoglobulins; second-line treatments using chemotherapeutic drugs, immunosuppressive drugs, and immunomodulatory drugs; or novel unconventional treatments using hematopoietic stem cells following high-dose chemotherapy, all have their associated side effects and induced comorbidities. These associated side effects and induced comorbidities may or may not be considered major or minor depending on the point of reference with respect to their physician, the patient, and the patient’s respective CIDP-associated comorbidities and symptomology [8,36,83,84].

While first-line, second-line, and HSCT following high-dose chemotherapy may halt the progression of CIDP, it does little to restore neurological function to the individual. We propose that telomerase positive stem cells would halt progression of CIDP and reverse its symptoms leading to remission and restoration of normal neurophysiological function. This would be accomplished by repairing and/or regenerating damaged nervous tissues, e.g., Schwann cells producing myelin, neurons (cell bodies) and their associated axons associated with myelinated motor neurons and unmyelinated sensory neurons and autonomic neurons located within mixed nerves throughout the extremities.

Development of ‘unmyelinated’ nerve fibers and myelinated nerve fibers within the peripheral nervous system occurs by a series of coordinated events between axons and neural crest-derived Schwann cells. Schwann cells provide additional functions to preserve axon integrity by creating nodes of Ranvier to increase salutatory impulse conduction, regulating the diameter of the axons, providing trophic and metabolic support, and protecting axons from toxic insults. There appears a symbiotic relationship between the axonal processes and the surrounding Schwann cells. Demyelinating diseases, such as chronic inflammatory demyelinating polyneuropathy, can progress into secondary axon degeneration resulting in clinical deficits and long-term disability. Understanding axonal degeneration/regeneration is essential for developing novel alternative therapies [85-87].

An alternative to previous therapies for axonal repair is the use of autologous ‘repair’ Schwann cells, chosen for their ability to promote axonal outgrowth, maintain a proliferative phenotype, and remyelinate axons. A second approach is to use autologous induced pluripotent stem cells to perform those same functions, e.g., maintain proliferative phenotype, promote axonal outgrowth, and remyelining growing axons [88].

Our alternative unconventional approach as a therapeutic treatment for CIDP would be to use not just autologous induced pluripotent stem cells as suggested [88], but to use autologous telomerase positive stem cells, e.g., totipotent stem cells, pluripotent stem cells, and mesodermal stem cells. This alternative approach is based on our previous clinical study data using adult telomerase positive stem cells for treating neurodegenerative, cardiovascular, pulmonary, autoimmune disorders, and orthopedic disorders, e.g., Parkinson disease [64-66], Alzheimer’s disease [67], age-related dry macular degeneration [68], traumatic blindness [69], traumatic spinal cord injury [70], myocardial infarction [71,72], chronic obstructive pulmonary disease [73,74], idiopathic pulmonary fibrosis [74,75], celiac disease [76], systemic lupus erythematosus [77], and osteoarthritis [78] (Table 1). In this approach, telomerase positive stem cells that normally comprise less than 4% of the stem cells in the body and are located throughout all stromal connective tissues of the body [89,90], are increased in numbers in the individual using a combination of plant-based nutraceuticals, thus making the person their own sterile bioreactor for generating large numbers of telomerase positive stem cells. Just prior to harvest, a
second nutraceutical is given to mobilize the telomerase positive stem cells into the blood stream, where they are harvested by simple venipuncture, separated from the blood elements, segregated into individual populations of stem cells, and activated.

With respect to neurodegenerative diseases, the telomerase positive stem cells repair and/or regenerate damaged neuronal tissues, restore the histoarchitecture to the damaged tissues, supply nutrients and remove waste products from the newly repaired/regenerated tissues. Telomerase positive totipotent stem cells and pluripotent stem cells have shown the capacity to differentiate into pyramidal neurons, dopaminergic neurons, interneurons, motor neurons, sensory neurons, radial glial cells, astrocytes, oligodendrocytes, Schwann cells, melanocytes, dorsal root ganglion cells, and autonomic ganglion cells in culture using induction with chemical agents, human recombinant proteins, and cell-specific exosomes (Figure 2) [84]. Telomerase positive totipotent stem cells and/or pluripotent stem cells have shown the ability to restore neurophysiological function in participants with Parkinson disease (Figures 3-5) [64,85], Alzheimer’s disease [65], age-related dry macular degeneration [66], traumatic blindness (Figure 6) [69], and traumatic spinal cord injury [70]; and restore appropriate physiological function in cardiovascular disease (Figure 7) [71,72], chronic obstructive pulmonary disease (Figure 8) [73,74], and idiopathic pulmonary fibrosis (Figure 9) [74,75]. In addition, telomerase positive mesodermal stem cells have the capacity to form loose fibrous connective tissues, dense fibrous connective tissues, smooth muscle, and the endothelial lining cells of arteries, veins, capillaries, and lymphatics and their associated tributaries (Figure 1) [84]. Telomerase positive mesodermal stem cells have been shown to restore blood vessel-like structures in Parkinson disease (Figure 4) [85] and cardiovascular disease (Figure 10) [91].

Utilizing the autologous telomerase positive adult stem cell technologies, results following their first autologous telomerase positive stem cell transplant demonstrated that two of the three persons treated ceased the progression of their CIDP for up to six months following their treatment. For every autologous telomerase positive stem cell transplant thereafter, these same two

Figure 1: Diagram of TSCs bypassing blood-brain barrier at cribriform plate to gain entry to central nervous system, e.g., brain and spinal cord. The nasal mucus from each nostril is removed by washing with 0.65% sterile saline. The patient is placed into the reversed Trendelenburg position (nostril openings pointing towards ceiling) and millions of TSCs are deposited dropwise onto the olfactory epithelium in the roof of the superior nasal meatus. The TSCs migrate between the olfactory epithelial cells in the roof of the superior nasal meatus.

TSCs migrate through cribriform plate to bypass blood brain barrier.

TSCs crawl along olfactory bulb to olfactory nerve, pass by optic nerve, and gain entrance to CNS via cisterns, subarachnoid spaces, sulci, ventricles, aqueduct cerebri (of Sylvius), foramina, and central canal of spinal cord.

From those positions, TSCs can migrate to any areas within brain and spinal cord to repair damaged neurons, interneurons, axons, dendrites, synapses, cell bodies, oligodendrocytes, astrocytes, vascular endothelium, etc.
Figure 2: Differentiation potential of telomerase positive stem cells as assessed by induction with chemical agents, human recombinant proteins, and cell-specific exosomes. Phenotypic expression markers for cell types were identified immunocytochemically, using enzyme-linked immuno-culture assay (ELICA), and molecularly, by expressed genes. Reprinted with permission from Young HE, Speight MO. Characterization of endogenous telomerase-positive stem cells for regenerative medicine, a review. Stem Cell Regen Med 2020; 4(2):1-14 [89].

Figure 3: Parkinson Disease model in adult rats. A: Adult rats were stereotactically injected with either saline (B) or a neurotoxin, 6-hydroxydopamine (6-OHDA), into the substantia nigra pars compactum of the ventral midbrain to kill dopaminergic neurons and to disintegrate their associated neural networks (C). Either saline or a Lac-Z-genomically-labeled clone of pluripotent stem cells (Scl-40β) was then stereotactically injected into the lesion site. The animals were kept for additional six weeks, euthanized, their brains removed and processed for immunocytochemical staining for dopaminergic neurons via the enzyme tyrosine hydroxylase or Beta-galactosidase to distinguish Scl-40β naïve or differentiated cells. The tissue sections were counterstained with methyl green to distinguish host glial cells from Scl-40β. D: Lesioned area injected with saline only. Note a line of green cells, depicting a glial scar within the needle tract. Very few visible neural networks were present. E: Lesioned area injected with Scl-40β. Note a line of dopaminergic neurons were located within the needle tract as well as extensive neural networks on either side of the line of dopaminergic neurons. Reprinted with permission from Young HE, Speight MO. Blunt force trauma-induced total bilateral vision impairment of 13 years duration treated with autologous telomerase positive stem cells. Stem Cells Regen Med. 2021; 5(1):1-22 [69].
Figure 4: Parkinson disease model in adult rats. Following stereotactic injection of Scl-40β into substantia nigra of 6-hydroxydopamine-lesioned animals, Scl-40β also migrated back into the cerebral cortex along the needle tract and regenerated all cell types that were damaged. A: White matter - glial cells and capillaries; B: Gray matter - interneurons and pyramidal neurons; and C: Gray matter - interneurons and pyramidal neurons. Reprinted with permission from Young HE, Speight MO. Treating Parkinson Disease with Autologous Telomerase-Positive Stem Cells, Update 2021. Stem Cells Regen Med. 2021; 5(1):1-13 [66].

Figure 5: Combined Hoehn-Yahr scoring data for small cohort clinical trial (n=12), encompassing 2013 Parkinson trial [37] and additional four participants [39]. No adverse effects were noted from participants or their caregivers from either trial. 33% (n=4) showed moderate to no benefit of telomerase positive stem cell treatment at 1-month (H-Y: 8-6), and either no benefit or a slow increase in Hoehn-Yahr scores from 7-month (H-Y: 8-5) to 14-month (H-Y: 8-5.5) post-treatment assessments. 33% (n=4) decreased their Hoehn-Yahr scores by about half by 1-month after treatment (H-Y: 4-2), but then remained in stasis at 7-months (H-Y: 4-1) and 14-months (H-Y: 4-1) during post-treatment assessments. The remaining 33% (n=2 + n=2) were either completely void of Parkinsonian symptoms (H-Y: 0, n=2) or continued to decrease in Hoehn-Yahr score at each assessment period following treatment, e.g., 1-month (H-Y: 1.0, n=2), 7-months (H-Y: 0.75, n=2), and 14-months (H-Y: 0.5, n=2). Reprinted with permission from Young HE, Hyer L, Black Jr AC, et al. Treating Parkinson Disease with adult stem cells. J Neurol Disord 2013; 2:1 [37] and reprinted with permission from Young HE, Speight MO. Treating Parkinson Disease with Autologous Telomerase-Positive Stem Cells, Update 2021. Stem Cells Regen Med. 2021; 5(1):1-13 [66].
Figure 6: A: A white placard with red and blue boxes containing black squares was used to test visual impairment in the participant. B: Before stem cell treatment began, she stated, “I can’t see anything, everything is black”. C: Two months following her first telomerase positive stem cell treatment, she stated, “I can see a fuzzy black spot on a fuzzy dark gray background”. D: Two months following her second stem cell treatment, she stated, “I can see a slightly less fuzzy black square on a slightly less fuzzy lighter gray background”. Reprinted with permission from Young HE, Speight MO. Blunt force trauma-induced total bilateral vision impairment of 13 years duration treated with autologous telomerase positive stem cells. Stem Cells Regen Med. 2021; 5(1):1-22 [69].

Figure 7: A: Human volunteer with cardiac output of 25% of six year’s duration following myocardial infarction. Ingested combinatorial nutraceuticals 30 days before first stem cell harvest and throughout treatments. Stem cells were harvest by simple venipuncture, separated from blood cells, segregated into TSCs, PSCs, and MesoSCs and activated. TSCs were given by slow systemic infusion and PSCs and MesoSCs were given by regular systemic infusion. Treatment consisted of two successive autologous stem cell transplants six months apart from each other. Six months following first autologous stem cell transplant cardiac output rose from 25% to 35%. Six months following 2nd autologous stem cell transplant cardiac output rose from 35% to 45%. Reprinted with permission from Young HE, Limnios IJ, Lochner F, et al. Adult healing cells and cardiovascular disease: From bench top to bedside. J Stem Cell Res 2017; 1(3) 002:1-8 [71]. B: Systemic Lupus Erythematosus (SLE) participant treated with S, Self (autologous) and D, Donor (Allogeneic) telomerase positive stem cells. SLE participant’s cardiac output dropped precipitously, 90% to 30%, during ingestion of hydroxychloroquine to slow progression of SLE. At time of first stem cell transplant, cardiac output was below 25%. First stem cell transplant (autologous) raised cardiac output to 25%. Second stem cell transplant from allogeneic 42-year-old A+ male raised cardiac output to approximately 40%. Third stem cell transplant from allogeneic 73-year-old O-negative male raise cardiac output to approximately 70%. A total of 29 adult-derived autologous and/or allogeneic telomerase-positive stem cell transplants thus far have maintained his cardiac output at approximately 70% for over nine years and counting. Reprinted with permission from Young HE, Speight MO. Cardiovascular disease treated with telomerase-positive stem cells. Stem Cells Regen Med. 2020; 4(2):1-8 [72].
Figure 8: Participant with chronic obstructive pulmonary disease (COPD), with a baseline FEV\(_1\) of 30% (GOLD-3), treated with multiple autologous and allogeneic telomerase-positive stem cell transplants over an eight-year time frame. Within one month following their initial autologous stem cell treatment (TSCs and PSCs nebulized, followed by MesoSCs by regular intravenous infusion into median cubital vein), their FEV\(_1\) increased to 46%, approximating a 50% increase in lung capacity. During the ensuing eight-year time frame their FEV\(_1\)'s fluctuated from 40% to 48%, due to pneumonia followed by stem cell transplant, followed by pneumonia, followed by stem cell transplant, and so on and so forth. After their initial stem cell transplant the individual was able to reduce supplemental oxygen from 4-L per minute to 2-L per minute for the ensuing eight years and still maintain a greater than 98% oxygen saturation of their blood. The individual succumbed to a severe case of pneumonia eight years after initial telomerase-positive stem cell treatment. Reprinted with permission from Young HE, Speight MO. Potential treatment of chronic obstructive pulmonary disease with allogeneic and autologous telomerase-positive stem cells. Stem Cells Regen Med. 2020; 4(3):1-11 [73].

Figure 9: Endogenous telomerase-positive stem cell treatment of two individuals with idiopathic pulmonary fibrosis (IPF), with baseline FEV\(_1\) values of less than 30% (Gold-4). The female, age 80 with a baseline FEV\(_1\) of 14%, was transplanted with a single treatment of autologous telomerase positive stem cells (TSCs and PSCs by nebulization and MesoSCs by intravenous infusion). Within one month after treatment, her FEV\(_1\) rose to 27% [5], and then stabilized at 25% for eight years. The male, age 61 with a baseline FEV\(_1\) of 25% was transplanted with a single autologous and three autologous/allogeneic telomerase-positive stem cell treatments throughout a seven-year time frame. The autologous/allogeneic treatments consisted of pooled autologous/allogeneic-TSCs and autologous/allogeneic-PSCs by nebulization and autologous MesoSCs only by intravenous infusion. His FEV\(_1\) has stabilized at approximately 70% for the past nine years (and counting). Reprinted with permission from Young HE, Speight MO. Telomerase-positive stem cells as a potential treatment for idiopathic pulmonary fibrosis. Stem Cells Regen Med. 2020; 4(2):1-11 [75].
participants regained proprioceptive (balance) and autonomic, sensory, and motor functions to their extremities for four to six months following each treatment, during their respective time-period(s) of treatment. The individual that demonstrated no change in their symptomology did not follow informed consent guidelines throughout their successive treatments.

No adverse reactions were reported from any participant in the trial. Treatment with adult autologous telomerase positive stem cells proved to be both safe and 66% efficacious in this small cohort clinical trial (n=3). This was noted as a cessation of disease progression and a restoration of neurophysiological function in participants with diagnosed chronic inflammatory demyelinating polyneuropathy that was refractory to established CIDP therapeutic treatments.

Conclusion
First described in 1975, chronic inflammatory demyelinating polyneuropathy (e.g., chronic inflammatory demyelinating polyradiculoneuropathy, CIDP) is a rare autoimmune mediated peripheral neuropathy. CIDP is defined as symptomology of greater than two months duration and electro diagnostic evidence of peripheral nerve demyelination. The estimated overall prevalence of CIDP is 4.8 to 8.9 cases per 100,000 people. Symptomology includes motor, sensory, and autonomic involvement resulting in symmetrical proximal and distal muscle weakness, loss of strength, reflexes of greater than eight weeks duration, numbness, weakness, sensory ataxia, paresthesia, peripheral temperature regulation, and gait disorder. As disease progresses there, is axonal loss within mixed peripheral nerves secondary to demyelination and associated with a poor prognosis. Autoantibodies identified for CIDP thus far include contactin-1 (CNTN1), contactin-associated protein-1 (Caspr1), contactin-2 (CNTN2), neurofascin-155 (Nfasc-155), neurofascin-140/186(Nfasc-140/186), LM1, gliomedin, and vinculin. Another marker of CIDP is sphingomyelin in the cerebral spinal fluid. Potential treatment options for CIDP are first-line therapies, such as corticosteroids, plasma exchange, and/or immunoglobulins. If patients are refractory to first-line therapies, then second-line therapies, such as chemotherapeutic drugs, immunosuppressive drugs, and/or immunomodulatory drugs, are utilized to halt progression of the disease. Lastly, if first- and second-line therapies fail, novel unconventional therapies have been utilized, such as high-dose cyclophosphamide to eradicate a defective immune system containing CIDP-associated autoantibodies to nodal and...
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