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WORLDWIDE STATUS OF CLINICAL EXPERIMENTATION WITH STEM CELLS IN NEUROLOGIC DISEASES

The adult brain contains small numbers of stem cells in restricted areas, but this intrinsic stem cell repertoire is small and does not contribute substantially to regeneration of damaged neurons. Transplantation of stem cells has long been suggested as a possible logical approach for CNS repair. Embryonic stem cells (ESC) possessing pluripotent and self-renewal properties represent the stem cell prototype¹ and have a tremendous transdifferentiation ability and, therefore, the potential for neural cell replacement. However, the transplantation of undifferentiated ESCs cannot provide a first-line option for clinical applications since it is associated with a high risk of potential carcinomatous transformation. There are additional somatic stem cells that may be easily harvested and expanded from various tissues during adult life, such as neuronal (NSC) and mesenchymal stem cells (MSC).² Fetal NSC, despite the advantage of being naturally “neuralized,” are accompanied by numerous ethical, scientific, and legislative hurdles upon transplantation into the human adult brain.³

MSC, which exert immunomodulatory effects and secrete various neurotrophic factors, are easier to obtain (usually from the bone marrow) and their use is not beset by contentious ethical issues.² As these cells seem to be able to pass the blood–brain barrier, no invasive intracerebral surgery is required and peripheral systemic administration or injection into the CSF compartment have been proven safe and efficient ways for cell delivery in humans.⁴ In vitro experiments provided the initial proof for differentiation (or transdifferentiation) of embryonic and adult type somatic stem cells into cells of the neuronal lineage.⁵ Additional (and more convincing) proof was provided by animal studies. Over the past decade, clinching evidence has emerged regarding the capability of various stem cell populations to induce regeneration in animal models of neurologic disorders such as Parkinson disease (PD), Huntington disease (HD), multiple system atrophy (MSA),

amyotrophic lateral sclerosis (ALS), Alzheimer disease (AD), cerebral ischemia, and multiple sclerosis (MS).⁶ A review of the literature in the PubMed site shows the phenomenal increase in published research papers in the field of stem cells during the past decade, the number of published articles related to stem cells growing from around 4,000/year to more than 30,000/year in the last 12 years.

Clinical experience: Pilot clinical studies with stem cell transplantation in neurologic diseases. As a natural consequence of the encouraging animal data obtained in models of neurologic diseases and the enthusiasm evoked by stem cells as the putatively optimal means for regeneration, a plethora of clinical trials, usually open and uncontrolled, have been performed in various neurologic diseases and in at least 50 countries.

Allogeneic transplantation using donor stem cells has a seemingly better potential for neuronal repair as, in such a setting, the transplanted stem cells do not carry the putative genetic defects which may be involved in the pathogenesis of the neurologic disease to be treated. In addition, they may actually provide the vehicles for transfer of normal genes in neurogenetic disorders. With the exception of small studies using hematopoietic stem cell (HSC), very limited clinical data on allogeneic stem cell transplantation are available in the literature. In the early 1990s, allogeneic transplantation of HSC and later of MSC were tried in patients with neurogenetic diseases, particularly lysosomal disorders (Hurler syndrome and metachromatic leukodystrophy), with some indications of beneficial effects.

The clear drawback of such an allogeneic approach is the high risk of rejection of the transplanted cells (despite their low immunogenicity) and the possible need for additional chemotherapy/immunosuppression to improve long-term viability of the stem cells.

The vast majority of the existing clinical data come from clinical trials with autologous stem cells. Early open clinical trials have provided data on the

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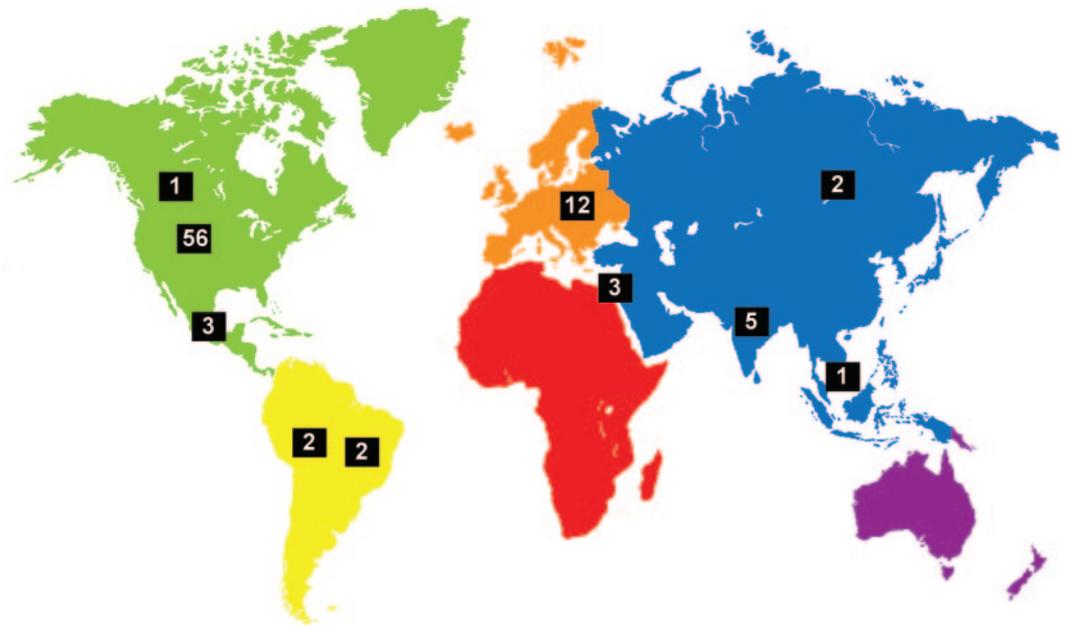
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Figure Registered stem cell companies worldwide



safety and feasibility of stem cell transplantation in cerebrovascular diseases (stroke), PD, HD, MSA, MS, and ALS. IV, intra-arterial, intrathecal, and intraspinal transplantation of stem cells (mainly MSC) proved to be safe, in the short run at least. In some of the studies there were initial indications of clinical efficacy.⁴ MSC have also been tested in acute and chronic muscle diseases, but the results were controversial. In general, the posttransplant cellular survival of transplanted stem cells, their host brain integration, synaptic innervation of target CNS regions, and morphologic and functional differentiation in vivo have yet to be proven, along with neurologic functional improvement of the treated patients.

HSC transplantation represents a unique case of stem cell therapy. HSC are injected, following a radical immunosuppressive protocol and leading to the replacement or the resetting of the whole immune system. It is only logical that such treatment protocols are used for severe inflammatory autoimmune diseases of the CNS and PNS or as a rescue therapy following intensive chemotherapy for solid somatic or brain tumors. The rationale for this type of therapeutic approach in neuroimmunologic diseases is derived from pivotal animal studies conducted back in the early 1990s.⁷ More than 350 patients with MS have been treated with HSC.⁸ In general, over the past 15 years, more than 1,500 patients have received HSC, mostly autologous, as treatment for severe autoimmune diseases (MS, $n = 345$; systemic sclerosis, $n = 175$; systemic lupus erythematosus, $n = 85$; rheumatoid arthritis, $n = 89$; juvenile idiopathic arthritis, $n = 65$; and idiopathic cytopenic purpura, $n = 37$). An overall 85% 5-year survival rate and a

43% progression-free survival rate was seen, with 100-day transplantation-related mortality ranging between 1% (rheumatoid arthritis) and 11% (systemic lupus erythematosus and juvenile idiopathic arthritis).

On a global basis, there are more than 200 ongoing active clinical trials using stem cells in neurologic disease registered in the NIH site. Of these, 164 meet the criterion of a proper clinical trial using stem cells as a treatment modality. The neurologic indications are extensive and include MS ($n = 23$), brain tumors ($n = 52$, almost all with autologous HSCT), stroke ($n = 18$), spinal injury ($n = 11$), ALS ($n = 7$), genetic-metabolic diseases and leukodystrophies ($n = 15$), as well as PD, HD, AD, MSA, cerebral palsy, peripheral neuropathy, myasthenia-myopathies, epilepsy, and systemic autoimmune diseases with neurologic complications. The list includes cases of hearing loss, hemifacial palsy, newborn ischemia of the brain, and even chronic low back pain. In 56 trials, MSC are the stem cells being used and in 88, HSC.

These studies are being performed not only in the Western world (United States, Australia, Canada, Ireland, Israel, France, Germany, Italy, Ireland, Spain, Norway, United Kingdom) but also in many other countries, including Brazil, Egypt, Turkey, Malaysia, India, Iran, Korea, China, Taiwan, and Mexico (table e-1 on the *Neurology*[®] Web site at www.neurology.org). Of these, 23 are financially supported by industry and private companies. The worldwide distribution of the registered companies dealing with stem cells is shown in the figure.

Unfortunately, in addition to these registered trials, there are numerous private or commercial stem

cell “centers” and companies that offer so-called stem cell treatments for various neurologic conditions. The development of relatively easy ways and feasible techniques for harvesting and producing large quantities of adult somatic stem cells has led to the appearance of a great number of “stem cell” laboratories and companies, worldwide. This is especially prominent in Asia and in the less developed countries and is usually not sufficiently controlled by a scientific institution. Even worse, in such centers stem cell treatments are provided on a basis of high fees and unrealistic promises of curing every neurologic condition, despite their experimental nature. In China, the authorities decided to freeze all stem cell–related activity for 1 year in order to reduce this phenomenon of stem cell medical tourism.

The exact number of patients who have been treated at such “stem cell facilities” remains unknown, but is estimated at several thousand. The sad results of this treatment not only include the “bad name” that is given to the whole field of stem cell clinical research, but also substantial dangers and life-threatening side effects. The development of a brain tumor was reported in 1 case and catastrophic encephalomyelitis in another, following “stem cell therapy” (of unknown quality) in such centers.^{9,10} This reinforces the need for proper control of cellular therapies with stem cells and their performance under strict, required conditions, in well-organized scientific centers.

In conclusion, a decade of intensive preclinical and clinical research has advanced our understanding of the role of stem cells in neurologic diseases, but these steps have still not clarified the picture. Despite a great deal of positive data supporting the possibility of neuronal regeneration and neuroprotection, information on long-term safety and scientifically proven efficacy is lacking. Stem cells should not represent a panacea for every neurologic condition, nor be the red flag in neurologic research. Future controlled studies using suitable clinical and surrogate markers (novel MRI and electrophysiologic techniques) to substantiate neuro-regeneration and restoration of neurologic function should provide the missing information and offer better answers to many open questions. In the meantime, the phenomenon of stem cell medical tourism and “stem cell” facilities on

a profitable basis should be effectively controlled, since it may jeopardize the overall progress of stem cell research.

DISCLOSURE

The author reports no disclosures relevant to the manuscript. **Go to Neurology.org for full disclosures.**

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