

Stem Cell Therapies in Clinical Trials: Progress and Challenges

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Clinical investigations using stem cell products in regenerative medicine are addressing a wide spectrum of conditions using a variety of stem cell types. To date, there have been few reports of safety issues arising from autologous or allogeneic transplants. Many cells administered show transient presence for a few days with trophic influences on immune or inflammatory responses. Limbal stem cells have been registered as a product for eye burns in Europe and mesenchymal stem cells have been approved for pediatric graft versus host disease in Canada and New Zealand. Many other applications are progressing in trials, some with early benefits to patients.

Introduction

Stem cell therapies have been expected to bring substantial benefit to patients suffering a wide range of diseases and injuries. It was expected that the benefits of bone marrow transplants for patients needing reconstruction of their hematopoietic and immune systems would apply to stem cell transplants of other cell types, and optimism has been high for the utilization of pluripotent stem cell types (embryonic stem cells [ESCs] and induced pluripotent stem cells [iPSCs]) for a variety of applications.

For the entire area of cell therapies in 2014, 70% of trials were sponsored by academic institutions (public funding) and 30% by companies (the private sector) (Bersenev, 2015). A combination of public and private funding was strongly advocated in the funding of translation and clinical stem cell trials for sustained capacity by the Californian Institute for Regenerative Medicine (CIRM) (Trounson et al., 2010). There is a very significant investment overall in the field of stem cell clinical trials that deserves monitoring and evaluation. Successful new therapies come at a considerable cost that cannot easily be sustained without evaluation and guidance. We have explored the clinical trials in which data have now been published and which the general and science community are anxious to follow given the investment of research resources and finance. These trial outcomes will deserve continuous evaluation to enable an understanding of the extended timeframes involved in realizing successful products and an understanding of the collateral losses for potential products that are unable to meet the demands of the regulatory system and clinical efficacy of therapy.

Since previous reviews of stem cells in clinical trials (Ratcliffe et al., 2013; Trounson et al., 2011), there has been a continuing expansion in the number and type of stem cells under study. We examined the reports of clinical trials in the NIH and European databases to classify them by stem cell type and disease application. We searched for clinical trial data published in peer-reviewed journals and sought out publically available information on trials performed by companies. Data for some studies are regularly published, but for many trials data are unavailable or not easily accessed. Given the relative immaturity of the cell therapy field, it is important to know the outcomes of early clin-

ical trials to help guide others in the processes. The overall impression is that considerable investment has been made in preclinical research and clinical trials, but as yet there is only a modicum of success being achieved. However, clinical reports will continue to evolve and general trends will emerge. It is clear that limbal stem cells have matured, neural stem cells show considerable promise for regenerative repair, pluripotent stem cells have an abundant potential in regenerative medicine, and mesenchymal stem cells (MSCs) are numerically the most favored cell type presently under clinical trial. These studies attract a lot of attention for commentary in the press and patient expectations of substantial benefits. We also considered placental-derived stem cells that are frequently MSC-like and endothelial stem or progenitor cells because of their close relationship to perivascular repair necessary in regenerative medicine.

The prevalence of cell therapies for injury and disease of the eye is a notable trend. This progress is a result of a few factors, including the relatively small numbers of cells required, easy accessibility for surgery, and straightforward assessment and visualization of grafts. There also appears to be some immune privilege for allogeneic transplants to the eye. Furthermore, one eye can be used as a control when cell therapy is applied to the other eye because disease is generally bilateral. It is also relatively easy to differentiate pluripotent cells into cell types needed for regenerative purposes in the eye. Consequently numerous types of cells have been used in clinical trials for eye disease and injury.

The present Review has been confined to published reports of stem cell clinical trials and excludes the very substantial literature on hematopoietic (blood) stem cells and associated gene therapies and cancer cell therapies. The latter has dramatically expanded with the success of chimeric antigen receptor technology but presently doesn't involve stem cells. The published data on registered clinical trials involving stem cells other than hematopoietic stem cells is relatively lean and we examine and discuss the safety and efficacy data that have been provided in publications or company reports. In this young field with considerable promise, there are exciting prospects for many different stem cell therapies that are arising from the early trials

Table 1. ESC Trials

Trial Sponsor (Location)	Disease Target	Cell Therapy	No. Patients	Phase
Chabiotech Co. Ltd. (S. Korea)	macular degeneration	human-ESC-derived RPE	12	phase I/II
Ocata Therapeutics (MA, USA)	Stargardt's macular dystrophy	human-ESC-derived RPE	16	phase I/II
	macular degeneration	human-ESC-derived RPE	16	phase I/II
	myopic macular degeneration	human-ESC-derived RPE	unknown	phase I/II
Pfizer (UK)	macular degeneration	human-ESC-derived RPE	10	phase I
Cell Cure Neurosciences Ltd. (Israel)	macular degeneration	human-ESC-derived RPE	15	phase I/II
ViaCyte (CA, USA)	type I diabetes mellitus	human-ESC-derived pancreatic endoderm cell	40	phase I/II
Assistance Publique-Hopitaux de Paris (France)	heart failure	human-ESC-derived CD15+ Isl-1+ progenitors	6	phase I
International Stem Cell Corp. (Australia)	Parkinson's disease	human parthenogenetic-derived neural stem cells	unknown	phase I/II
Asterias Biotherapeutics (CA, USA)	spinal cord injury	human-ESC-derived oligodendrocyte precursor cells	13	phase I/II

as well as some disappointments that are tempering the optimism for new cures occurring rapidly across a large spectrum of disease and injury.

Pluripotent Stem Cells

Both ESCs and iPSCs are making their way into clinical trials (Table 1) after considerable optimism for their therapeutic potential. They are of most interest where functional adult stem cell types are difficult to access, expand, or derive. It appears that applications in the eye, pancreas, and various neural degenerative disorders or injuries such as Parkinson's disease, amyotrophic lateral sclerosis (ALS), and spinal cord injury are leading candidates for pluripotent stem cell-based cell therapy.

The original Geron Inc. clinical trial of human ESC (hESC)-derived oligodendrocyte progenitors for the treatment of spinal cord injury, the first of its kind to use ESCs, was terminated when the company decided to discontinue their cell therapy program to concentrate on cancer treatments. They treated five patients without any adverse findings with a dose below that expected to show any efficacy. The estimated costs of the preclinical studies (US\$200 million) (Keirstead, 2012, Spinal cord injury: what are the barriers to cure? Bedford Center Workshop) were very high because of the pioneering data required to show safety against teratoma formation and animal model efficacy needed for the first in human studies of hESCs. The actual clinical trials were also very costly because of the number of trial sites, training for the transplant procedure, and cell manufacturing. The study is now continuing under the direction of Asterias Biotherapeutics who have registered a dose escalation phase I safety trial with the FDA, using the same hESC-derived oligodendrocyte progenitor cells administered 1–2 weeks after spinal cord injury.

Preliminary results have been reported by the company Ocata Therapeutics (formally ACT) on clinical safety trials for the use of retinal pigmented epithelial cells (RPEs) derived from hESCs for dry macular degeneration and Stargardt's macular dystrophy (Schwartz et al., 2012, 2015). They were able to derive RPEs that were 99% pure from hESCs. There were 9 patients with macular degeneration and 9 patients with Stargardt's disease in dose cohorts of 50,000, 100,000, and 150,000 cells administered to one eye of each patient. The only adverse events were

associated with surgery and immunosuppression. Visual acuity improved in 10 treated eyes, was stable in 7 eyes, and decreased in 1 eye over 22 months. Patches of regenerated retinal epithelium were observed in 72% of the patients although the spread was variable and incomplete, suggesting that improvements could be made to the methodology to achieve greater RPE monolayer coverage of the macula. Other clinical studies are emerging on macular degeneration, which include studies in the UK and in California, where ESC-derived RPEs are grown as a monolayer on ultra-thin scaffolds and inserted under the photoreceptor cells to cover the entire macula. There is also a report of one Japanese patient who received a transplant of a sheet of iPSC-derived RPE (Cyranoski, 2014). This is the first in human study that may be the leader in many other applications of iPSC derivatives. While it might be expected that iPSCs will be used as autologous therapies, there is a strong movement for their use as allogeneic transplants or as partially compatible HLA haplotyped derivatives (Turner et al., 2013).

Reports of progress for other indications undergoing treatment with pluripotent stem cells are not available as yet. This includes the use of insulin-producing β Islet cells contained in a subcutaneous capsule to prevent cell-mediated autoimmunity in patients with type I diabetes (Schulz et al., 2012). This study is an open label dose-escalating phase I/II trial involving 40 patients. The first patient received a transplant in November 2014 of two subcutaneous capsules of β Islet progenitors differentiated from ESCs. This study is being conducted by the company ViaCyte in California and the results will be interesting because there will be a functional readout of the transplanted cells controlling diabetes. In the Viacyte studies the final stages of maturation to glucose-responsive insulin-producing cells needs to be done in vivo. More recently two research groups reported the apparent complete maturation of cells into β Islet cells in vitro, but at this stage it is not known if this may benefit their efficacy when used in clinical trials or not (Kushner et al., 2014).

There was also a recent announcement by International Stem Cell Corporation that they will begin clinical studies in Australia in 2015. The study will use parthenogenetic ESC-derived neural cells for the treatment of Parkinson's disease (ISCO, 2015). The main concern for this study may be how well

the differentiation protocol is able to derive pure A9 dopaminergic neurons, given the potential for associated dyskinesia from the contamination of serotonergic neurons (CIRM, 2013). Attempts to replicate the positive outcomes from human fetal ventral mesencephalon tissue transplants, using pluripotent stem cells, are a major focus that has challenged researchers to derive the nigral A9 dopaminergic neurons that are able to functionally recover the 6-OHDA animal model of Parkinson's disease when grafted at a dose equivalent to that used for fetal VM, as recently shown by Grealish et al. (2014). These challenges have been summarized by Barker (2014) in discussing the consortia involved in fetal brain transplants and the newly formed Parkinson's Global Force (Abbott, 2014) that is guiding researchers to optimize their cell characterization and the patient subgroups likely to respond to therapeutic transplants. There is concern that clinical trials based on less robust criteria may again set back the clinical progress toward successful therapy for this disease.

Limbal Stem Cells

Limbal stem cell transplants have been used very successfully to restore functional corneal epithelium that is transparent and self-renewing in patients who have corneal destruction, usually due to burns (Rama et al., 2010). The limbal cells are autologous transplants obtained from the limbus, providing even a tiny part in either of the patient's two eyes has been spared from injury, and they are expanded in culture on fibrin (Rama et al., 2010) or human amniotic membrane (Kolli et al., 2010) that preserves and enables expansion of the holoclone cells. Allogeneic limbal cells do not persist long-term after transplantation (Pellegrini and De Luca, 2014).

iPSC derivation of the limbal lineage may eventually provide a therapeutic source of limbal cells for patients for whom complete bilateral destruction or loss or absence of the limbus has occurred. Recent advances in the identification of key regulatory genes in limbal development, differentiation, and expansion are likely to accelerate this therapeutic opportunity (Pellegrini et al., 2014). In the meantime, transplantation of in vitro cultured non-ocular autologous oral mucosal epithelium has been used in patients with bilateral limbal cell deficiency, particularly for acute chemical burns. This procedure can give satisfactory results (Burillon et al., 2012; Chen et al., 2009) and provide adequate re-epithelialization and stabilization of the surface of the cornea if the cultured autologous thin sheets (with a few cells' worth of thickness) of oral mucosal epithelium are lifted with temperature sensitive cell sheet-lifting technology that preserves the cultured cell-cell junctions and an intact basement membrane for transplantation (Burillon et al., 2012). This method appears to prevent the vascularization and loss of corneal opacity previously associated with oral mucosal transplants that often had multiple epithelial layers of stratification and numerous mucosal cell structures (Chen et al., 2009).

Cadaveric limbal tissue can be preserved with intact structure at 4°C for up to 8 days by airlift culture (which is a method wherein the stromal component of the cornea is submerged in liquid culture medium and the epithelium is exposed to air for culture or cold preservation) and used for allogeneic transplants that provide complete corneal re-epithelialization for at least 1 month (Li et al., 2013). This result suggests allogeneic limbal

stem cell therapies are steadily progressing. However, a recent study on allografts in Aniridia and Stevens-Johnson Syndrome that used a defined outcomes set procedure for cultured limbal cell epithelium transplants for bilateral limbal cell deficiency showed improvements in epithelial integrity and visual acuity up to 12 months but then a gradual decline over 3 years (Shortt et al., 2014). Typically restoration of the corneal epithelium can now be achieved in the majority (~67%) of auto- and allogeneic transplants for partial and total limbal stem cell deficiency without easily detectable alteration to visual acuity (Zakaria et al., 2014).

Neural Stem Cells

Neural stem cell derivatives are in a number of clinical trial applications (Table 2). The applications are primarily aimed at repairing the damaged central nervous system. The best type of neural cell for regenerative repair of the central nervous system is still yet to be determined and may vary according to the disease or injury. It is generally considered that a neural stem cell is probably ideal for establishing a stem cell pool for continuous supply of the desired neuron, astrocyte, or oligodendrocyte. However, mature neural cells may also be necessary when specific cell types are needed to achieve normal function. For example, nigral A9 dopaminergic neurons are needed in Parkinson's disease. It can be surprising that a brain neural stem cell can repair loss of RPE in macular degeneration. Clinical studies will also eventually determine whether a neural stem cell or oligodendrocyte progenitor is best for spinal cord repair.

Studies by the Stem Cells Inc. group have used human fetal-derived neural stem progenitors, which show lifelong lysosomal enzyme production, to treat very advanced infantile or late-infantile ceroid lipofuscinosis (Batten's disease) in children without any detectable adverse events (Selden et al., 2013). Doses of 1 billion cells into the brain were well tolerated in these patients. Furthermore, the allogeneic cells showed long-term survival of the transplanted cells in autopsy 2.5 years later and 1.5 years after the termination of immunosuppression. Three patients (of six) are more than 5 years post-transplant. The company has also treated young patients with the fatal genetic demyelination condition known as Pelizaeus-Merzbacher disease (PMD) (Gupta et al., 2012). The neural progenitors were surgically implanted into the frontal lobe white matter in four young patients with an early-onset severe form of PMD and some modest gains in neurological function were observed in three patients. Cranial magnetic resonance imaging and MR spectroscopy indicated that myelination occurred in the site of transplantation when compared to white matter sites distant to transplantation. Further progress has been limited because it is difficult to recruit young patients prior to the exhibition of the advanced disease phenotype. These studies indicate that it may be possible to halt the advance of severe genetic disorders by providing neural stem cell transplants that are vehicles for delivery of the correct protein.

Perhaps more challenging is the treatment of stroke and other disorders of the brain and spinal cord. Despite a very large number of studies in animals using neural, embryonic, mesenchymal, bone marrow, and cord blood cell types, there appears "little evidence that transplanted stem cells or their derivatives can replace damaged cells, reconstruct neural circuits, or improve

Table 2. Neural Stem Cell trials

Trial Sponsor (Location)	Disease Target	Cell Therapy	No. Patients	Phase
City of Hope (CA, USA)	recurrent high grade gliomas	<i>E. Coli</i> CD-expressing neural stem cells	24	phase I
	recurrent high grade gliomas	carboxylesterase-expressing neural stem cells	53	phase I
Neuralstem Inc. (MD, USA)	ALS	fetal-derived neural stem cells	18	phase I
	ALS	fetal-derived neural stem cells	18	phase II
	chronic spinal cord injury	fetal-derived neural stem cells	4	phase I
ReNeuron Ltd. (UK)	stroke	human neural stem cells	12	phase I
	stroke	human neural stem cells	41	phase II
	lower limb ischemia	human neural stem cells	9	phase I
Stem Cells Inc. (CA, USA)	neuronal ceroid lipofuscinosis	human CNS stem cells	6	phase I
	cervical spinal cord injury	human CNS stem cells	50	phase II
	macular degeneration	human CNS stem cells	15	phase I/II
	thoracic spinal cord injury	human CNS stem cells	12	phase I/II
	Pelizaeus-Merzbacher disease	human CNS stem cells	4	phase I
TRANSEURO (UK)	Parkinson's disease	fetal-derived dopaminergic cells	40	phase I
Wroclaw Medical University (Poland)	spinal cord injury	olfactory ensheathing cells, autologous	10	phase I

loss of function following stroke" (Huo et al., 2014). However, the company ReNeuron uses immortalized human fetal neural stem cells for transplantation to stroke patients and has reported no cell-related or immunological adverse events in a phase I study of 11 patients in their followup after 12 months (ReNeuron, 2014). These immortalized human neural stem cells do not colonize brain tissue and are a transient population that appears to have a trophic influence on brain function. While the study was not designed to measure efficacy, some improvements were observed in patient spasticity and neurological impairment. A second phase II trial is underway for the evaluation of the benefit of these neural stem cell transplants 2–4 months after stroke, involving a futility study of 41 patients (no controls) in two separate trial cohorts.

ALS is an adult onset neurodegenerative disease that is a result of motor neuron degeneration in the cerebral cortex, brain stem, and spinal cord. A phase I study by the company Neuralstem for ambulatory and non-ambulatory ALS patients used intraspinal injection of 500,000 to 1 million human fetal spinal cord neural stem cells into the lumbar and cervical regions of the spinal cord. This study showed no cell-related adverse events but little indication of improved survival benefit (Feldman et al., 2014; Glass et al., 2012; Riley et al., 2012). An ambulatory phase II study involved multiple cervical injections of 2–8 million cells or 160 million cells into the lumbar and cervical spinal cord regions (Thomsen et al., 2014). While preclinical ALS animal model studies show some efficacy of prolonged survival after neural cell transplants (Lee et al., 2014a; Thomsen et al., 2014), significant benefit is still awaited for ALS in human phase II clinical trials.

Neural stem cells are also in clinical trials for spinal cord repair. The use of adult olfactory nasal ensheathing cells for differentiation into neural progenitors for spinal transplantation (Tabakow et al., 2013) is complicated by the possible retention of the unwanted growth of a multicystic mass of mixed nasal cell phenotypes (Dlouhy et al., 2014). This has not been the experience

with transplants of fetal-brain-derived neural stem cell progenitors. The company Stem Cells Inc. has been undertaking a Phase I/II clinical trial of their fetal neural stem cell progenitors in 12 chronic stage (ASIA-A and B) patients with T2–T11 injuries in Switzerland. They received a total dose of 20 million cells in four injections above and below the site of injury. There have been no adverse cell-related effects reported in these patients, and there have been segmental gains in sensory and electrophysiological response that occur over time. Several patients progressed from ASIA-A to B (patients with some rectal control) and some had a return of minor motor control capacity. Patients are now being recruited for phase II trials in Canada and the USA involving the more common cervical injuries (StemCells Inc., 2014).

Based on evidence in animal studies for the capacity of human neural brain stem cells to protect against retinal degeneration and maintenance of photoreceptor health (McGill et al. 2012; Cuenca et al., 2013), the company Stem Cells Inc. has also used its neural stem cells for treating human blindness due to dry macular degeneration. In a phase I/II dose escalation study (200,000 to 1 million cells), they showed stable and improved visual acuity in subjects at 6 and 12 months after subretinal injection of neural stem cells with reduced growth of retinal geographic atrophy of the treated eye versus the non-treated eye (StemCells Inc., 2015). A phase II proof-of-concept study is now underway to confirm the maintenance of sight in this type of patient.

Transformed neural stem cell lines have also been used to carry a payload of cytotoxic drugs to the site of glioblastoma tumors in the brain. These studies rely on the homing characteristics of neural stem cells to tumors (Aboody et al., 2000). Researchers at the City of Hope, LA have genetically modified neural stem cells with enzymes that are able to convert prodrugs administered to patients to highly potent cytotoxins in the localized sites of the tumor (Aboody et al., 2013). The primary clinical studies have shown conversion of the prodrug flucytosine (5-FC)

Table 3. Placental Stem Cell Trials

Trial Sponsor (Location)	Disease Target	Cell Therapy	No. Patients	Phase
Celgene Corporation (NJ, USA)	stroke (terminated)	human placenta-derived cells	44	phase II
	pulmonary sarcoidosis (terminated)	human placenta-derived cells	4	phase I
	CD	human placenta-derived cells	14	phase I
	MS	human placenta-derived cells		phase I
	peripheral artery disease	human placenta-derived cells	24	phase I
	rheumatoid arthritis	human placenta-derived cells	26	phase II
Karolinska Institute (Sweden)	GVHD	decidual stromal cells (MSC-like)	30	phase I/II
	hemorrhagic cystitis	decidual stromal cells (MSC-like)	12	phase I/II
Prince Charles Hospital/Mater Medical Research Institute (Australia)	idiopathic pulmonary fibrosis	placental mesenchymal stromal cell	8	phase I
New York Medical College (NY, USA)	immune disorders	human placental-derived stem cells	30	phase I

to 5-fluorouracil (5-FU) and patient tolerance to administration of the prodrug. A dose escalation study is underway to assess efficacy of this treatment on glioma reduction (Hirmand, 2014). The group is also exploring the use of engineering carboxyl esterase into neural stem cells to activate the potent cytotoxin CPT-11 for destruction of lung and brain cancers (Hong et al., 2013). There are no data available from these clinical studies as yet.

Endothelial Stem or Progenitor Cells

There are many (>60) clinical trials listed on the NIH clinical trials website (<https://clinicaltrials.gov/>) for endothelial stem/progenitor cells, the majority with unknown status. Of the 12 studies of known status, all are autologous transplants, 11 are phase I/II trials, and 1 is phase II. In these studies the cells are either sourced from the bone marrow or peripheral blood. Treatments include transfusion of endothelial progenitor cells in patients with idiopathic pulmonary arterial hypertension, where improvements were observed in walking distance, mean pulmonary artery pressure, pulmonary vascular resistance, and cardiac output (Wang et al., 2007). They have also been used for refractory angina in an attempt to foster angiogenesis (Jimenez-Quevedo et al., 2014). In this trial of 28 patients (19 treated and 9 controls), there were no adverse cell-related effects (one patient in the treatment group and one in the control group died) but there was a reduction in the mean number of angina episodes per month in the treatment group. Otherwise efficacy parameters were not different. Some benefit of autologous endothelial cell transplants was seen in post-mastectomy lymphedema volume, but other parameters were not different from those of controls (Maldonado et al., 2011). A number of trials have also been undertaken for critical limb ischemia, using the autologous CD34⁺ fraction (endothelial and hematopoietic stem cells) of granulocyte colony-stimulating factor (GC-SF) mobilized blood cells (Kawamoto et al., 2009; Kinoshita et al., 2012). These have shown strong favorable trends in efficacy parameters that encourage further randomized and controlled phase II trials to protect against serious disease sequelae. While a genuine therapeutic role for endothelial progenitor cell transplantation remains highly desirable for repair of vascular injury, strong evidence for repair of the cardiovascular system by endothelial progenitor cells from human clinical trials remains to be demonstrated (Mitchell et al., 2015).

It is of interest that bone marrow MSCs are being trialed for critical limb ischemia without endothelial cells with very minor benefits noted in phase I/II trials (Gupta et al., 2013). Serious adverse events occurred in both placebo and treatment arms. Umbilical cord blood MSCs have also been used in phase I studies without influencing serious events and showing some very minor improvements in angiographic scores (Yang et al., 2013). It would be interesting to compare MSCs with and without endothelial cell combination treatments.

Placental Stem Cells

Cells derived from the human placenta are in clinical trials for a variety of therapeutic applications (Table 3). A fraction identified as placental MSCs by its adherence to plastic and expression of typical cell surface markers has been used to treat patients with idiopathic pulmonary fibrosis. In a single-center, non-randomized, intravenous dose escalation (1–2 million cells/kg) phase I study, some minor and transient acute adverse effects were shown and no observable improvement in any parameters relating to the disease condition was seen 6 months after transplantation (Chambers et al., 2014). The company Celgene is also using placental derived cells (MSC-like) to treat Crohn's disease (CD) (Mayer et al., 2013) and multiple sclerosis (MS) (Lublin et al., 2014). Crohn's patients treated with two injections (1 week apart) of 2 million cells showed improved clinical response and half were in remission 6 months after placental cell injection. At a higher dose of 8 million cells, only one-third of patients that were treated responded, and none were in remission after 6 months. These data indicate clinical variations in response to cell therapy that are critically dose related. In patients with relapsing-remitting and secondary progressive MS, the cells were well tolerated but the treatment resulted in a variety of minor adverse events. Data for clinical responses were variable and generally indicated that the cells did not improve the MS condition. It is apparent that more information is needed on the mechanism of action of placental cells to enable better strategic design for potential benefits to MS patients to warrant expanded cell therapy trials.

There is interest in using cells of the amnion for clinical improvement of lung function in preterm babies and for other adult respiratory disorders (Murphy et al., 2014). However, these cells cannot be expanded in vitro and there is evidence that

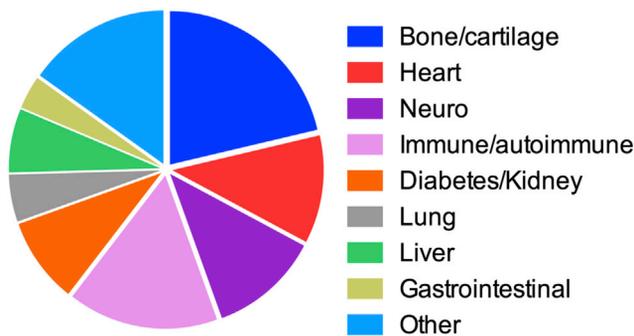


Figure 1. Indications Being Addressed using MSCs in Clinical Trials
Data for 352 registered clinical trials.

amniocytes obtained from preterm placentas have limited differentiation and reparative capacity *in vitro* and in animal models of pulmonary fibrosis (Lim et al., 2013). Amniotic fluid cells have also been studied in preclinical models for a wide range of therapeutic applications including repair of brain injury (Rennie et al., 2013), but they have never progressed to first in human clinical studies.

MSCs

Cell therapies utilizing MSCs are being explored in a large number of clinical trials. There is considerable heterogeneity in the cells described as MSCs and a variety of sources used to isolate and manufacture the MSC populations for clinical trials. Important perspectives on the very different nature of the MSC populations in use clinically and their various sources have been critically addressed recently by Bianco (2014). MSCs are classically the “postnatal, self-renewing, and multipotent stem cells giving rise to all the skeletal tissues” (Bianco, 2014). They are clonogenic and form stromal progeny *in vitro* and, when transplanted, form miniature organoids of bone including bone and marrow, with host hematopoietic contributions. The stromal cell type that is called MSC in use clinically is defined differently from the classical MSC because they are isolated from various tissues (including bulk cultures of bone marrow stromal cell types) by their adhesive characteristics to plastic culture dishes and other plastic vessels. These stromal cell types all show common expression of general fibroblastic markers and when transplanted, they have properties of modulating the host immune system and other systems. These are generally transient cells that exist briefly in the host and cannot be identified after a few days or possibly a week or two. Their safety as allogeneic cell transplants may be closely related to their short-term existence. Their anti-inflammatory properties, homing to sites of damage and inflammation, and their trophic influence on tissue repair have made them very popular for clinical study.

In the NIH clinical trials database there are 374 registered clinical trials (excluding those of unknown status) using MSCs (Figure 1). This is a 3-fold expansion of trials over the number noted in 2011 (Trounson et al., 2011), but the distribution of trials by phase is much the same (Figure 2). This might suggest that products are not moving out of the clinical pipeline. The one phase IV study is for umbilical cord blood MSCs treating aplastic anemia that is presently recruiting patients in China. The majority

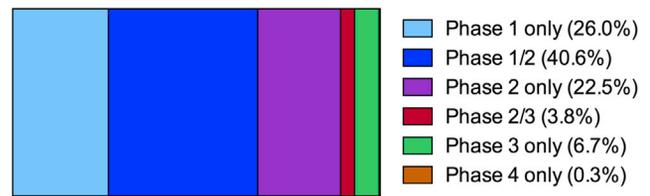


Figure 2. MSC Clinical Trials Classified by Clinical Phase
Data for 315 registered clinical trials.

of the MSC trials are with allogeneic cells and these trials are happening all over the world with the highest activity in the USA, Europe, and China. Of the phase 3 clinical trials, only three have reported completion.

The pleiotropic properties of MSCs that include anti-apoptosis, angiogenesis, growth factor production, neuroprotection, anti-fibrosis, and chemo-attraction provide a broad spectrum for their potential in disease therapies. This includes their properties of suppression of inflammation and their abilities to downregulate pathogenic immune responses commonly observed with allogeneic transplantation (Glenn and Whartenby, 2014). We have subdivided the discussion of MSC clinical trials into conditions that utilize their immune suppression properties, applications for regeneration in organ diseases, osteoarthritis and related lower back pain (treatments for which primarily utilize their anti-inflammatory properties), and repair of neurodegenerative disease and injury.

Immune Suppressive Properties of MSCs

MSCs and their derivatives have important roles in suppressing activated T cell proliferation and their cytokine production. They also increase Regulatory T cells (Tregs) that dampen killer T cell attack on foreign cells or tissues (see the reviews of Bernardo and Fibbe, 2013; Glenn and Whartenby, 2014). These functions of MSCs have made them popular for studies involving containment of immune rejection in allogeneic grafting.

Systemic immunosuppression by bone marrow MSCs (1 million/kg) has been indicated in kidney allograft transplant patients for the possible improvement of rejection and fibrosis in donor organs (Reinders et al., 2013, 2014). Graft versus host disease (GVHD) is a serious consequence of the host immune system recognizing and rejecting allogeneic grafts. MSCs have important immune suppressive properties that inhibit GVHD and they have been studied in clinical trials for steroid resistant, severe, acute GVHD disease for some time. Early phase II studies by Le Blanc and colleagues showed that more than 50% of GVHD patients responded completely to one to five doses of a mean of 1.4 million bone marrow MSCs (Le Blanc et al., 2008). These complete responders had lower transplant-related mortality than the patients with partial or no response (37% versus 74%) and higher survival rate after 2 years (53% versus 16%). These data were supported for stage III–IV GVHD in children (0.4–15 years) receiving Prochymal MSCs (Prasad et al., 2011). Complete responses were observed in 58% of patients infused with 2–21 (mean 8) doses of 2 or 8 million MSCs. Five of the twelve (42%) children survived for a medium of 611 days. These studies led to registration for approval for the use of Prochymal MSCs in steroid resistant severe pediatric GVHD in Canada and New Zealand (Ratcliffe et al., 2013). Other

phase I/II studies in adults have confirmed the safety of MSC infusion for acute and chronic GVHD with variable but improved results for complete response and survival (Herrmann et al., 2012; Introna et al., 2014; Kuzmina et al., 2012; Liu et al., 2011; Muroi et al., 2013; Pérez-Simon et al., 2011). Data reported by Joanna Kurtzberg in 2015 for 160 children with GVHD not responsive to steroids who were enrolled in an expanded multicenter access program of Mesoblast Pty Ltd. MSCs again showed survival benefits for bone marrow transplants. Around 80% of grade B/C patients and 50% of the more severe grade D patients survived to 100 days. Only 5%–20% of these severe poor prognosis patients were expected to survive without MSC therapy (Mesoblast, 2015).

While clinical benefits were shown to be very minor and not of clinical value when MSCs were co-administered in haploidentical hematopoietic stem cell transplants for leukemia (Maziarz et al., 2015), the Athersys Multistem MSCs have shown some apparent benefit in reducing GVHD when used as adjunct therapy for myeloablative allogeneic bone marrow cell transplants (Liu et al., 2011). However, purification of hematopoietic stem cells and, in particular, the removal of alloreactive T cells can probably accomplish this even more effectively (Logan et al., 2012; Shizuru et al., 1996).

The immunosuppressive properties of MSCs have been proposed as treatments for CD, despite these properties being retained by CD patients' own endogenous MSCs (Duijvestein et al., 2010). The study showed that infusion of donor MSCs from healthy normal patients had little effect on recipient CD parameters, as would be expected (Duijvestein et al., 2010). However, another study showed a decrease in endoscopic active luminal CD (42%) in 7/15 patients given 2 million MSCs/kg (Forbes et al., 2014), suggesting that there may be clinical benefits of MSC therapy for CD. Likewise, intrathecal or intravenous injections of MSCs have been tried for advanced progressive and relapsing and remitting MS, with little detectable clinical benefit (Bonab et al., 2012; Connick et al., 2012; Llufríu et al., 2014; Yamout et al., 2010). There were some indications of minor reductions in MRI inflammatory parameters in the relapsing and remitting type of MS (Llufríu et al., 2014).

Myocardial Injury Benefits of MSCs

There has been a concerted effort to demonstrate a benefit of MSCs for cardiovascular repair, particularly a benefit to patients with severe myocardial infarct. Generally, autologous bone marrow cell transplants have been ineffective (Nowbar et al., 2014). Allogeneic MSC transplants have had variable benefits to patients with ischemic heart disease. Left ventricular ejection fraction was improved in patients given Prochymal MSCs when compared to placebo in a randomized, double blind, dose escalation study (Hare et al., 2009). Randomized comparisons of autologous and allogeneic MSCs (20–200 million) delivered as transendocardial injections showed a few differences (autologous cells improved 6 min walking), and only low dose allogeneic MSCs improved left ventricular ejection fraction (Hare et al., 2012). Furthermore, autologous MSCs appeared better than autologous bone marrow cells when administered as transendocardial injections (Bartunek et al., 2013; Heldman et al., 2014). Intracoronary administration of MSCs has had a minor benefit on the left ventricular ejection fraction (Lee et al., 2014b), and a meta-analysis of all cell therapies by intracoronary administra-

tion shows that there is no clinical benefit on left ventricular function (Gyöngyösi et al., 2015). Minor benefits were observed in weaning myocardial infarct patients from left ventricular assist devices when compared with sham controls when the former were treated with intramyocardial injections of 25 million of Mesoblast's MSCs (Ascheim et al., 2014). Genuine sustained benefits now need to be demonstrated in phase III studies. It is of interest to note that in at least one comparison of heart-derived cells and MSCs, the cardiosphere cell type outperformed MSCs (which were bone marrow and adipose derived) in a preclinical animal model (Li et al., 2012). The relative benefits of the intramyocardial injection of transient allogeneic MSCs and cultured cadaveric cardiospheres (CapricorTherapeutics, 2015) in clinical trials will be interesting to evaluate. It is also of some interest that scar size reduction and ventricular function occurs in sites of MSC injection rather than non-cell injection sites (Sun-ion et al., 2014). This suggests that the benefits of cells are localized to sites of injection.

MSCs for Osteoarthritis and Lower Back Pain

Bone marrow MSCs would be expected to contribute to bone and cartilage repair. In delayed bone fracture union, MSCs, when mixed with demineralized bone and platelet-rich plasma, halved the time to fracture union (Liebergall et al., 2013). Intra-articular injection of MSCs in osteoarthritic patients resulted in strong improvement in cartilage coverage and quality in the vast majority of treated cases (Orozco et al., 2013). Clinical parameters of pain, disability, and quality of life were improved. Likewise, patients with severe back pain due to degenerative disc disease improved dramatically, with 71% of optimal efficiency in the improvement of clinical parameters of pain and disability, but without disc height recovery (Orozco et al., 2011). Mesoblast has also reported the benefits of a single injection of MSCs (6 or 18 million) in a randomized, placebo-controlled phase II study of 100 patients with chronic low back pain due to degenerative disc disease. A single injection of 6 million MSCs gave substantial and sustained pain relief with 48% having no or minimal pain after 24 months compared with only 13% of patients without pain who received saline control injections (Mesoblast, 2015). The improvement in pain is a very important clinical benefit for this group of patients and further trials should confirm this benefit and hopefully improve the proportion of treated pain-free cases.

MSCs for Pulmonary Disease

The use of MSCs in pediatric bronchopulmonary disorders has been actively pursued. In preterm infants at high risk of bronchopulmonary dysplasia (BPD), umbilical cord blood MSCs (1 or 2 million MSCs/kg) were administered as intratracheal transplants (Chang et al., 2014). Levels of inflammatory cytokines were significantly reduced in lung aspirates 3 days after transplantation and BPD severity was lower in transplant patients. Studies in the adult have focused on acute respiratory distress syndrome (ARDS) treated with infusions of 1, 5, or 10 million MSCs/kg (Wilson et al., 2015). Three of nine patients had serious adverse events, although they were not believed to be related to cell infusion. Further studies are needed to determine benefits of MSC therapy for these types of patients.

MSCs for Liver Disease and Diabetes

Phase I/II clinical trials of MSC therapy for liver disease have shown some minor improvements in liver function. Liver in end

stage liver disease (cirrhosis) due to hepatitis B and C and alcoholic and cryptogenic causes showed some response in function as assessed by changes in creatinine, serum albumin, and bilirubin in response to autologous MSCs (El-Ansary et al., 2012; Kharaziha et al., 2009). The anti-fibrotic effects of autologous MSCs (which were 50 million MSCs administered on two occasions 4 weeks apart) were explored in patients with alcoholic liver cirrhosis (Jang et al., 2014). Improvements in histological liver biopsy samples were observed in 55% patients as well as some change in type-1 collagen and α -smooth muscle actin. Further studies are needed to confirm the clinical benefits of MSCs to patients with liver disease.

Some clinical studies are underway using MSCs in patients with type II diabetes. Data suggest some temporary change in metabolic parameters may occur with intravenous or intrapancreatic endovascular injection of Wharton's jelly (umbilical cord) MSCs (Liu et al., 2014).

MSCs for Ischemic Stroke and ALS

MSCs are also being used in ischemic stroke patients. Fat-derived allogeneic MSCs are being studied by intravenous injection within 2 weeks of stroke (Diez-Tejedor et al., 2014). The company Athersys is also undertaking a phase II double blind clinical evaluation of MSCs given intravenously 24–36 hr after stroke (Hess et al., 2014), but this was reported recently to show no clinical benefit (FierceBiotech, 2015). It is difficult to understand the mechanism of action of these approaches given the transient nature and lineage differentiation properties of MSCs. Clinical trials are also underway using MSCs for therapy in ALS (Karussis et al., 2010; Mazzini et al., 2010, 2012). No response to MSC injections was seen in MRI structures in the brain or spinal cord and there were no apparent post mortem indicators of beneficial change (Mazzini et al., 2010). Few clinical benefits were reported for either intrathecal or intravenous administration of autologous MSCs (Karussis et al., 2010; Mazzini et al., 2012).

Failures and Concerns for Stem Cell Clinical Trials

There have been many claims for multi- or pluri-potentiality for cells of various origins, such as the very small cells of the vascular system (multipotent adult progenitor cells, or MAPCs), umbilical cord blood cells, amniotic fluid cells, and others, that have not really converted to the broad spectrum of applications initially envisaged. There are autologous bone marrow stem cell trials being explored for many conditions, including stroke and ischemic heart disease. However, in the case of the latter, benefit has been related to factual discrepancies in the clinical data collected, rather than the administered cell therapy (Nowbar et al., 2014).

Clinical trial failures have been frequent for MSC therapies, and, more recently (Bersenev, 2015), MSC trials for ulcerative colitis and ischemic stroke (Athersys), cardiac repair (3 studies by Miltenyi Biotec; FBC Pharmicell, Korea; and Stempeutics Research), acute kidney injury (Allocure), ischemic stroke (Manipal Acunova, India), ARDS (China), critical limb ischemia (Raval et al., 2014), and MS (Spain) have failed or been terminated. While clinical trial failures are to be expected in the early days of clinical research, these disappointments are a reasonably common feature of this first wave of cell therapy trials involving autologous and allogeneic MSC products.

While there is little scientific basis for the differentiation of MSCs to functional neurons, there is a registered phase I/II clinical trial in Russia using autologous MSC-derived neural cells (with “a matrix scaffold as necessary”) in 30 patients with traumatic spinal cord injury (Averyanov, 2014). As yet, there are no results available for this study, which began recruitment in July 2014; there were no preclinical data provided to support this dubious type of approach.

In contrast to the care taken to ensure the appropriate cell type is used for transplantation by others in the field, there has been one clinical trial reported using undifferentiated and partially differentiated ESCs to treat cerebral palsy in children in India under approval of an “independent ethics committee” and a “national apex body” (Shroff et al., 2014). The cells were delivered by intravenous or intramuscular injection and a variety of other routes. It is possible that most of the cells were dead because of the methods used, but this is a potentially dangerous treatment of transplanting undifferentiated pluripotent stem cells that could have resulted in the formation of teratomas in these children. These types of studies are very concerning for the field.

Progress and Cautionary Notes

The progresses of stem cell clinical trials are encouraging given that the majority are in the early phase I/II stage and in most cases, clinical data is still being accumulated. It remains too early to be confident that pluripotent stem cells will deliver their considerable promise. As yet iPSCs have not received regulatory approval to begin appearing in first in human studies, although one patient has been treated for macular degeneration. Neural stem cells are progressing with some interesting applications. It is interesting that Stem Cells Inc. brain stem cells are capable of acquiring some of the RPE cell properties such as phagocytosis and secretion of neuroprotective factors. There is no evidence that they make photoreceptors, but they do seem to preserve synaptic connections between the photoreceptors and the bipolar and horizontal cells as evidenced by the presence of synaptic ribbons in eyes receiving transplants (Cuenca et al., 2013). The neural stem cells derive from primitive brain tissue of the early fetus, which may include anterior neural plate cells from which RPEs are derived (Graw, 2010). Studies on spinal cord injury show some touch sensitivity benefit but little motor response for neural stem cell therapies as yet. There is also little evidence of benefit of neural stem cell therapy for stroke patients as yet, despite well-organized consensus-based guidelines for clinical stem cell therapies for stroke (Savitz et al., 2011, 2014). The majority of clinical trials to date have used non-neural cell types.

Autologous limbal stem cell expanded cultures (Holoclar) have been recently formally approved and registered for clinical use by the European Medicine Agency and the European Commission as the first advanced therapy medicinal product containing stem cells (European Medicines Agency, 2015). Holoclar will be used for moderate to severe limbal stem cell deficiency caused by physical or chemical burns to the eye in adults. This is a major development for global stem cell medicine. Research will continue to explore the opportunity to establish allogeneic limbal stem cells for effective corneal therapies from pluripotent stem cell sources.

Autologous endothelial stem or progenitor cells show preclinical value for vascular disease and deficiency such as that seen in critical limb ischemia. These cells in combination with MSCs or other drug regimes may be shown to be effective as the early clinical trials continue to evolve. Presently it is too early to make strong predictions of their likely clinical benefits but there are some encouraging data beginning to appear that warrant further study.

Placental, bone marrow, and fat-derived stromal cells or MSCs feature far and away in the largest number of clinical trials currently underway. They have been shown to be remarkably safe although transitory in their presence following transplantation. It has not been determined if this is due to a rapid process of removing foreign cells or their short half-life. Since they are immune suppressive it is likely that they are rapidly turned over in tissues such as the lung where they generally lodge in large numbers when administered by intravenous injection. There appears to be very little difference between autologous and allogeneic MSCs in their actions or clinical effects, suggesting that they deliver a payload of cytokines that have immune-modulatory effects and other influences on endogenous tissue regeneration. They appear to migrate to inflammatory sites and have inflammatory suppressing effects that are pro-regenerative for the affected tissue. They are rarely identified as colonizing in tissue repair mechanisms. However, there is a general lack of knowledge around their actual mechanism of action that is a handicap for modifying clinical strategies to improve their actions (see discussion of “Roadblocks to translation of stem cell therapies” in [Dimmeler et al., 2014](#)). Nevertheless, clinical benefits have been observed in many early clinical trials that have attracted continued funding for larger-scale efficacy studies. The contributions of bone marrow MSCs to bone and cartilage repair and reduction of osteoarthritic and lower back pain are impressive. Likewise, their use for controlling GVHD, particularly in children, is important for cancer and transplantation medicine. Whether MSCs from sources other than bone marrow can also show these clinical benefits is less certain. Notably the Janssen Company has MSC-like umbilical cord tissue cells in early clinical trial for macular degeneration but there are no clinical data available as yet. It is also too early to decide if placental stem cells, whether stromal or otherwise (such as amniocytes) have a future significant role in clinical medicine. Clearly the research will continue to probe these opportunities.

Some of the failures in clinical trials may be predicted on the basis that there was insufficient scientific data to support a strong clinical benefit ([Dimmeler et al., 2014](#)). In other cases, there is insufficient clinical benefit apparent in early efficacy studies to warrant further commitment of relatively scarce finances. It is critically necessary to show clear and significant clinical benefit in phase II studies because the heterogeneity of human disease in more extensive phase III or IV studies will often erode the significance of minor benefits apparent in early trials. The new regulatory pathway established in Japan ([Konomi et al., 2015](#)), where products may enter the marketplace with provisional approval if phase II studies show efficacy, will test the robustness of the entire global regulatory systems. If products become available without testing for sufficient benefit then patients will not be served well by the evolving cell therapies. If the need for regulated phase III studies can be dispensed

with, many more products may become available in a shorter timeframe and more cost-effective manner. The present Review shows that cell therapies are rapidly evolving but few at present would have demonstrated sufficient clinical benefit to warrant their adoption as useful therapies in an abbreviated regulatory system. As studies with stronger scientific evidence of likely clinical benefit and demonstrated mechanisms of action evolve from preclinical trials, it might be expected that the conversion to registered stem cell therapies will increase strongly with time. We are optimistic from the present Review that there will be many stem cell products that will meet the criteria for registered products in the established regulatory systems over the next 5 years.

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