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Clinical neurorestorative cell therapies: Developmental process, current state and future perspective

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ABSTRACT
Clinical cell therapies (CTs) for neurological diseases and cellular damage have been explored for more than 2 decades. According to the United States Food and Drug Administration, there are 2 types of cell categories for therapy, namely stem cell-derived CT products and mature/functionally differentiated cell-derived CT products. However, regardless of the type of CT used, the majority of reports of clinical CTs from either small sample sizes based on single-center phase 1 or 2 unblinded trials or retrospective clinical studies showed effects on neurological improvement and the ability to either partially or temporarily thwart the deteriorating cellular processes of the neurodegenerative diseases. There have been only a few prospective, multicenter, randomized, double-blind placebo-control clinical trials of CTs so far in this developing novel area that have shown negative results, and more clinical trials are needed. This will expand our knowledge in exploring the type of cells that yield promising results and restore damaged neurological structure and functions of the central nervous system based on higher level evidence-based medical data. In this review, we briefly introduce the developmental process, current state, and future prospective for clinical neurorestorative CT.

1 Introduction
Clinical cell therapies (CTs) have been explored for neurological diseases for more than 20 years. Preliminary results showed that most CTs restore neurological structure and functions to some degree for a period of time. These results were promising and evoked hope in patients, health care providers, and the clinical scientific community. However, compared with the initial clinical results, follow-up studies of CTs exhibited more or less similar results without any breakthroughs. According to the United States Food and Drug Administration (USFDA)
for cell categories (Guidance for Industry: Preclinical Assessment of Investigational Cellular and Gene Therapy Products; http://www.fda.gov/BiologicsBloodVaccines/GuidanceComplianceRegulatoryInformation/Guidances/default.htm), CTs are divided into either stem cell-derived CT products and mature/functionally differentiated cell-derived CT products. In this review, we briefly emphasize the main clinical neurorestorative CTs with developmental processes, current state of the art, and future perspectives.

2 Developmental process and current state of mature/functional cells

Mature/functional cells used in the nervous system include neuronal cells, olfactory ensheathing cells (OECs), mononuclear cells (MNCs), mesenchymal stromal cells (MSCs), Schwann cells (SCs), fetal brain or spinal cord cells, and similar cell types.

2.1 Neuronal cells

In 2000, a study was reported indicating that transplanting neurons originating from teratocarcinoma showed functional improvements in patients with chronic stroke [1]. However, in a later randomized, observer-blinded trial, these cells did not show any effect [2]. Interestingly, when fetal porcine cells were transplanted into patients with basal ganglia infarcts, the patients exhibited significant neurological improvements [3].

2.2 Olfactory ensheathing cells

Human olfactory tissue has the ability to regenerate and restore itself throughout one’s whole life [4]. Olfactory neurons show the characteristic of photoreceptor cells in vitro in special medium [5]. OECs share characteristic of SCs and oligodendrocytes and have a strong ability to secrete neurotrophic factors. These properties alleviate the lesioned area and improve the microenvironment to trigger or restore the damaged neurons through the neurorestorative mechanisms [6, 7]. Olfactory neurons and OECs are novel and the most potent cells for restoring the damaged neurological structure and functions in the central nervous system (CNS). Transplantation of OECs from aborted fetal olfactory bulbs were shown to improve neurological function in patients with chronic complete spinal cord injury (SCI) [8, 9]. This was further confirmed by Rabinovich et al., who found similar results for OEC transplantation in patients with SCI [10]. A majority of researchers observed similar positive results after OEC transplantation in SCI patients across the world [11–28]. However, only a few studies observed negative results [28, 29] which probably due to the damage caused by the procedure itself [30]. Using transplantation of olfactory mucosal autografts in SCI patients, Lima et al. showed some functional improvements [31, 32]. There have also been some negative reports using Lima’s technique [33, 34]. On the other hand, Dlouhy et al. reported the formation of a mass after olfactory mucosal tissue transplantation [35]. Apart from SCI, other diseases or damage of the CNS, such as stroke, cerebral palsy (CP), amyotrophic lateral sclerosis (ALS), and brain injury, also exhibited neurorestorative effects after OEC therapy [36–50].

2.3 Mononuclear cells

Unmanipulated MNCs are generally derived from the bone marrow, cord blood, and the peripheral blood. Syková et al. transplanted autologous bone marrow MNCs (BMMNCs) and described neurological improvements in patients with subacute and chronic SCI [51]. Autologous undifferentiated peripheral blood MNCs also showed recovery of the somatosensory evoked potential responses [52]. Later several studies demonstrated similar results using
autologous BMMNC therapy [53–58]. In one study, autologous umbilical cord blood trans-
fusions were used for CP and showed significant improvements in gross motor function
classification system [59]. Intrathecal infusion of autologous BMMNCs in CP also improved
patients’ motor, sensory, cognitive, and speech functions [60]. These observations have been
further confirmed by several reports of autologous BMMNCs in CP showing similar clinical
functional improvements [61–74]. However, compared with placebo, Rah et al. reported that
intravenous infusion of peripheral blood MNCs in a randomized, double-blind, crossover study
failed to show any significant effect on upper extremity function in children with CP [75].

Autologous BMMNC therapy was also used in children with brain injury and was found to
improve neurological function in most patients [76]. Recently, BMMNC therapies have exhibited
similar positive effects for brain injury patients [77–79].

Mendonça et al. found that intra-arterial autologous BMMNC transplantation was safe in
acute ischemic stroke patients [80]. Autologous BMMNC therapies for stroke exhibited similar
results in several later studies [81–99]. However, in a multicenter, randomized trial with blinded
outcome assessment, Prasad et al. found that autologous BMMNC therapy did not show
beneficial effects in subacute ischemic stroke patients [100]. Similarly, a recent multicenter,
randomized, blinded assessment, sham-controlled trial demonstrated that autologous bone
marrow-derived ALD-401 cells given through the internal carotid artery in patients recovering
from ischemic stroke did not result in any differences between the groups [101].

A series of reports showed that autologous BMMNC therapy could improve quality of life
in muscular dystrophy patients [102–105], and that it showed good benefit in autism [106], ALS
[107], and brachial plexus injury [108]. Hogen-
doorn et al. reported that local injection of autologous BMMNCs in patients with traumatic
brachial plexus injury enhances muscle reinnervation and induce regeneration [109].

2.4 Mesenchymal stromal cells

Before 2005, the plastic-adherent cells isolated from bone marrow and other sources were
widely named as either mesenchymal stem cells or MSCs. However, the International Society for
Cellular Therapy stated that “the recognized biologic properties of the unfractionated popula-
tion of cells do not seem to meet generally accepted criteria for stem cell activity, rendering
the name scientifically inaccurate and potentially misleading to the lay public” [110]. Thus, the
cells should be named MSCs, and their criteria should be established [111, 112]. In this article,
we use MSCs to replace mesenchymal stem cells, except when identified by special stem cell
markers or differentiated into target or effector cells. MSCs have been used to treat patients
with varying diseases through intravascular, subarachnoid, or direct injection into the lesion
area.

Data revealed that autologous MSCs were safe and well-tolerated in patients with ALS [113,
114]. This treatment significantly slowed down the linear decline of the forced vital capacity
[115]. Later, most clinical studies using MSCs reported neurological stabilization or functional
improvements in ALS [116–124]. On the other hand, in a few studies, using MSCs did not interfere with the course of the disease [125].

Intravenous infusion of autologous MSCs appeared to be a feasible and safe treatment to
improve functional recovery in stroke patients [126], followed by a series similar results
[127–132]. A randomized, double-blind, placebo-controlled, phase 2 trial of multipotent adult
progenitor cells derived from bone marrow for
patients with acute ischemic stroke did not show any difference in neurological recovery between CT and placebo groups at 90 days [133]. Using MultiStem from Athersys, Inc. and a protocol similar that reported by Hess et al. [134], Osanai et al. conducted another clinical trial [135].

A study using umbilical cord MSC transplantation reported improvement in sensory perception and mobility of a patient with SCI [136]. This finding was corroborated in later studies of MSC therapy resulting in similar results [137–148]. Interestingly, using the same setup, Chotivichit et al. reported a negative result [149]. Likewise, in a phase 3 study, Oh et al. also reported no improvement in neurological function in the majority of the patients in their study [150].

Autologous bone marrow MSC transplantation was applied in patients with paraplegia and was found to result in improved neurological function and enhanced quality of life [151–153], diffused axonal injury [154], neuropathic pain [155], post-traumatic syringomyelia [156], and Alzheimer’s dementia [157].

In addition, there have been several explorations of MSCs in clinics that have shown remarkable neurorestorative effects with improved quality of life in patients with multiple system atrophy and spinocerebellar ataxia [158, 159], MS [160, 161], brain injury [162, 163], CP [164–168], and autonomic nervous system dysfunctions [169].

In a randomized, placebo-controlled, multiple-dose study of human placenta-derived cells (PDA-001) in patients with multiple sclerosis (MS), Lublin et al. found that, although it was safe and well-tolerated, its efficacy was uncertain [170].

### 2.5 Fetal brain and spinal cord cells

Clinical studies have shown that intraspinal transplantation of fetal spinal cord cells for patients with ALS is safe [171–174] and capable of improving their functions [175]. However, it did not show differences in the mean rates of progression compared with historical control groups [176]. Transplantation of neural cell-derived fetal brain in a patient with primary torsion dystonia showed some functional improvement [177]. Liu et al. transplanted human fetal-derived retinal progenitor cells in patients with retinitis pigmentosa and reported significant improvement in the visual acuity [178].

### 2.6 Schwann cells

One study of autologous SC transplantation in patients with chronic thoracic SCI was completed. It was observed that, although it was safe, the procedure did not show any beneficial effects [179, 180]. On the other hand, transplantation of SCs could improve some functions in patients with SCI [181] and even in Parkinson’s disease [182].

### 2.7 Combination cell therapies

Cells from immature nervous and hematopoietic tissues were subarachnoidally transplanted in patients with subsequent consequences of brain stroke and improved their neurological function [36]. They also found similar functional neurological improvements using this method in patients with CP and brain injury, including patients in a comatose state [37–40].

Patients with progressive muscular dystrophy improved their functions after bone marrow and umbilical cord blood MSC transplantations [183]. Intravenous transplantation or the intrathecal injection of human umbilical cord blood MNCs with umbilical cord-derived MSCs induced a marked benefit in autism patients [184]. Yazdani et al. found that autologous SC and bone marrow MSC cotransplantation was safe in patients with chronic SCI [185]. In a long-term follow-up study, the patients showed improvement in some sensation with bladder compliance, but no further motor function improvement [186].

Chen et al. described the amelioration of
neurological functions after multiple cell transplantation, including OEC, neural progenitor cells, umbilical cord MSCs, and SCs, in patients with chronic stroke [46]. Multiple cell therapy, including umbilical cord MSCs, SCs, neural progenitor cells, and OECs, was also able to improve or stabilize the neurological status of patients with multiple system atrophy [47]. A combination of OECs and SCs also showed some functional improvement in patients with chronic complete SCI [187].

Scaffold implantation after scar resection with autologous BMMNCs in patients with complete chronic SCI exhibited some functional improvements [188–190]. It should be strongly cautioned that the procedure of total scar resection deprives the ability of nerves in autorestoring possibilities. Currently, CT with intensive neuro-rehabilitation could partially restore standing and walking abilities in patients with complete chronic SCI with improved qualities of daily life [15].

Bone marrow MSC and BMMNC transplantation for spastic CP showed neurorestorative effects [191]. Local transplantation of autologous type 1 macrophages, autologous tissue-specific T helper 1 cell, and autologous muscular progenitor cells in patients with atrophied muscles exhibited progressive muscle volume increase with gradual replacement of hyperechogenic muscle tissues [192].

3 Developmental process and current state of stem cell-derived cell therapy products

Stem cell-derived CT products in the nervous system include hematopoietic stem cells (HSC), cells differentiated from embryonic stem cells (ESCs), induced pluripotent stem cells, mesenchymal stem cells, and neural stem cells (NSCs).

3.1 Hematopoietic stem cells

Several research teams have started to use blood HSCs for MS since the last decade of the 20th century. Fassas et al. reported a distinct clinical benefit of peripheral blood HSC transplantation in patients with progressive MS [193] that was much better than any other treatments [194]. However, multicenter data has suggested significant mortality risks associated with HSC therapy [195].

Later, the teams of Burt et al. [196–201], Nash et al. [202–206], and others described similar results [207–240]. General autologous HSC transplantation may not be a curative treatment for MS, but it could prolong stabilization or changes in the aggressive course of the disease [241].

Because most of the studies have been conducted in small, single-center, phase 1 and 2 non-double-blind trials, it is important for a prospective, randomized, double-blind, controlled multicenter trial to assess the clinical efficacy of HSC transplantation for the treatment of highly active MS [242]. Unfortunately, there have been no such trials reported so far in this field.

HSCs could also improve the function and quality of life of patients with other nervous system diseases or damage. Umbilical cord blood HSC transplantation may restore dystrophy in muscles and improve the locomotor functions in patients with Duchenne muscular dystrophy [243, 244]. A direct injection of autologous bone marrow HSCs may improve movements and sensations in patients with chronic SCI and could effectively treat ALS patients [245, 246]. However, unmodified HSCs did not benefit patients with sporadic ALS [247]. Purified autologous leukapheresis derived CD34+ and CD133+ stem cells improved segmental sensory functions in patients with chronic SCI during long-term evaluation and follow-up [248]. After
mobilizing bone marrow CD34+ stem cells by granulocyte-colony stimulating factor, it may offer some benefit to stroke patients as well [249–253].

3.2 Cell differentiated from embryonic stem cells
In the first clinical trial from Geron regarding human ESCs, enrolled patients did not show any benefits [254]. Transplantation of human ESC-derived retinal pigment epithelium in patients with age-related macular degeneration and Stargardt's macular dystrophy showed improvements in visual acuity [255]. Transplantation of an embryonic stem cell-derived retinal pigment epithelium patch in 2 patients with age-related macular degeneration resulted in a significant gain in visual acuity [256].

3.3 Cell differentiated from induced pluripotent stem cells
Autologous induced stem-cell-derived retinal cells for macular degeneration did not show any improvement in visual acuity [257].

3.4 Cell differentiated from mesenchymal stem cells
Neural stem cell-like cells derived from autologous HSCs have been used in patients with CP and have shown improvements in motor deficit [258]. Intraspinal delivery of bone marrow stromal cell-derived NSCs in patients with ALS resulted in a temporary stabilization for the first few months after injection, then gradually deteriorated [259]. Transplantation of cell-derived MSCs in patients with chronic stroke improves clinical outcome [260, 261]. Patients with severe traumatic brain injury showed improved neurological functions in different degrees after autologous MSC-derived NSC-like cell transplantation [262].

3.5 Cell differentiated from neural stem cells
After USFDA approval [263], Selden et al. applied HuCNS-SC transplantation in children with neuronal ceroid lipofuscinosis [264]. Levi et al. reported intramedullary transplantation HuCNS-SC in patients with SCI [265]. Later, in a similar single-blind, randomized proof-of-concept study the following year, cell transplantation was found below the required clinical efficacy threshold [266]. Some reports of neural stem and progenitor cell therapy showed their safety with or without neurological improvement in children with CP [267], SCI [268, 269] or stroke [270, 271].

3.6 Others
Autologous transplantation of CD133+ stem cells for patients with ALS was found to be safe [272, 273]. CD133-positive enriched bone marrow progenitor CT in children with CP showed possible short-term neurological improvements [274].

3.7 Combination cell therapy
Combined protocol of CT (autoimmune T and NSCs transdifferentiated from bone marrow MSCs) have been used in 2 patients with SCI and resulted in motor and sensory improvements [275]. In a follow-up study by the same team, it was observed that BMMNC in combination with T cell autologous NSCs therapy dramatically improves neurological function in patients with chronic complete SCI [276]. In addition, the autologous NSC treatment combined with T cells also showed some benefits in ALS patients [277]. Cotransplantation of neural stem and progenitor cells and MSCs resulted in improvements of some functions in patients with stroke [278]. Co-infusion of autologous adipose tissue-derived neuronal differentiated MSCs and bone marrow-derived
HSCs in a patient with post-traumatic brachial plexus injury showed sustainable recovery [279, 280]. Motor and objective sensory improvements have been noted using biological scaffold with autologous HSCs and platelet-rich protein in patients with SCI [281].

4 Reasons of limited effects

Compared with the clinical neurorestorative effects of OEC transplantation in early 2001, the overall effects of these CTs are now at the plateau or in the period of bottleneck without any breakthrough. So far, CT explorations have expanded horizontally, showing certain neurorestorative effects on a larger scale, e.g., different cell types, various implantation cell ways or methods, different implant sites, and implanting cell numbers together with different lesions or disease stages.

The following could be reasons for these limited effects: (1) unable to know which type of CTs are more potent candidates, or which method of transplantation or dosage is more suitable with the appropriate CT window for different diseases or damage, as well as whether repeated CTs have better effects; and (2) CT products with different quality control and standards have different effects [282].

5 Summary and future prospective

Varying CTs have been explored for use in CNS diseases over the past two decades. The majority of CTs have shown positive results, but most of them were small, single-center, phase 1 and 2 non-double-blind trials or retrospective clinical studies in CNS. At present, a few prospective, multicenter, randomized, double-blind placebo-control clinical trials of CTs have been conducted but did not show positive results. These CTs have been shown to restore damaged neurological function and/or structure in lower level evidence-based medical practice. Thus, more clinical trials of CTs in the CNS should be conducted in the future to explore the types of cells that have affirmative effects with a high level of evidence-based medical practice. Also, greater professional standards of CT products and quality control are needed in such clinical trials.

Conflict of interests

The authors declare they have no competing interests.

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