

# Chapter

## Mesenchymal Stromal Cells to Treat Brain Injury

Ciara C. Tate and Casey C. Case

*SanBio, Inc.*

*Mountain View, California*

*United States of America*

### 1. Overview of traumatic and ischemic brain injury

Brain injury occurs from either a traumatic (mechanical), ischemic (decreased oxygen; accounts for 83% of stroke cases), or hemorrhagic (ruptured blood vessel; accounts for 17% of stroke cases) insult to the brain. Stroke and traumatic brain injury (TBI) are major contributors worldwide to both deaths and persistent disabilities. Stroke is the third leading cause of death (behind heart disease and cancer) in the United States, with 137,000 Americans dying from stroke each year (Heron *et al.*, 2009). Stroke is the leading cause of serious, long-term disability in the United States. Currently, 795,000 people have a stroke each year and 15-30% of survivors have a permanent disability (Roger *et al.*, 2011). Annually, 1.7 million people sustain a TBI in the United States, resulting in 52,000 deaths and over 124,000 permanent disabilities each year (Faul *et al.*, 2010). Annual direct (e.g., medical) and indirect (e.g., loss of productivity) costs to the United States are \$41 billion and \$60 billion for stroke and TBI, respectively (Finkelstein *et al.*, 2006; Roger *et al.*, 2011).

Though the etiology differs between traumatic and ischemic injury, there are many similarities in their pathology (Bramlett & Dietrich, 2004; Leker & Shohami, 2002). The primary insult initiates a cascade of secondary events such as edema, excitotoxicity, and increases in free radicals, which act to spread the injury to surrounding tissue (for reviews of the pathology, see Greve & Zink, 2009 for TBI and Mitsios *et al.*, 2006 for ischemic stroke). Note that ischemia is part of the secondary injury response for TBI (Coles, 2004; Garnett *et al.*, 2001). The brain attempts to repair and regenerate, but depending on such factors as injury severity, age of onset, and prior injuries, these endogenous attempts are often insufficient to restore normal function. A treatment that limits the spread of secondary damage and/or promotes repair and regeneration is needed. Current clinical treatment practices for TBI primarily aim to reduce intracranial pressure in an effort to minimize brain damage caused by swelling. For ischemic stroke, the only approved treatment is breaking down blood clots with tissue plasminogen activator. However, patients must meet strict criteria for receiving this therapy, including a 4 hour time window and no evidence of the following: bleeding, a severely elevated blood pressure or blood sugar, recent surgery, low platelet count, or end-stage liver or kidney disorders. Numerous pharmacological treatments that seemed promising in animal models have failed in clinical trials (Maas *et al.*, 2010; O'Collins *et al.*, 2006). Patients with brain injury vary widely with respect to demographics, severity of injury, location of injury, and co-morbidity factors making clinical trials challenging. Most treatments previously tested involved pathways that are both deleterious and beneficial, making the dosage and timing critical to not interfere with normal homeostasis or reparative mechanisms in the brain. Furthermore, these treatments targeted single mechanisms, which may not be enough in light of the multi-faceted pathology. Therapies that currently seem more promising, such as progesterone administration (Wright *et al.*, 2007) and cell transplantation, address multiple pathological events.

### 2. Mesenchymal stromal cells to treat brain injury

#### 2.1 Mesenchymal stromal cells (MSCs)

Mesenchymal stem cells are multipotent cells that can differentiate into cells of the mesoderm germ layer. These cells can be isolated from adipose tissue, amniotic fluid, placenta and umbilical cord, though are most commonly and efficiently derived from adult bone marrow. Marrow-derived cells that adhere to tissue-culture plastic *in vitro* are a heterogeneous population of cells that contain mesenchymal stem cells, but the entire population is more correctly defined as mesenchymal stromal cells (Horwitz *et al.*, 2005). As we learn more about these cell populations, the terminology evolves and the acronym MSC is used (and sometimes misused) for mesenchymal stem cell, mesenchymal stromal cell, multipotent stromal cell, and marrow stromal cell. For the purposes of this chapter, we will not distinguish amongst these cell populations and use MSC as a general acronym.

## 2.2 Using MSCs to treat brain injury

MSCs are an attractive cell source for transplantation because they are relatively easy to obtain, expand, and manipulate *in vitro*. In addition, adult human MSCs do not have the tumorigenicity risks that pluripotent cells carry. Ample preclinical data demonstrate that MSC transplantation promotes functional recovery following experimental cerebral ischemic or TBI (for review, see Li & Chopp, 2009 or Parr *et al.*, 2007). Autologous MSC therapy has already shown promise for treating clinical stroke (Battistella *et al.*, 2011; Honmou *et al.*, 2011; Lee *et al.*, 2010; Suarez-Monteagudo *et al.*, 2009) and TBI (Cox *et al.*, 2011; Zhang *et al.*, 2008). Collectively, these trials demonstrate that transplanting MSCs either intra-arterially, intravenously, or intracerebrally is safe and no cell-related adverse events were reported. These groups also indicate that some patients receiving MSCs had improved functional outcome; however, these hints at efficacy must be cautiously interpreted because these were primarily safety trials and were not designed to show robust efficacy.

Important considerations for using MSCs in the clinic include timing (acute versus chronic), delivery route (most commonly intravenous, intra-arterial, or intracerebral), and donor source (autologous versus allogeneic). There are advantages and disadvantages for each of these issues, which are outlined in Table 1. According to [www.clinicaltrials.gov](http://www.clinicaltrials.gov) (searched in August 2011; summarized in Table 2), there are 11 ongoing clinical trials worldwide using MSCs (either primary or derivatives) to treat stroke. Of these 11 studies, 5 are using autologous MSCs and the other 6 are using allogeneic MSCs from either bone marrow, placenta (1 study) or umbilical cord (1 study). Two of the trials are injecting cells directly into the injured brain (either into the injury cavity or the peri-infarct tissue), 1 trial is injecting cells into the carotid artery, and the other 8 are injecting MSCs intravenously. With regard to timing, 2 of the trials are delivering the cells during the acute phase (within 72 hours post-stroke), 7 trials during the sub-acute phase (between 4 days and 6 weeks post-stroke), and 2 studies are delivering cells during the chronic phase (over 6 months post-stroke). As trials more definitively reveal that MSCs transplantation is both safe and effective for treating brain injury in humans, issues of delivery timing and route and donor source, as well as dosage and the use of immunosuppression will need to be more carefully compared.

Issue	Options	Advantages	Disadvantages
Timing	Acute phase	supports neuroprotection	volatile environment
			strict timing may limit availability
	Chronic phase	supports regeneration	endogenous regeneration efforts are stabilized
		easier to distinguish between effects of cell therapy and normal recovery	
	targets larger patient population		
Delivery	Intravenous or Intra-arterial	less invasive	cells accumulate in the lungs and spleen
		cells home to site of injury	requires high cell numbers
			possible systemic effects
		requires blood brain barrier permeability (thus limits time window)	
	Intracerebral	cells placed at site of injury	more invasive
			extent and location of injury is variable
Donor Source	Autologous	immunocompatible	patients undergo additional procedures
	Allogeneic	MSCs are immunoprivileged	may require immunosuppression
		more cost-effective	requires storage of cell product
		better for repeat dosing	
		off-the-shelf treatment	
cells can be manipulated <i>ex vivo</i> without treatment delays			

Table 1. Clinical considerations for using MSCs to treat brain injury

<u>Sponsor</u>	<u>Country</u>	<u>Start Date</u>	<u>Phase</u>	<u># Px</u>	<u>Donor</u>	<u>Cell Description</u>	<u>Route</u>	<u>Timing (post-stroke)</u>	<u>Follow-up</u>	<u>clinicaltrials.gov ID</u>
National Cardiovascular Center	Japan	2008-May	I/IIa	12	Auto	Bone marrow mononuclear cells	IV	7-10 days	30 days	NCT01028794
CellMed AG, a subsidiary of BTG plc.	Germany	2008-October	I/II	20	Allo	GLP-1 CellBeads: alginate microcapsules with mesenchymal cells transfected to secrete glucagon like peptide-1	IC	acute	6 months	NCT01298830
University of Texas Health Science Center	USA	2009-January	I	30	Auto	Bone marrow mononuclear cells	IV	24-72 hours	5 years	NCT00859014
University of California, Irvine	USA	2010-January	I	33	Auto	Bone marrow mononuclear cells OR Cultured marrow mesenchymal stromal cells	IV	Mononuclear: 4 days; Mesenchymal: 23 days	90 days	NCT00908856
University Hospital, Grenoble	France	2010-August	II	30	Auto	Mesenchymal stem cells	IV	Up to 6 weeks	24 months	NCT00875654
Stempeutics Research Pvt. Ltd.	Malaysia	2010-December	I/II	78	Allo	Cultured adult mesenchymal stem cells	IV	Up to 10 days	12 months	NCT01091701
SanBio, Inc.	USA	2011-January	I/IIa	18	Allo	SB623: modified marrow stromal cells	IC	6-24 months	24 months	NCT01287936
Stemmedica Cell Technologies, Inc.	USA	2011-February	I/II	35	Allo	Adult mesenchymal bone marrow stem cells	IV	Beyond 6 months	12 months	NCT01297413
Celgene Corporation	USA	2011-March	IIa	44	Allo	Human placenta-derived cells PDA001- (cenplacel-L)	IV	1 OR 1 and 8 days	24 months	NCT01310114
Aldagen	USA	2011-March	II	100	Auto	ALD-401: derived from bone marrow	IA	13-19 days	12 months	NCT01273337
General Hospital of Chinese Armed Police Forces	China	2011-April	II	120	Allo	Umbilical cord mesenchymal stem cells	IV	1st TP: 10-21 days (hemorrhage) OR 7-24 days (ischemic); 2nd TP: lumbar puncture 7d after 1st TP	12 months	NCT01389453

Table 2. Ongoing clinical trials for using MSCs to treat stroke

# Px= planned number of patients to enroll; Auto=autologous; Allo=allogeneic; IV=intravenously; IC=intracerebral (cavity or peri-infarct tissue); IA=intra-arterial (carotid); TP=transplant

### 3. Mechanisms of action underlying beneficial effects

Transplanting stem cells is attractive because they can potentially differentiate into multiple cell types and replace cells lost to injury or disease. MSCs normally give rise to cells along the mesodermal lineage (including bone, cartilage, and adipose tissue); however, there are reports suggesting that they can trans-differentiate into neural cells in certain *in vitro* (Sanchez-Ramos *et al.*, 2000; Woodbury *et al.*, 2000) and *in vivo* (Kopen *et al.*, 1999; Munoz-Elias *et al.*, 2004) environments. Though some studies show a small percentage of donor MSCs express neuronal markers in the injured brain, there is little evidence that these cells functionally incorporate into the endogenous neuronal circuitry. In fact, there is a decidedly lack of evidence that neuronal replacement is the primary mechanism of action for MSC therapy; moreover, there are data demonstrating artifacts associated with MSC to neuron trans-differentiation (Barnabe *et al.*, 2009; Lu *et al.*, 2004; Neuhuber *et al.*, 2004; Phinney & Prockop, 2007; Wells, 2002). There is also the possibility that MSCs replace supporting glial cells (astrocytes, oligodendrocytes, or microglia), which outnumber neurons 10:1 in the brain (reviewed in Boucherie & Hermans, 2009). However, ample evidence shows that benefits and functional recovery occur rapidly and persist long after the donor cells are gone, indicating permanent cell replacement is not required. The most likely governing mechanism is that MSCs provide trophic support to the injured brain, which augments endogenous repair and regeneration pathways. Trophic support, by definition, acts through secreted molecules called trophic factors. MSCs may act as mini-pumps delivering beneficial factors to their microenvironment. Using cells as pumps is preferred to actual engineered pumps because they can deliver a plethora of factors at the site of injury in physiologic concentrations and also respond to the needs of the injured tissue with appropriate feedback. Trophic factors can either directly or indirectly (via a mediator cell) promote neuroprotection (enhance cell survival through repair) or neuroregeneration (enhance cell survival through repair) or neuroregeneration. MSCs also secrete factors that augment angiogenesis - another important aspect of regeneration after brain injury. An additional likely mechanism of action contributing to the benefit of MSCs is immunosuppression. MSCs can affect immune cells via secreted factors, which would fall under trophic support. For the purposes of this chapter, we will treat it as a separate category since targeting immune functions indirectly promotes recovery compared to acting directly on neural or vascular cells. There is a great deal of overlap between these functions and these categories are fluid. Figure 1 summarizes hypothesized mechanisms of action for MSCs in the injured brain, which are mediated by secreted factors and direct cell-cell contacts.

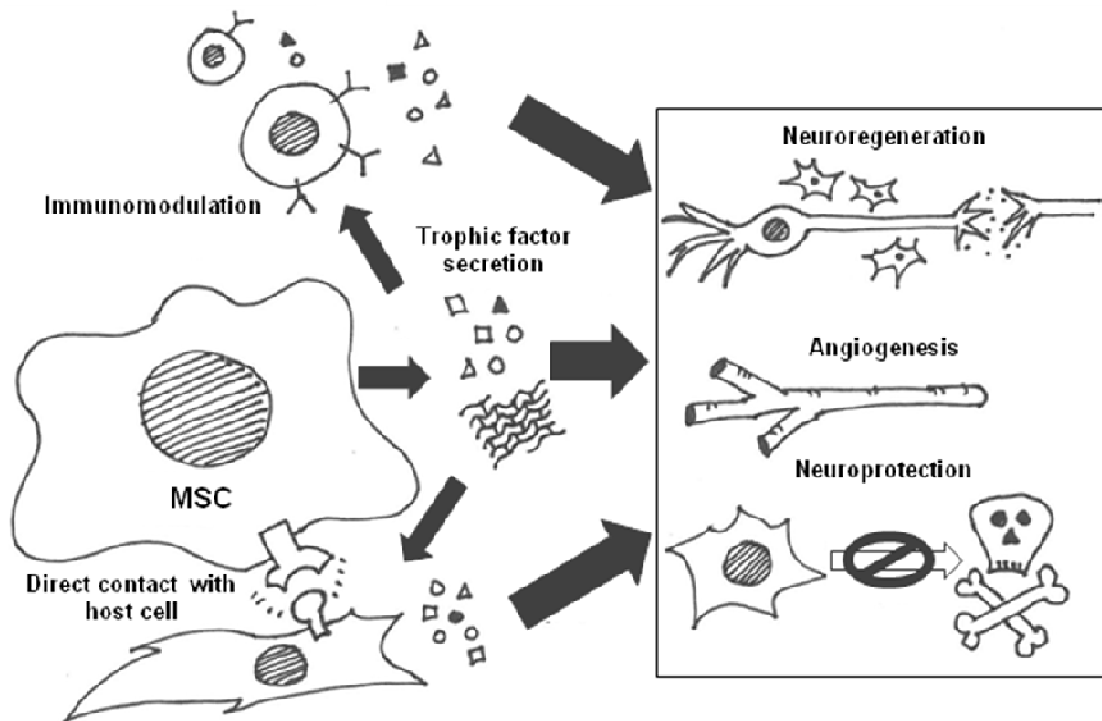


Figure 1. Summary of likely mechanisms of action for MSCs in the injured brain, highlighting the interconnectivity.

### 3.1 Terminology

Trophic support classically means to provide nutrition, but the definition has been expanded to include promoting cellular growth, survival, differentiation, or migration. Similarly, the terms “trophic factor” and “growth factor” have also become more inclusive. Neurotrophic factors are trophic factors acting specifically on neural cells, i.e., promoting the growth, survival, differentiation, or migration of primarily neurons, but also glial cells (astrocytes, oligodendrocytes, microglia and Schwann cells). The name neurotrophin is sometimes used synonymously with neurotrophic factor; however neurotrophins specify a family of four structurally-related proteins: nerve growth factor (NGF), brain-derived neurotrophic factor (BDNF), neurotrophin-3 (NT-3), and neurotrophin-4/5 (NT-4/5). Cytokines were initially used to distinguish factors that had specific immunomodulatory properties (produced by and act on immune cells), such as interleukins, lymphokines, and interferons. However, it is now known that many classic cytokines are also produced by and act on non-immune cells. Chemokines are a subclass of cytokines that promote chemotaxis (cell movement in response to a chemical concentration gradient). In general, as more functions are discovered about these proteins, definitions and classifications broaden and the terms are often used interchangeably. While trophic factors commonly refer to soluble proteins, extracellular matrix (ECM) proteins that are immobilized in the intercellular space also fall into this category since they direct cell growth, survival, differentiation, and migration.

### 3.2 Trophic support

Transplanted MSCs augment host repair and recovery primarily through direct and indirect trophic support. MSCs secrete a plethora of factors that are known to promote neural cell survival and regeneration through paracrine signaling to neural, vascular, and immune cells. An overview of relevant trophic factors found to be secreted by human bone marrow-derived MSCs *in vitro* is provided in Table 3. Which of these factors are secreted in the injured brain is under current investigation. Research is also ongoing to determine the exact or even the most critical mechanism(s) governing the beneficial effects of MSC transplantation. For now, we make a leap of knowledge based on existing evidence. There are numerous studies demonstrating that transplanted MSCs promote certain aspects of recovery (e.g., decrease apoptosis, increase neurogenesis, synaptogenesis, and angiogenesis) in the injured brain. Concurrently, there are other studies showing that factors known to be secreted by MSCs are involved in mechanisms that promote these same aspects of recovery. The assumption is that some combination of these pro-recovery mechanisms occurs when MSCs are transplanted into the injured brain and that MSC-secreted factors are essential for these effects. Table 4 reviews potential beneficial mechanisms of action for repair and regeneration of the injured brain provided by MSC-secreted factors. The table provides references that demonstrate that the protein of interest enhances either 1) neuroprotection, 2) neural stem/progenitor cell proliferation or migration, 3) neural stem/progenitor cell differentiation, 4) neuritogenesis or synaptogenesis, 5) angiogenesis, or 6) another mechanism involved in recovery (such as reducing inhibitory components of the glial scar). While these entries are based on a thorough search, it is not intended to be completely exhaustive. Also, only the beneficial aspects of the various growth factors are presented. Some factors that enhance one pathway act as inhibitors in another (e.g., the pro-inflammatory molecule interleukin-17 potentiates neuronal cell death but supports angiogenesis). Since these studies often examine pathways individually, it is not clear which are the primary mechanisms that occur when (if) the molecule is secreted by MSCs in the injured brain. Further, the exact timing and concentration of the trophic factor are likely critical in determining to which pathways they contribute.

<b>Reference</b>	<b>Detection Method</b>	<b>Trophic Factors Found</b>	<b>Abbreviation</b>
(Haynesworth <i>et al.</i> , 1996)	ELISA of Conditioned Medium	Granulocyte colony stimulating factor Granulocyte-macrophage colony stimulating factor Interleukin-11 Interleukin-6 Leukemia inhibitory factor Macrophage colony stimulating factor Stem cell factor	G-CSF GM-CSF IL-11 IL-6 LIF M-CSF SCF
(Potian <i>et al.</i> , 2003)	Cytokine Array of Conditioned Medium	Angiogenin Granulocyte colony stimulating factor Granulocyte-macrophage colony stimulating factor Growth related oncogene- $\alpha$ Interleukin-6 Interleukin-8 Monocyte chemoattractant protein-1	Angiogenin G-CSF GM-CSF GRO $\alpha$ IL-6 IL-8 MCP-1

		Oncostatin M Transforming growth factor- $\beta$	OSM TGF $\beta$
(Kinnaird <i>et al.</i> , 2004)	ELISA or Immunoblotting of Conditioned Medium	Angiopoietin-1 Fibroblast growth factor-2 Interleukin-6 Monocyte chemoattractant protein-1 Platelet derived growth factor Placental growth factor Vascular endothelial growth factor-A	ANG-1 FGF-2 IL-6 MCP-1 PDGF PIGF VEGF-A
(Arnhold <i>et al.</i> , 2006)	ELISA of Conditioned Medium	Brain derived neurotrophic factor Glial cell line-derived neurotrophic factor Nerve growth factor	BDNF GDNF NGF
(Crigler <i>et al.</i> , 2006)	ELISA of Conditioned Medium	Brain derived neurotrophic factor Interleukin-11 Nerve growth factor Stromal derived factor-1	BDNF IL-11 NGF SDF-1
(Wang <i>et al.</i> , 2006)	ELISA of Conditioned Medium	Hepatocyte growth factor Insulin-like growth factor-1 Vascular endothelial growth factor	HGF IGF-1 VEGF
(Potapova <i>et al.</i> , 2007)	ELISA of Conditioned Medium	Angiogenin Bone morphogenetic protein-2 Fibroblast growth factor-2 Interleukin-6 Interleukin-8 Interleukin-11 Monocyte chemoattractant protein-1 Vascular endothelial growth factor	Angiogenin BMP-2 FGF-2 IL-6 IL-8 IL-11 MCP-1 VEGF
(Schinkothe <i>et al.</i> , 2008)	Cytokine Array of Conditioned Medium	Angiopoietin-2 Fibroblast growth factor-2 Fibroblast growth factor-4 Fibroblast growth factor-9 Granulocyte colony stimulating factor Growth related oncogene Hepatocyte growth factor Interleukin-8 Interleukin-11 Interleukin-17 Monocyte chemoattractant protein-1 Neurotrophin-4/5 Oncostatin M Placental growth factor Tissue inhibitors of metalloproteinase-1 Vascular endothelial growth factor	ANG-2 FGF-2 FGF-4 FGF-9 G-CSF GRO HGF IL-8 IL-11 IL-17 MCP-1 NT-4/5 OSM PIGF TIMP-1 VEGF
(Tate <i>et al.</i> , 2010)	Cytokine Array of Conditioned Medium	Bone morphogenetic protein-4 Bone morphogenetic protein-7 Dickkopf-1 Fibroblast growth factor-7 Heparin-binding epidermal growth factor-like growth factor Hepatocyte growth factor Interleukin-6	BMP-4 BMP-7 DKK-1 FGF-7 HB-EGF HGF IL-6

		Monocyte chemoattractant protein -1 Platelet derived growth factor-AA Vascular endothelial growth factor	MCP-1 PDGF-AA VEGF
(Lai <i>et al.</i> , 2010)	Immunofluorescence of Extracellular Matrix	Collagen I Decorin Fibronectin Laminin Perlecan	Collagen I Decorin Fibronectin Laminin Perlecan

Table 3. Factors secreted *in vitro* by human bone marrow MSCs that may affect neural recovery.

	Neuroprotection (↓Apoptosis)	Promotes Neuroregeneration			↑Angiogenesis	Additional
		↑ NSC Proliferation or Migration	↑ NSC Differentiation	↑ Neurite Outgrowth or Synapse Formation		
Angiogenin					(*Distler <i>et al.</i> , 2003)	
ANG-1	(*Hansen <i>et al.</i> , 2008)	(*Ohab & Carmichael, 2008)		(*Hansen <i>et al.</i> , 2008)	(*Distler <i>et al.</i> , 2003)	Restore BBB (Nag <i>et al.</i> , 2011)
ANG-2		(Liu <i>et al.</i> , 2009)	neuronal (Liu <i>et al.</i> , 2009)		in presence of VEGF (*Distler <i>et al.</i> , 2003)	
BDNF	(*Lykissas <i>et al.</i> , 2007)	(*Bath & Lee, 2010; *Schabitz <i>et al.</i> , 2007)	neuronal (*Bath & Lee, 2010)	(Gascon <i>et al.</i> , 2005; *Lipsky & Marini, 2007; *Lykissas <i>et al.</i> , 2007)	(Qin <i>et al.</i> , 2011)	
BMP-2	(Iantosca <i>et al.</i> , 1999)		astrocytic (*Sabo <i>et al.</i> , 2009)	(Gratacos <i>et al.</i> , 2001)		
BMP-4	(Iantosca <i>et al.</i> , 1999)		astrocytic (*Sabo <i>et al.</i> , 2009)			
BMP-7	(Yabe <i>et al.</i> , 2002)	(Chou <i>et al.</i> , 2006)	astrocytic (Gajavelli <i>et al.</i> , 2004)			
DKK-1				(Endo <i>et al.</i> , 2008)		
FGF-2	(*Alzheimer & Werner, 2002; *Zechel <i>et al.</i> , 2010)	(*Mudo <i>et al.</i> , 2009; *Zechel <i>et al.</i> , 2010)	(*Mudo <i>et al.</i> , 2009; *Zechel <i>et al.</i> , 2010)	(*Zechel <i>et al.</i> , 2010)	(*Distler <i>et al.</i> , 2003; Kumar <i>et al.</i> , 1998)	↑MSC homing (Schmidt <i>et al.</i> , 2006); Restore BBB (Bendfeldt <i>et al.</i> , 2007)
FGF-4		(Kosaka <i>et al.</i> , 2006)	neuronal (Kosaka <i>et al.</i> , 2006)		(*Fan & Yang, 2007)	
FGF-7	(Sadohara <i>et al.</i> , 2001)			(Terauchi <i>et al.</i> , 2010)	(Gillis <i>et al.</i> , 1999)	
FGF-9	(Lum <i>et al.</i> , 2009)	(Lum <i>et al.</i> , 2009)	neuronal (Lum <i>et al.</i> , 2009)		(Frontini <i>et al.</i> , 2011)	
G-CSF	(Schabitz <i>et al.</i> , 2003; Schneider <i>et al.</i> , 2005; Sehara <i>et al.</i> , 2007; Solaroglu <i>et al.</i> , 2006)	(Schneider <i>et al.</i> , 2005; Shyu <i>et al.</i> , 2004)	neuronal (Schneider <i>et al.</i> , 2005)		(Minamino <i>et al.</i> , 2005; Sehara <i>et al.</i> , 2007)	↑MSC homing (Deng <i>et al.</i> , 2011)

GM-CSF	(Huang <i>et al.</i> , 2007)			(Bouhy <i>et al.</i> , 2006)	(Buschmann <i>et al.</i> , 2003)	
GDNF	(Lu <i>et al.</i> , 2005; Shang <i>et al.</i> , 2011; Shirakura <i>et al.</i> , 2004)	(Dempsey <i>et al.</i> , 2003)		(Shirakura <i>et al.</i> , 2004)		
GRO $\alpha$			oligodendrocytic (Robinson <i>et al.</i> , 1998)		(Bechara <i>et al.</i> , 2007)	
HB-EGF	(Opanashuk <i>et al.</i> , 1999)	(Jin <i>et al.</i> , 2002)	neuronal (Jin <i>et al.</i> , 2004) and glial (Korblum 1999)			
HGF	(Honda <i>et al.</i> , 1995; Shang <i>et al.</i> , 2011)	(Shang <i>et al.</i> , 2011)	neuronal and glial (Shang <i>et al.</i> , 2011)	(Hamanoue <i>et al.</i> , 1996; Shang <i>et al.</i> , 2011; Shimamura <i>et al.</i> , 2006)	(*Distler <i>et al.</i> , 2003; Shang <i>et al.</i> , 2011; Shimamura <i>et al.</i> , 2006)	$\uparrow$ MSC homing (Neuss <i>et al.</i> , 2004; Ponte <i>et al.</i> , 2007; Son <i>et al.</i> , 2006); $\downarrow$ glial scar (Shang <i>et al.</i> , 2011; Shimamura <i>et al.</i> , 2006)
IGF-1	(Wilkins <i>et al.</i> , 2001; Yamada <i>et al.</i> , 2001)	(Dempsey <i>et al.</i> , 2003; *Joseph D'Ercole & Ye, 2008)	neuronal and glial (*Joseph D'Ercole & Ye, 2008)	(*Joseph D'Ercole & Ye, 2008)	(*Distler <i>et al.</i> , 2003; Lopez-Lopez <i>et al.</i> , 2004)	$\uparrow$ MSC homing (Ponte <i>et al.</i> , 2007)
IL-6	(Swartz <i>et al.</i> , 2001)		neuronal (Oh <i>et al.</i> , 2010) and astrocytic (Taga & Fukuda, 2005)	(Oh <i>et al.</i> , 2010)	(*Fan & Yang, 2007)	
IL-8	(Araujo & Cotman, 1993)				(*Fan & Yang, 2007)	$\uparrow$ MSC homing (Wang <i>et al.</i> , 2002)
IL-11			neuronal (Mehler <i>et al.</i> , 1993)			
IL-17					(Numasaki <i>et al.</i> , 2003)	
LIF	(Nobes & Tolkovsky, 1995)	(Bauer <i>et al.</i> , 2003; Shimazaki <i>et al.</i> , 2001)		(Blesch <i>et al.</i> , 1999)		$\uparrow$ cell homing (Sugiura <i>et al.</i> , 2000)
MCP-1		(Widera <i>et al.</i> , 2004; Yan <i>et al.</i> , 2007)				$\uparrow$ MSC homing (Wang <i>et al.</i> , 2002)
M-CSF	(Vincent <i>et al.</i> , 2002)				(Minamino <i>et al.</i> , 2005)	
NGF	(*Lykissas <i>et al.</i> , 2007; Shirakura <i>et al.</i> , 2004)		neuronal (Yung <i>et al.</i> , 2010; Zhu <i>et al.</i> , 2011)	(Gascon <i>et al.</i> , 2005; *Lykissas <i>et al.</i> , 2007)	(*Lazarovici <i>et al.</i> , 2006)	
NT-4/5	(*Lykissas <i>et al.</i> , 2007)		neuronal (Shen <i>et al.</i> , 2010)	(*Lykissas <i>et al.</i> , 2007)		
OSM	(Weiss <i>et al.</i> , 2006)		oligoendrocytic (Glezer & Rivest, 2010)		(Vasse <i>et al.</i> , 1999)	
PDGF	(Iihara <i>et al.</i> , 1997; Vana <i>et al.</i> , 2007)	(Forsberg-Nilsson <i>et al.</i> , 1998)	neuronal (Johe <i>et al.</i> , 1996)		(*Beck & Plate, 2009; *Fan & Yang, 2007)	$\uparrow$ MSC homing (Ponte <i>et al.</i> , 2007)
PIGF	(Du <i>et al.</i> , 2010)				(*Beck & Plate, 2009)	

	SCF	(Dhandapani <i>et al.</i> , 2005; Erlandsson <i>et al.</i> , 2004; Li <i>et al.</i> , 2009)	(Bantubungi <i>et al.</i> , 2008; Erlandsson <i>et al.</i> , 2004; Zhao <i>et al.</i> , 2007)		(Sun <i>et al.</i> , 2006)	↑MSC homing (Bantubungi <i>et al.</i> , 2008; Erlandsson <i>et al.</i> , 2004)
	SDF-1		(*Ohab & Carmichael, 2008; Thored <i>et al.</i> , 2006)			↑ MSC homing (Ponte <i>et al.</i> , 2007; Son <i>et al.</i> , 2006) and survival (Kortesidis <i>et al.</i> , 2005)
	TGFβ	(*Buisson <i>et al.</i> , 2003; Lu <i>et al.</i> , 2005)	(Ma <i>et al.</i> , 2008; Mathieu <i>et al.</i> , 2010)		(Yi <i>et al.</i> , 2010)	(*Beck & Plate, 2009; *Fan & Yang, 2007)
	TIMP-1	(Tan <i>et al.</i> , 2003)				
	VEGF	(Jin <i>et al.</i> , 2000; Sun <i>et al.</i> , 2003)	(Sun <i>et al.</i> , 2003; Wang <i>et al.</i> , 2007a; Wang <i>et al.</i> , 2007b)		(Erskine <i>et al.</i> , 2011; Jin <i>et al.</i> , 2006)	(*Greenberg & Jin, 2005; *Shibuya, 2009)
Matrix Proteins	Collagen I		(Ma <i>et al.</i> , 2004)	neuronal (Ma <i>et al.</i> , 2004)		(*Sottile, 2004)
	Decorin				(Davies <i>et al.</i> , 2004)	↓ glial scar (Davies <i>et al.</i> , 2004)
	Fibronectin	(Sakai <i>et al.</i> , 2001; Tate <i>et al.</i> , 2007)	(*Henderson & Copp, 1997; Tate <i>et al.</i> , 2004; Testaz & Duband, 2001)	oligodendrocytic (Hu <i>et al.</i> , 2009)	(Einheber <i>et al.</i> , 1996; *Pires Neto <i>et al.</i> , 1999)	(*Sottile, 2004)
	Laminin	(Hall <i>et al.</i> , 2008)	(Hall <i>et al.</i> , 2008; *Perris & Perissinotto, 2000; Tate <i>et al.</i> , 2004)	neuronal (Boote Jones & Mallapragada, 2007; Tate <i>et al.</i> , 2004)	(*Colognato and Yurchenco, 2000; *Pires-Neto 1999)	(*Sottile, 2004)
	Perlecan	(*Bix & Iozzo, 2008; Lee <i>et al.</i> , 2011)				(*Bix & Iozzo, 2008; Lee <i>et al.</i> , 2011)

Table 4. Evidence of MSC-secreted factors promoting neuroprotection or regeneration.

\*Indicates review article; NSC=Neural stem/progenitor cell; Growth factor abbreviations are defined in Table 3

### 3.2.1 Neuroprotection

Following the initial insult, secondary injury mechanisms persist and cause cell death to surrounding tissue. While the initial ischemic or mechanical insult causes immediate necrotic death, secondary cell death primarily occurs through apoptosis. MSCs secrete multiple factors known to promote neural cell survival (see Table 4). Human MSCs have been shown to rescue neural cells following *in vitro* injury (e.g., oxygen glucose deprivation, glutamate toxicity) via secreted soluble factors (Tate *et al.*, 2010; Zhong *et al.*, 2003) and ECM proteins (Aizman *et al.*, 2009). There are several reports of decreased apoptotic markers and enhanced preservation of neural cells in the injury penumbra when transplanting MSCs following experimental ischemic stroke (Li *et al.*, 2010; Li *et al.*, 2002; Xin *et al.*, 2010) or TBI (Kim *et al.*, 2010; Xiong *et al.*, 2009). For example, delivering human MSCs intravenously 1 day following experimental cerebral ischemia in rats led to significant reduction in apoptotic cell death in the injury penumbra as well as functional behavioral recovery (Li *et al.*, 2002). This study also found an increase in BDNF and NGF in the ipsilateral hemisphere of MSC-treated rats at 7 days post-stroke; however, they did not distinguish whether these trophic factors were produced by the donor or host cells. Li *et al.* (2010) show that transplanting human MSCs into the injury penumbra 1 week following experimental cerebral ischemia in monkeys decreased apoptotic cell death and the lesion volume. Human MSCs transplanted into the injury cavity 1 week following experimental TBI in rats lead to enhanced cell survival in the hippocampus and improved functional recovery, and this was further improved when the MSCs were delivered within a collagen I scaffold (Xiong *et al.*, 2009). Kim *et al.* (2008) found that delivering human MSCs intravenously 1 day post-TBI in rats improved functional recovery and enhanced host cell survival by increasing pAkt

and decreasing caspase-3 cleavage. Further, this group reports increases in BDNF, NGF, and NT-3 in the MSC-treated brains, though they did not distinguish between donor or host origin. Clearly, exogenous MSCs provide neuroprotection following brain injury and this is one probable mechanism of action for their benefit.

### 3.2.2 Neuroregeneration

After brain injury, the brain attempts to regenerate by resorting to a developmental-like state with increased neurogenesis, neurite outgrowth, synaptogenesis, re-myelination, re-formation of the blood brain barrier, and angiogenesis. Once thought to be unable to regenerate, it is now known that neural stem cells persist in the normal adult brain (neurogenic zones include the subventricular zone in the lateral ventricles and the subgranular zone in the dentate gyrus of the hippocampus). After an ischemic or traumatic injury, endogenous neural stem cells proliferate, migrate to the site of injury, and differentiate into neurons and glia (Kernie & Parent, 2010). Neuroplasticity is the reorganization of neuronal circuitry by changing the number and strength of neurites and synapses. Such remapping occurs throughout life for learning and memory formation, and compensatory plasticity occurs in the spared tissue following brain injury (Nishibe *et al.*, 2010). Neuroregeneration collectively includes neural stem/progenitor cell proliferation, migration and differentiation, neurite outgrowth, and synapse formation.

There are multiple *in vitro* studies showing that MSCs direct neuroregenerative processes. Bai *et al.* (2007) show that mouse neural stem cells had increased migration and neuronal and oligodendrocytic differentiation when they were cultured with either human MSCs or MSC-conditioned medium, indicating that soluble proteins are responsible for these effects. In related work, co-culture of human MSCs with rat neural stem cells revealed that MSCs promote differentiation into primarily astrocytes and oligodendrocytes (Robinson *et al.*, 2011). However MSC-conditioned media promoted primarily oligodendrocytic differentiation (Robinson *et al.*, 2011), indicating that matrix components or direct cell-cell contact also account for the effects of MSCs on neural stem cell differentiation. Indeed, Aizman *et al.* (2009) demonstrate that human MSC-derived ECM promotes differentiation of cortical cells into neurons, astrocytes and oligodendrocytes and also enhances neuronal neurite networks compared to single ECM proteins. Transplantation of MSCs augments endogenous regeneration following experimental ischemic stroke (Bao *et al.*, 2011; Li *et al.*, 2010; Li *et al.*, 2002; Xin *et al.*, 2010; Yoo *et al.*, 2008) and TBI (Mahmood *et al.*, 2004; Xiong *et al.*, 2009). For example, both Bao *et al.* (2010) and Yoo *et al.* (2008) show that intracerebral transplantation of human MSCs 3 days following experimental cerebral ischemia in rats increases proliferation and migration of host neural stem cells and also decreases their apoptosis, thus enhancing neurogenesis. They also report enhanced behavioral recovery, and Bao *et al.* demonstrate increases in BDNF, NT-3, and VEGF in the brains of MSC-treated rats, though they do not identify the source of these cytokines. Xin *et al.* (2010) found that intravenous delivery of mouse MSCs 1 day following experimental stroke in mice lead to increases in axon fiber density, synaptogenesis and myelination. Following experimental TBI in rats, transplanted rat MSCs promoted increased proliferation and neuronal differentiation in neurogenic zones along with improved motor and sensory recovery (Mahmood *et al.*, 2004). Xiong *et al.* (2009) also report that transplanting human MSCs intracerebrally 1 week post-TBI in rats leads to increased axonal fiber length and that the fiber length was directly proportional to performance on the behavior tasks. Multiple trophic factors secreted by MSCs may contribute to enhancing neuroregeneration (see Table 4).

The glial scar that forms following brain injury acutely acts to sequester the injury. Cellular components of the glial scar include reactive astrocytes, which help buffer excess glutamate and secrete neurotrophic factors, and activated microglia / macrophages which clear out dead tissue and secrete neurotrophic factors. However, extracellular components of the glial scar that persists adjacent to the injury site have been found to inhibit neurite extension (e.g., neurocan, Nogo protein), thus limiting regeneration (for review, see Properzi *et al.*, 2003). Transplantation of MSCs helps overcome this glial scar limitation following experimental stroke (Li *et al.*, 2010; Li *et al.*, 2005; Pavlichenko *et al.*, 2008; Shen *et al.*, 2008) and TBI (Zanier *et al.*, 2011). Following ischemic stroke, rats treated with rat MSCs transplanted intravenously had decreased glial scar thickness at both the acute (3 and 6 days post-stroke; Pavlichenko *et al.*, 2008) and chronic (4 months post-stroke; Li *et al.*, 2005) phases. Along with decreased glial scar thickness, these studies report decreased lesion volume, enhanced regeneration, and functional recovery for animals treated with MSCs. Shen *et al.* (2008) show a decrease in neurocan (an inhibitory chondroitin sulphate proteoglycan) and enhanced axonal outgrowth in the injury penumbra when ischemic rats were treated with rat MSCs. Zanier *et al.* (2011) transplanted human umbilical cord blood MSCs into the traumatically injured mouse brain and observed a decrease in reactive astrocytes in the glial scar region along with decreased lesion volume and functional recovery. Collectively, these data illustrate that exogenous MSCs promote neuroregeneration following brain injury by directly affecting neural stem/progenitor cells and neurons and/or by reducing inhibitory glial scar components.

### 3.2.3 Angiogenesis

Another important aspect of regeneration is angiogenesis, which is the formation of new blood vessels from existing vasculature. In the adult, angiogenesis occurs after injury to help supply the damaged tissue with oxygen and nutrients. The process includes basement membrane disruption, endothelial cell migration and proliferation, three-dimensional tube formation, maturation, and stabilization by vascular smooth muscle cells. Each step is regulated by multiple cytokines and ECM molecules (for review, see Distler *et al.*, 2003 or Fan & Yang 2007). Studies show that MSC-conditioned medium enhances endothelial cell proliferation (Kaigler *et al.*, 2003) and promotes angiogenesis *in vitro* and *in vivo* (Kinnaird *et al.*, 2004). Transplanting MSCs increases angiogenesis following experimental ischemic stroke (Omori *et al.*, 2008; Onda *et al.*, 2008; Pavlichenko *et al.*, 2008) and TBI (Xiong *et al.*, 2009). Potential pro-angiogenic factors secreted by MSCs are provided in Table 4. Notably, there is overlap between factors that promote angiogenesis and neurogenesis/neuritogenesis (reviewed in Emanuelli *et al.*, 2003 and Lazarovici *et al.*, 2006). A unique feature of brain vasculature is the existence of the blood-brain barrier (BBB), formed by astrocyte end-feet surrounding specialized capillary endothelial cells in order to tightly regulate brain homeostasis. After injury, there is increased permeability of the BBB leading to edema (reviewed in Nag *et al.*, 2011). Part of the repair process includes restoring the BBB, and regeneration includes formation of the BBB for new vasculature. Specific MSC-secreted factors such as ANG-1, FGF-2, and laminin may be involved in reforming the BBB following injury.

### 3.3 Immunomodulation

There is a potent immune response following ischemic and traumatic brain injury. The innate immune response is a part of the normal wound healing process; however, persistent inflammation can become cytotoxic. In addition to interacting with neural and vascular cells, MSCs communicate with immune cells and are now known to be immunosuppressive. Examining the interactions of MSCs with immune cells *in vitro* reveals that MSCs suppress T cell proliferation and activation, inhibit B cell proliferation and IgG production, prevent dendritic cell differentiation and migration, and shift the cytokine secretion profile of dendritic cells, helper T cells, and natural killer cells towards anti-inflammation (reviewed in Mezey *et al.*, 2010 and Nauta & Fibbe, 2007). Interestingly, studies that separate the MSCs from the immune cells using semi-permeable membranes indicate that soluble factors are critical for these effects. Candidate immunomodulatory factors secreted by MSCs include interleukin-6 (IL-6), transforming growth factor  $\beta$  (TGF $\beta$ ), prostaglandin E2, hepatocyte growth factor (HGF), indoleamine 2,3-dioxygenase (IDO), and monocyte colony stimulating factor (M-CSF) (reviewed in Mezey *et al.*, 2010 and Nauta & Fibbe, 2007). Moreover, ECM proteins, such as fibronectin, also interact with immune cells (Mosesson, 1984; Nasu-Tada *et al.*, 2005). Since shifting to a less inflammatory environment may facilitate neural repair and regeneration, immunomodulation is another feasible therapeutic mechanism of action for transplanted MSCs. Note that many immunomodulatory factors also have potential roles for directly promoting neural cell survival and regeneration (see Table 4). Likewise, NGF, the prototypic neurotrophic factor, has been shown to be anti-inflammatory (Villoslada & Genain, 2004). The interaction between angiogenesis and inflammation is also well-documented (for review, see Jackson *et al.*, 1997 or Noonan *et al.*, 2008), which further underscores the complexity and interrelatedness of these recovery mechanisms.

### 3.4 Challenges of identifying critical factors and mechanisms

Cell transplantation is a dynamic treatment that can target multiple therapeutic mechanisms. Advantages of transplanting cells compared to pharmaceutical treatments include the ability to 1) easily localize the treatment to the affected tissue, 2) supply a variety of trophic factors at physiologic concentrations, 3) persist long enough to alter the microenvironment of the injured brain tissue; and 4) interact with host cells. The beneficial effects of transplanted MSCs have been corroborated *in vitro* and *in vivo* and some potential pathways have been identified as described above. It is probable that a combination of multiple mechanisms of action synergistically contribute to improve functional recovery. While this ability to intervene along multiple pathways is desirable for a robust treatment, it makes identifying key mechanisms and factors challenging. Clarifying critical mechanisms of action would allow for treatments to be optimized to best facilitate these roles. Furthermore, difficulty pinpointing key mechanisms is a hurdle for developing potency assays for the clinical use of MSCs. Potency assays are critical for ranking and qualifying different cell lots on their ability to promote recovery. Another complication for determining potency of cells *ex vivo* is that transplanted cells interact with the host cells via paracrine signaling and possibly direct cell-cell contact. MSCs alter the secretion profile of host neural and immune cells, such as astrocytes and microglia (Gao *et al.*, 2005; Xin *et al.*, 2010), which further acts to promote repair and regeneration. Additionally, the secretion profile of MSCs is a function of the microenvironment and changes in the presence of injured brain tissue (Chen *et al.*, 2002a, 2002b). Thus, there is a complex and dynamic web of players involved in MSC-mediated effects. Ideally, potency assays would be easily reproducible *in vitro* assays, however the interplay between donor cells and the host environment is difficult to model *in vitro*. Elucidating critical aspects of this therapy will be the focus of intense research for years to come.

## 4. Conclusion

Stroke and TBI are major contributors to death and persistent disability, and treatments that effectively promote repair and regeneration are desired. Cell transplantation is a promising treatment for brain injury, and MSCs are an attractive cell source due to their technical and safety advantages. Pre-clinical *in vivo* data show that transplanting MSCs enhances neuroprotection, promotes regeneration and/or suppresses inflammation. MSCs secrete numerous soluble and insoluble factors that are known to benefit the injured brain, which are likely crucial to the mechanisms of action governing MSC-mediated recovery. MSCs aid injured brain tissue by targeting multiple, non-mutually exclusive pathways, which is an advantage for a potential treatment, but a challenge for elucidating critical mechanisms and factors.

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