Chapter 2
Stem Cell Therapy in Traumatic Brain Injury

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2.1 Introduction

Traumatic brain injury remains a leading cause of mortality and long-term disability worldwide. Traumatic brain injury results in enormous losses to individuals, families, and communities (Corrigan et al. 2010). World Health Organization has estimated that 25 % of road traffic collisions requiring admission to a hospital suffered traumatic brain injury in 2004 (Corrigan et al. 2010; Atlas: country resources for neurological disorders home page; Global burden of disease estimates). World Health Organization has also introduced the new metric tool – the disability adjusted life year, which quantifies the burden of diseases, injuries and risk factors. The worldwide leading causes of traumatic brain injury include road traffic accidents that were estimated being 41.2 million disability adjusted life year in 2008, violence being responsible for 21.7 million disability adjusted life year, and self-inflicted injuries being 19.6 million disability adjusted life year, respectively. All these will leave disability associated with traumatic brain injury in survivors (Atlas: country resources for neurological disorders home page; Global burden of disease estimates).

However, no effective therapy or program is available for treatment of individuals with traumatic brain injury; nonetheless, researchers had tried some therapeutic agents like levodopa/carbidopa and some neurotrophic factors in brain injury with persistent vegetative state with the aim of augmenting and slowing the progression from persistent vegetative state into some degree of consciousness.

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P.V. Pham (ed.), *Neurological Regeneration*, Stem Cells in Clinical Applications, DOI 10.1007/978-3-319-33720-3_2

This still needs experimentation to confirm if these dopamine precursors and other neurotrophic factors have any role in traumatic brain injury. Several other therapeutic agents like carnabinoid dexanabinol, erythropoietin, and gamma-glutamylcysteine ethyl ester have all shown to have neuroprotective effect in human at experimental stage with remarkable improvement in post-traumatic brain injury outcome (Nori et al. 2012; Ugoya and Akinyemi 2010; Biegon 2004; Lok et al. 2011; Maas 2001).

Recent advancement in knowledge about stem cells promotes the translation of stem cells to therapy in traumatic brain injury. The stem cells may play an important role in the treatment of traumatic brain injury by replacing damaged cells, and helping long-term functional recovery. The search for stem cell therapy for traumatic brain injury is promising and progressing. One obstacle in the search for an effective stem cell therapy is that the pathophysiology of traumatic brain injury is largely unknown. This is because multiple cell types like neuronal cells, glial, and endothelial cells are usually involved in traumatic brain injury. Furthermore, cerebral vasculature, especially the blood brain barrier may be affected in traumatic brain injury; this injury may be focal or diffuse axonal injury. Taming these burgeoning effects of traumatic brain injury requires neural stem cells which can differentiate into neurons and glial cells. It has been reported that progenitor cells differentiated into neurons and glial in adult brain, and an increase in astrocytic progeny forming reactive astrocytes to primarily limit cyst enlargement in posttraumatic syringomyelia (Mammis et al. 2009; Stoica et al. 2009; Tu et al. 2010, 2011).

This chapter is an optional extra to confirm whether we can achieve the translation of basic knowledge of neural stem cells into therapeutic options in persons with traumatic brain injury by enhancing and integrating these neural precursor cells unto neurogenesis and directing these cells to the specified targets or through multipotency where the transplanted stem cells can differentiate into glial cells, neurons and endothelial cells. As traumatic brain injuries are not always focal but diffuse we need to induce these transplanted stem cells differentiating into appropriate phenotype for long term structural and functional recovery. This chapter critically reviews current literatures on neural stem cell research and proposing an approach for quality clinical translation of stem cell research to therapy in traumatic brain injury. The author explains the pathophysiology of traumatic brain injury and proposes the "six point schematic approach" to achieving quality bench to bedside translation of neural stem cells to therapy for traumatic brain injury. The author also highlights the need for suitable clinical translation, coordination, and administration of research in the field of stem cell therapy for traumatic brain injury.

2.2 Neuropathology of Traumatic Brain Injury

Neuropathology of traumatic brain injury involves two main phases. These are the primary brain injury following the trauma, and the secondary injury which are mediated by inflammatory response to the primary brain injury.

2.2.1 *Primary Injury After Traumatic Brain Injury*

Neuropathology of the initial brain injury has been postulated to include acceleration, deceleration, and rotational forces which may or may not be as a result of the trauma. This sequence of events leads to the initiation of inertia which is both acceleration and rotational head movement. This impact on the cortical and sub-cortical brain structures causes focal or diffuse axonal injury and these inertial forces disrupt the blood brain barrier (Albert-Weissenberger et al. 2012). The primary events also involve massive ionic influx referred to as traumatic depolarization. The major inflammatory neurotransmitters released from the damaged tissue are excitatory amino acids, which may explain the neuropathology of diffuse axonal injury in traumatic brain injury. This is followed by cerebral edema with associated increase in intracranial pressure, usually forms the major immediate consequences of traumatic brain injury. Brain edema may come from astrocyte swelling and disruption of the blood brain barrier (Povlishock 1992; Greve and Zink 2009). The blood brain barrier is disrupted in acute phase of severe traumatic brain injury. The expression of high levels of glucose transporter 1 was observed in capillaries from acutely injured brain, which occurs in association with compromised blood brain barrier function. Vascular endothelial growth factor also plays a role in neuronal tissue disruption and increases the permeability of the blood brain barrier via the synthesis and release of nitric oxide. Figure 2.1 depicts the neuropathology of the primary injury after traumatic brain injury.

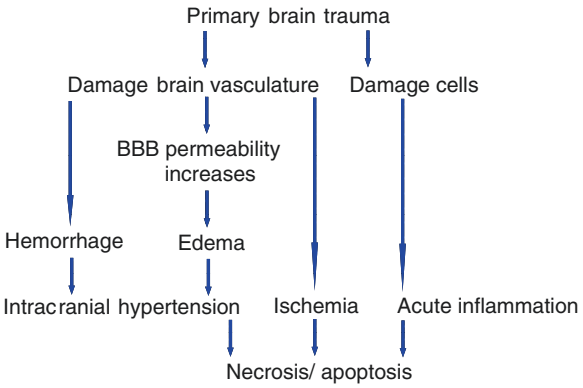

Fig. 2.1 Sequential events of the primary injury in traumatic brain injury. Initial impact is usually by direct trauma to the head either open or closed head injury. This trauma causes mechanical damage to neurons, axons, glia, and blood vessels by shearing, tearing or stretching. Blood vessel ruptures cause hemorrhage. Even in unruptured blood vessels, the permeability of blood brain barrier increases resulting in edema. Hemorrhage and edema often lead to intracranial hypertension. Following hemorrhage, ischemia could occur in brain tissue. Traumatic brain injury caused cell damage induces macrophage and lymphocytes migrant to the injury site releasing inflammatory mediators that triggers a cascade of events towards necrosis and/or apoptosis. Necrosis and/or apoptosis also can be a consequence of hemorrhage and ischemia

2.2.2 *Secondary Injury After Traumatic Brain Injury*

The secondary events are a complex association of the inflammatory response initiated by the trauma leading to diffuse neuronal degeneration of neurons, glial, axonal tearing, and genetic predisposition (Fig. 2.2). Furthermore, excitatory amino acids release, oxygen radical reactions, and nitric oxide production lead to the activation of N-methyl-D-aspartate, 2-amino-3-(5-methyl-3-oxo-1,2-oxazol-4-yl)propanoic acid, alpha-7 nicotinic receptor (α7), and nicotinic acetylcholine receptor (Hinzman et al. 2012; Goforth et al. 2009; Kelso and Oestreich 2012) and subsequent calcium influx. All these cascades of events cause mitochondrial disruption and free radical release with eventual tissue peroxidation. One theory is that excitatory amino acid release leads to calcium influx into neurons and other brain cells which promote oxygen free radical reactions. High calcium and the presence of free-radical molecules create an unstable environment in the brain cells that lead to increased

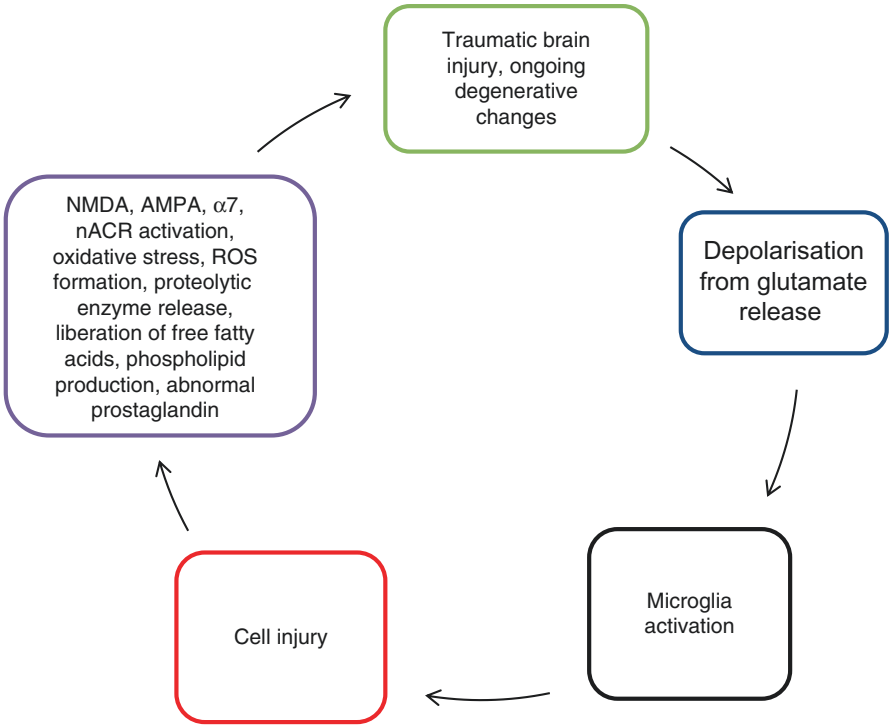

Fig. 2.2 Sequential events of the secondary injury in traumatic brain injury. This includes variety of processes, such as depolarization, disruption of ionic homeostasis and release of neurotransmitters, lipid degradation, and oxidative stress. These events are a result of interaction between the excitatory amino acids released with an influx of oxygen free radicals that ultimately set up N-methyl-D-aspartate, 2-amino-3-(5-methyl-3-oxo-1,2-oxazol-4-yl)propanoic acid, α7 and nicotinic acetylcholine receptor to sustain the unstable environment for cell injury and degenerative changes

production and release of nitric oxide and excitatory amino acids, such as glutamate. Nitric oxide participates in oxygen radical reactions and lipid peroxidation in neighboring cells (Stoffel et al. 2001). A summary of the secondary injury after traumatic brain injury is shown in Fig. 2.2. The secondary injury plays a major role in the outcome of traumatic brain injury. Therapeutic interventions should target this phase as it is the major determinant of morbidity and mortality in traumatic brain injury (Nawashiro et al. 1994). Clinically, the application of stem cell therapy early to patients with traumatic brain injury is ethically challenging because of the difficulty in obtaining informed consent immediately following the brain injury. Genes implicated to influence the outcome of traumatic brain injury include *apoe*, *comt*, *drd2*, *ace*, and *cacna1a. Apoe* multifactorially affects the clinicopathological consequences of traumatic brain injury (Potapov et al. 2010). *Apoe* is associated with increased amyloid deposition, amyloid angiopathy, larger intracranial hematomas, and more severe contusional injury. *Comt* and *drd2* are genes which influence dopamine-dependent cognitive and behavioral processes, such as executive or frontal lobe functions. The *ace* gene affects traumatic brain injury outcome *via* alteration of cerebral blood flow and/or autoregulation. The *cacna1a* gene exerts an influence *via* the calcium channel pathways and its effect on delayed cerebral edema (Jordan 2007). Increased signal transducers and activator of transcription 3 signaling has been reported in a rodent model of traumatic brain injury (Oliva et al. 2012). Although several potential genes that may influence the outcomes following traumatic brain injury have been identified, future investigations are needed to validate these genetic studies, and identify new genes that might contribute to the patient outcomes after traumatic brain injury.

2.3 Current Pharmacotherapy for Traumatic Brain Injury

Pharmacotherapies aim at promoting neurorepair, neuroregeneration, and neuroprotection following traumatic brain injury. Clinical trials evaluating these interventions apply standardized clinical outcome measures to demonstrate efficacy. In the past, drug research and development for traumatic brain injury focused on limiting secondary brain injury after the initial traumatic event because of lacking evidence that the central nervous system could be repaired or regenerated. Growing body of evidence indicates that the adult brain can be repaired and regenerated after traumatic brain injury. Potential drug targets for post-traumatic injury brain repair include angiogenesis, axon guidance and remodeling, remyelination, neurogenesis, and synaptogenesis. Pharmacotherapies may also target brain regeneration by enhancing the capacity of pluripotent cells to differentiate into neurons, glia, and vascular endothelium (Jin et al. 2011; Valable et al. 2010; Xiong et al. 2008a, 2010a; Yatsiv et al. 2005; Zhang et al. 2009, 2010). Brain repair and regeneration processes can be activated or enhanced by pharmacotherapy over a longer therapeutic window than pharmacologic interventions designed to limit injury. Pharmacotherapies are potentially effective in the acute, subacute, post-acute, and chronic phases after

traumatic brain injury. Thus, repair and regeneration therapies have the potential advantage of being effective over a prolonged period of time following traumatic brain injury.

Currently, no effective pharmacologic agent has received approval from the U.S. Food and Drug Administration for the treatment of patients with traumatic brain injury. Table 2.1 lists candidate compounds currently undergoing clinical evaluation for traumatic brain injury treatment. Because traumatic brain injury damages the brain tissue by multiple mechanisms, combination therapy designed to simultaneously target multiple mechanisms of injury is likely required. To date, all phase II/III traumatic brain injury clinical trials have failed (Xiong et al. 2012; Watanabe et al. 2013). Stem cell therapy offers an alternative option for traumatic brain injury.

2.4 Stem Cell Therapy in Traumatic Brain Injury

There are at least two strategies involving stem cell therapy to repair injured brain tissue. They are transplantation of exogenous stem cells to replace damaged cells and stimulation of endogenous stem cells to proliferate to the number of cells needed and differentiate them to the phenotype of cells required for normalization of brain function.

2.4.1 Transplantation of Exogenous Stem Cells in Traumatic Brain Injury

There is great number of attempts to transplant various types of cells, such as neurons, and neural stem cells to repair damaged brain tissue. The main objectives of transplantation experiments are (1) growth facilitation: the transplant fills the lesion site and serves as a cellular bridge; (2) new neurons: the transplant can provide new neurons, which in turn provide new targets and sources of innervations and thus repair the damaged neural circuits; (3) factor secretion: the transplant can produce a variety of substances, such as neurotrophic factors, that promote the brain tissue repair process (Barami and Diaz 2000). Several characteristics of neural stem cells make them potentially suitable to repair damaged brain tissue after traumatic brain injury. Firstly, they can serve as a renewable supply of transplantable cells by clonal expansion in cell culture. Secondly, they are of central nervous system origin and the stem cells generated from the grafts have neural characteristics. Thirdly, neural stem cells can be manipulated by genetic engineering methods to produce specific proteins, such as neurotrophins, neurotransmitters and enzymes (Pincus et al. 1998).

It has been reported that autologous cultured cells harvested at time of emergency surgery from patients with traumatic brain injury, and subsequently engrafted into damaged part of the brain can be detected using magnetic resonance imaging

Table 2.1 Pharmacotherapies currently undergoing clinical evaluation for traumatic brain injury treatment

Compound	Neuroprotective mechanism	Preclinical evidence	Clinical evidence	References
Progesterone	Enhances behavioral and functional outcomes, myelination and neurogenesis Decreases brain edema, apoptosis, pro-inflammatory cytokines Inhibits gamma-aminobutyric acid receptors Prevents neuronal cell death	Reduces IL-6, IL-1β, TNF-α, mitochondrial dysfunction, neuronal loss, axonal injury, tissue loss, lesion size, intracranial pressure, astrocytic accumulation Inhibits neuronal calcium signalling, Toll-like receptor signalling Modulates aquaporin 4 expression, NFk-B signalling, cell proliferation Enhances CD55 production, superoxide dismutase activity, levels of neurotrophin factors Protects against lipid peroxidation Improves spatial learning and memory, locomotor activity and outcomes, anxiety-like behaviors, motor and cognitive performance	Ongoing Phase III clinical trials are positive	Atif et al. (2013), Abdel Baki et al. (2010), Hammond et al. (1983), Lacroix et al. (1987), Lanthier and Patwardhan (1986), Weill-Engerer et al. (2002), Koenig et al. (1995), Liu et al. (2009), Porcu et al. (2009), Sayeed et al. (2006, 2009), Hua et al. (2011, 2012), Cutler et al. (2006, 2007), Galani et al. (2001), Grossman et al. (2004, 2011), Shahrokhi et al. (2010, 2012), Kasturi and Stein (2009), Pan et al. (2007), Guo et al. (2006), Robertson et al. (2006), Roof et al. (1992, 1994, 1996, 1997), Cekic et al. (2012), Chen et al. (2007a, 2008a, b), O'Connor et al. (2007), Yao et al. (2005), Djebaili et al. (2004, 2005), He et al. (2004), Sarkaki et al. (2013), VanLandingham et al. (2007), Jones et al. (2005), Peterson et al. (2012), Luoma et al. (2011, 2012), Garcia-Estrada et al. (1993, 1999), Pettus et al. (2005), Barha et al. (2011), Anderson et al. (2011), Wali et al. (2011), Gilmer et al. (2008), Wright et al. (2007), Xiao et al. (2008), Benvenga et al. (2000)
Growth hormone	Normalize growth hormone deficiency/insufficiency occurred as a result of direct pituitary or indirect hypothalamic injury in 20 % TBI patients Has neuroprotective and neuroregenerative effects	Improves motor function, spatial learning and memory Enhances learning and memory retention Corrects impairments of endothelial progenitor cells Has direct autocrine and/or paracrine neuroprotective effects, anti-apoptotic effect, wound healing effects	Cognitive improvement in growth hormone deficiency/insufficiency TBI patients FDA-approved for adult patients with acquired growth hormone deficiency	Benvenga et al. (2000), Berg et al. (2010), Kelly et al. (2000), Lieberman et al. (2001), Urban (2006), Wilkinson et al. (2012), Giordano et al. (2005), Saatman et al. (1997), Doulah et al. (2009), Svensson et al. (2006), Thum et al. (2007), Creyghton et al. (2004), Ling et al. (2007), Barlind et al. (2010), Sanders et al. (2008, 2010), Demling (1999, 2005), Herndon et al. (1990), Luo et al. (2000), Devesa et al. (2013), High et al. (2010), Reimunde et al. (2011), Takala et al. (1999)

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Table 2.1 (continued)

Compound	Neuroprotective mechanism	Preclinical evidence	Clinical evidence	References
Acetylcholinesterase inhibitors: Physostigmine, Donepezil, Rivastigmine, Galantamine	Increases synaptic acetylcholine by inhibiting its breakdown in the synaptic cleft	Reduces TBI-induced neuronal death, BBB disruption, vasogenic brain edema Preserves neurons hippocampal region, neurologic and motor function	FDA-approved for treating cognitive disorders, including moderate and severe TBI	Cardenas et al. (1994), McLean et al. (1987), Ballesteros et al. (2008), Blount et al. (2002), Bourgeois et al. 2002, Foster and Spiegel (2008), Fujiki et al. (2006, 2008), Hayashida et al. (2007), Kaye et al. (2003), Khateb et al. (2005), Liepert (2008), Lombardi (2008), Masanic et al. (2001), Morey et al. (2003), Sugden et al. (2006), Taverni et al. (1998), Tenovuo (2005), Trovato et al. (2006), Walker et al. (2004), Wheaton et al. (2011), Whelan et al. (2000), Whitlock (1999), Zhang et al. (2004), Chen et al. (1998a, b), Noble and Hauser (2007), Silver et al. (2006, 2009), Tenovuo et al. (2009), Weinstock et al. (2001)
Huperzine A	A selective and reversible acetylcholinesterase inhibitors extracted from a Chinese herb An NMDA antagonist Neuroprotective effects through the activation of cholinergic systems and by potentially upregulating β-amyloid precursor protein metabolism	Modulates both amyloidogenic and non-myloidogenic pathways Attenuates cognitive deficits Improves memory	Huperzine A is classified as an herbal remedy, has beneficial effects in cerebral blood flow, general cognitive function, global clinical status, behavior disturbance, and functional performance.	Zhang et al. (2008), Wang et al. (2002, 2012), Fan et al. (2005), Li et al. (2008), Amen et al. (2011)

Lithium	Exerts neuroprotective effects through reduction of excitotoxicity, ischemic damage, and apoptosis Attenuates several pathways involving pro-inflammatory cytokines, β-APP-cleaving enzyme-1 expression, β-amyloid accumulation, microglial activation, cyclooxygenase-2 activity, glycogen synthase kinase-3β activity, and MMP-9 expression Preserves the integrity of the BBB	Attenuates Aβ load, amyloid precursor protein load, β-APP-cleaving enzyme-1 overexpression, Tau protein phosphorylation, TBI-induced neuronal death Reduces brain edema, neuronal and hemispheric volume loss, levels of IL-1β Improves spatial learning and memory	The primary drug for the treatment of bipolar disorder	Shapira et al. (2007), Yu et al. (2012a, b), Zhu et al. (2010), Dash et al. (2011), Bellus et al. (1996), Glenn et al. (1989), Haas and Cope (1985), Hale and Donaldson (1982), Parmelee and O'Shanick (1988), Schiff et al. (1982)
N-acetyl cysteine	Deacetylates to cysteine in the liver Both N-acetyl cysteine and cysteine are anti-oxidants that largely scavenge cytosolic radicals Increases levels of the endogenous anti-oxidant glutathione and extracelullar levels of glutamate	Anti-inflammatory activity by decreasing the activation of NF-kB, lowering IL-1β, TNF-α, and ICAM-1 levels Reduces lesion volume, levels of the putative neuroprotective enzyme heme oxidase Prevents myelin loss Restores memory	Significant increases in symptom resolution in individuals who suffer post-concussive symptoms	Abdel Baki et al. (2010), Atkuri et al. (2007), Dodd et al. (2008), Olive et al. (2012), Hicdonmez et al. (2006), Chen et al. (2008c), Yi and Hazell (2005), Hanci et al. (2010), Thomale et al. (2006), Hoffer et al. (2013)

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Table 2.1 (continued)

Compound	Neuroprotective mechanism	Preclinical evidence	Clinical evidence	References
Cyclosporine A	Inhibits opening of the mitochondrial permeability transition pore, and protein phosphatase calcineurin Reduces reactive oxygen species	Have beneficial effects on axonal injury, contusion volume, cerebral microcirculation	Phase II clinical trial, a positive effect on 6-month Glasgow Outcome Scale score was observed in TBI patients	Abdel Baki et al. (2010), Brustovetsky and Dubinsky (2000), Sharov et al. (2007), Alessandri et al. (2002), Büki et al. (1999), Colley et al. (2010), Kilbaugh et al. (2011), Mbye et al. (2009), Okonkwo and Povlishock (1999), Okonkwo et al. (2003), Scheff and Sullivan (1999), Setkowicz and Guzik (2007), Signoretti et al. (2004), Suehiro and Povlishock (2001), Sullivan et al. (1999, 2000a, b, 2011), Turkoglu et al. (2010), Van Den Heuvel et al. (2004), Gijtenbeek et al. (1999), Wijdicks et al. (1996), Empey et al. (2006), Mazzeo et al. (2006, 2008, 2009), Hatton et al. (2008)
FK 506	Inhibits calcineurin	Have beneficial effects on axonal injury, cerebral microcirculation	Chronic neurotoxicity	Singleton et al. (2001), Campbell et al. (2012), Oda et al. (2011), Piilgaard et al. (2011), Rhodes et al. (2009), Saganová et al. (2012), Grimbert et al. (1999)
Methylphenidate	Increases synaptic dopamine by blocking dopamine transporters and inhibiting dopamine reuptake Enhances synaptic norepinephrine levels by blocking norepinephrine reuptake	Promotes striatal dopaminergic neurotransmission Enhances spatial learning and retention and motor performance	FDA-approved for the treatment of attention deficit hyperactivity disorder Ongoing clinical trials in TBI patients	Moeller et al. (2012), Volkow et al. (1998, 2001, 2002a, b, 2012), Koda et al. (2010), Marsteller et al. (2002), Wagner et al. (2007, 2009a, b), Kline et al. (2000), Alban et al. (2004), Willmott and Ponsford (2009), Kim et al. 2006, 2012), Whyte et al. (1997, 2004), Plenger et al. (1996), Speech et al. (1993), Mahalick et al. (1998), Lee et al. (2005), Mooney and Haas (1993), Williams et al. (1998), Gualtieri and Evans (1988), Moein et al. (2006)
Atomoxetine	Inhibits norepinephrine transporters Increases extracellular norepinephrine and dopamine.	Enhances spatial learning and retention and motor performance	ibid	Koda et al. (2010), Swanson et al. (2006), Bymaster et al. (2002), Reid and Hamm (2008)

Erythropoietin	A pleiotropic cytokine involved in erythropoiesis Attenuates glutamate and nitric oxide toxicity, anti-apoptotic, anti-oxidant, and anti-inflammatory effects Stimulates neurogenesis and angiogenesis Protects mitochondria	Increases hematocrit by 60%	Ongoing Phase III clinical trials are safe and beneficial, resulting in lower hospital mortality	Jin et al. (2011), Valable et al. (2010), Xiong et al. (2008a, b, 2009, 2010a, b, 2011), Yatsiv et al. (2005), Zhang et al. (2009, 2010), Lu et al. (2005), Akdemir Ozisik et al. (2007), Bian et al. (2010), Chauhan and Gatto (2010), Chen et al. (2007b), Cherian et al. (2007), Cherian et al. (2011), Hartley et al. (2008), Liao et al. (2009), Lieutaud et al. (2008), Oztürk et al. (2008), Verdonck et al. (2007), Gonzalez et al. (2007), Ehrenreich et al. (2009), Tseng et al. (2009), Heeschen et al. (2003), Miskowiak et al. (2010), Wüstenberg et al. (2011)
Glyburide	A sulfonylurea binds sulfonylurea receptors blocking ATP-sensitive K^+ channels in neurons.	Reduces inflammation, hemorrhage, vasogenic edema, hippocampal injury	Ongoing Phase II clinical trial shows changes in edema and/or hemorrhage in moderate or severe TBI	Silver et al. (2009), Simard et al. (2009, 2012), Patel et al. (2010), Ortega et al. (2012), Kunte et al. (2007)
Minocycline	Has anti-inflammatory, anti-apoptotic, and anti-oxidant activity	Inhibits microglia, T cells, neutrophils, metaloproteases, apoptosis, reactive oxygen species Reduces lesion volume Maintains myelin content Protects grey and white matter	Confirmed as an anti-inflammatory drug	Abdel Baki et al. (2010), Kim and Suh (2009), Bye et al. (2007), Homsi et al. (2010), Sanchez Mejia et al. (2001), Kovesdi et al. (2012), Casha et al. (2012), Racette (2008), Sacktor et al. (2011)
Statins: Simvastatin	Has beneficial effects in brain edema, BBB integrity, cerebral blood flow, neuroinflammation, axonal injury, cell death, trophic factor production	Against neuronal death	Ongoing Phase II clinical trial in adults with TBI	Chauhan and Gatto (2010), Abrahamson et al. (2009), Béziaud et al. (2011), Chen et al. (2008d, 2009), Indraswari et al. 2012, Li et al. (2009), Lu et al. (2004a, b, c, 2007), Wang et al. (2007), Sierra et al. (2011), Boimel et al. (2009)

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Table 2.1 (continued)

Compound	Neuroprotective mechanism	Preclinical evidence	Clinical evidence	References
Amantadine	Increases extracellular dopamine by blocking dopamine reuptake, facilitating dopamine synthesis Has postsynaptic effects on dopamine circuits by increasing dopamine receptor density antagonist of NMDA receptors		Phase III clinical trial in 184 patients in the vegetative state or minimally conscious state shows improvement in the Disability Rating Scale, representing the first and only evidence to date that pharmacologic intervention can affect recovery from TBI.	Bales et al. (2009), Gianutsos et al. (1985), Stoof et al. (1992), Dixon et al. (1999), Meythaler et al. (2002), Schneider et al. (1999), Whyte et al. (2005), Giacino et al. (2012)

Abbreviations: *IL* interleukin, *TNF* tumor necrosis factor, *NFkB* nuclear factor kappa-light-chain-enhancer of activated B cells, *TBI* traumatic brain injury, *FDA* the U.S. Food and Drug Administration, *BBB* blood brain barrier, *NMDA* N-methyl-D-aspartate, *Aβ* β-amyloid, *MMP* matrix metalloproteinase, *ICAM* intercellular adhesion molecule

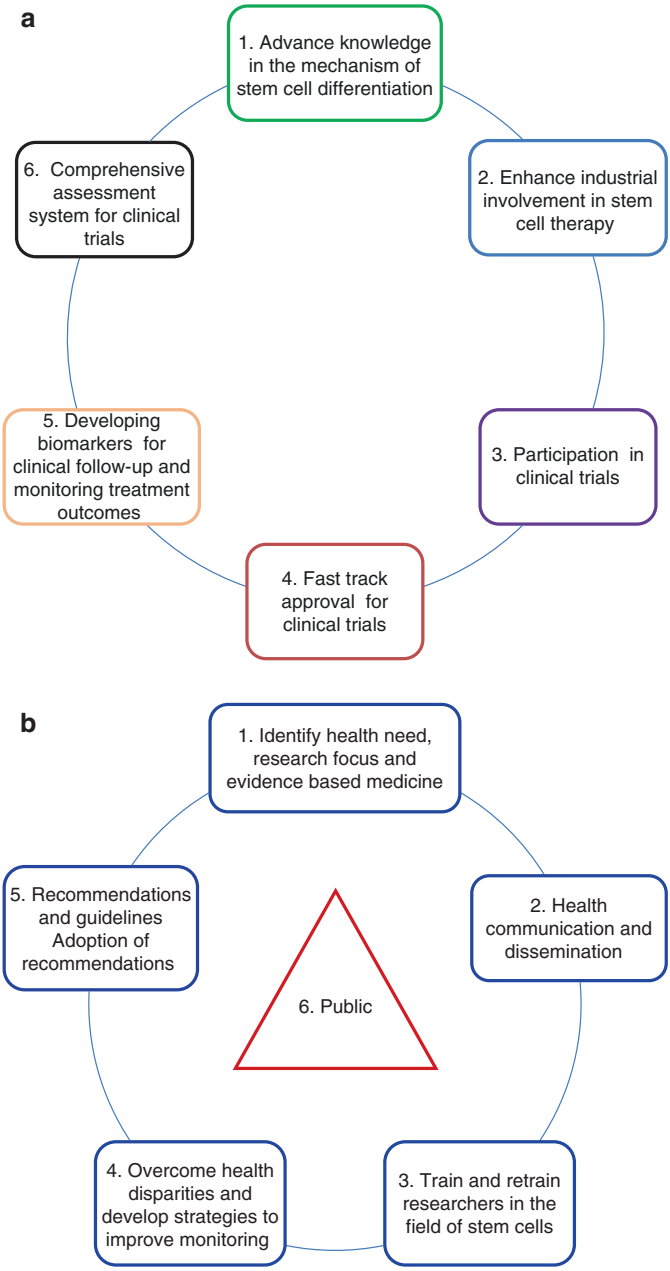

Fig. 2.3 (**a**) Proposed schema for effective translation of stem cells to therapy in traumatic brain injury involving concerted effort of multilevel strategies of six main stakeholders. (**b**) Proposed framework for the reinforcement of the multilevel strategies effective bench to bedside translation of stem cells to therapy in traumatic brain injury

(Nakamura et al. 2003). The efficacy of transplantation largely depends on a grafting method that optimizes the survival of the transplanted stem cells and minimizes the graft-induced lesion. Most transplantation studies involved intraparenchymal injection into the central nervous system, in which cells were grafted directly into or adjacent to the lesion (Chow et al. 2000; Cao et al. 2001; Jendelová et al. 2004). The optimal time for transplantation may not be immediately after injury. The levels of various inflammatory cytokines (tumor necrosis factor alpha, interleukin-1α, interleukin-1β and interleukin-6) in the injured brain peak 6–12 h after injury and remain elevated until the 4th day. Although these inflammatory cytokines are known to have both neurotoxic and neurotrophic effects, they are believed to be neurotoxic within a week after injury, which causes the microenvironment to be unsuitable for survival of the grafted stem cells (Zhu et al. 2006). However, if too much time passes after the injury, glial scar forms a barrier surrounding the lesion site and inhibits revascularization of the graft preventing local blood circulation which is needed for graft survival. Thus, it is considered those 7–14 days after traumatic brain injury is the optimal time for stem cell transplantation (Ogawa et al. 2002; Okano et al. 2003).

2.4.2 Stimulation of Endogenous Neural Precursor Cells in Traumatic Brain Injury

Endogenous neurogenesis has been identified in adult brain (Luskin et al. 1996; Alvarez-Buylla et al. 2000). In adult rodent brain, neural stem cells migrate from ventricular zone to the olfactory bulb and integrate into the neuronal network. This is called the rostral migratory stream. However, the potential success of stimulating endogenous neural precursor cells is hinged on delivery of various growth factors. This is the most common way to stimulate neural precursor cells. The following growth factors are needed to stimulate neural precursor cells: epidermal growth factor, fibroblast growth factor-2 (Martens et al. 2002; Kojima and Tator 2000, 2002), basic fibroblast growth factor (Rabchevsky et al. 2000), acidic fibroblast growth factor (Lee et al. 2004), brain-derived neurotrophic factor (Namiki et al. 2000; Wang et al. 2013), vascular endothelial growth factor (Sharma 2003; Chang et al. 2013), nerve growth factor, neurotrophin-3 (Namiki et al. 2000; Widenfalk et al. 2003), glial cell line-derived neurotrophic factor (Iannotti et al. 2004), insulin-like growth factor-1 (Sharma 2003), and stromal cell-derived factor-1 alpha (Imitola et al. 2004). They were administrated by intraventricular (Martens et al. 2002), intraparenchymal (Namiki et al. 2000; Sharma 2003) or intrathecal (Kojima and Tator 2000, 2002; Rabchevsky et al. 2000; Iannotti et al. 2004) injection. They were reported not only to enhance the proliferation, migration and gliogenesis of neural precursor cells (Martens et al. 2002; Kojima and Tator 2000, 2002; Imitola et al. 2004) but also to protect the spinal cord from further damage (Sharma 2003; Widenfalk et al. 2003). In addition, these growth factors facilitate the regrowth of

axons and remyelination (Lee et al. 2004; Namiki et al. 2000; Gensert and Goldman 1997). Functional recovery has been reported after growth factors were delivered into injured spinal cord (Martens et al. 2002; Kojima and Tator 2000, 2002; Lee et al. 2004). However, the mechanisms of functionary recovery by stimulating endogenous neural precursor cells are not fully understood.

In addition to growth factors, other molecules are shown to stimulate endogenous neural precursor cells. Proliferation of endogenous neural precursor cells was demonstrated when the sodium channel blocker, tetrodotoxin and the glycoprotein molecule, sonic hedgehog were injected into the parenchyma (Rosenberg et al. 2005; Bambakidis et al. 2003). It has been reported that cognate chemokine receptor type 4 expressed by neural precursor cells can regulate their proliferation and direct their migration towards the injury site (Imitola et al. 2004). In addition, antibodies blocking interleukin-6 receptors were reported to not only inhibit differentiation of endogenous neural stem cells into astroglia *in vivo* and *in vitro*, but also to promote functionary recovery (Okada et al. 2004; Nakamura et al. 2005). The functionary recovery is resulting from blocking interleukin-6 and consequently inhibiting the formation of glial scars and promoting axonal regeneration (Okada et al. 2004; Okano et al. 2005). Notably, studies of ATP-binding cassette (ABC) transporters have emerged as a new field of investigation. ATP-binding cassette transporters, especially ATP-binding cassette sub-family A member 2, ATP-binding cassette sub-family A member 3, ATP-binding cassette sub-family B member 1, and ATP-binding cassette sub-family G member 2, play an important role in proliferation and differentiation of neural stem cells (Lin et al. 2006; Eckford and Sharom 2006; Leite et al. 2007; Li et al. 2007; Saito et al. 2007; Tamura et al. 2006).

In contrast to transplantation of exogenous neural precursor cells, stimulation of endogenous neural precursor cells to repair damaged spinal cord has three main advantages: (1) there is no ethical issue involved in human embryonic stem cells, (2) it is usually less invasive since no surgical procedure required, and (3) no immunogenicity, which avoids immunorejection that observed in the transplantation of exogenous neural precursor cells (Mohapel and Brundin 2004). Similar to the transplantation studies of adult neural precursor cells in spinal cord injury, no neurogenesis has been reported from the stimulation of endogenous neural precursor cells. It has been reported that up-regulation of the Notch signal pathways leads to poor neuronal differentiation (Yamamoto et al. 2001). The increased levels of various cytokines within the microenviroment surrounding the area of injury cause a lack of trophic support for differentiation of neural precursor cells into neuronal lineage (Okano et al. 2003; Frisén et al. 1995; Johansson et al. 1999; Widenfalk et al. 2001).

Recently, more attention has been drawn to cAMP response element binding protein/p300-phosphorylated Smad protein complex. It was found that cAMP response element binding protein/p300-phosphorylated Smad protein complex can be bound in neural stem cells, which determines the differentiation of neural stem cells. If the complex is bound with phosphorylated signal transducers and activator of transcription 3, the neural stem cells differentiate into astroglia lineage cells. On the other hand, if the complex is bound with proneural-type of the basic

helix-loop-helix factor, such as neurogenin 1 and 2, they differentiate into the neuronal lineage (Okano et al. 2005; Sun et al. 2001; Nakashima et al. 1999). Apart from that, SOX gene may also play an important role in neural differentiation (Pevny and Placzek 2005). Once neural stem cells decide to differentiate into neuronal lineage, a cascade of hundreds of genes is regulated over time to lead the immature neuron into its mature phenotype. Many of these neural genes are controlled by RE1-silencing transcription factor. RE1-silencing transcription factor acts as a repressor of neural genes in non-neural cells, while regulation of RE1-silencing transcription factor activates large networks of genes required for neural differentiation (Gage and McAllister 2005; Ballas et al. 2005; Ballas and Mandel 2005).

2.5 Bench to Bedside Translation of Stem Cell Therapy in Traumatic Brain Injury

The main purpose of state-of-the-scientific studies is to translate our discoveries into daily clinical practice. The basic research laboratory takes its observations obtained at molecular or cellular levels in a cutting edge state and implements this into acceptable clinical practice to the benefit of the public. However, this is always met with a lot of challenges, such as ethics, governmental regulations, funding constraints, paucity of adequate collaboration among clinical and basic scientists, and the challenges during conducting clinical trials. From the identified gaps in the current state of the stem cell science and inherent challenges faced by the field, the author proposes six point schema for improving bench to bedside translation of stem cell therapy in Fig. 2.3a involving a rigorous network of six stakeholders: basic researchers, pharmaceutical companies, patients or general public participating in clinical trials, regulatory bodies or government agencies for providing research grant approval, collaborative research between basic and clinical scientists with the plan of developing biomarkers for potential drug targets and creating a concerted network of groups that identifies some of the medical problems relating to traumatic brain injury. Patients with moderate traumatic brain injury who suffer long-term complications are a major unmet medical need. Within our capabilities to clinically assess improvement, historically, the majority of individuals with moderate traumatic brain injury are likely to recover to their pre-injury state. Early identification of those individuals likely to experience long-term complications is essential to maximize benefit of stem cell therapy. Strategies to delineate this population from a larger population of individuals with moderate traumatic brain injury could include enrollment of patients with persistent symptoms 1–2 weeks after injury, because recovery is most rapid in the first few days. Patients who are unlikely to fully recover could be identified using prognostic biomarkers including neuroimaging, biochemical, and objective clinical measures. Prognostic biomarkers are defined by the U.S. Food and Drug Administration as indicators that inform the natural history of a disorder in the absence of a therapeutic intervention (Drug Administration 2010).

Although identifying individuals with traumatic brain injury who are most likely to respond to stem cell therapy and evaluating the biologic response to the therapy are essential for successful clinical trials, the ability to do either is lacking. Predictive biomarkers of stem cell therapeutic response are needed to address this challenge. Predictive biomarkers are baseline characteristics that identify individuals by their likelihood to respond to a stem cell therapy and may include biochemical markers including oxidative stress, inflammation, neuronal, and glial integrity, molecular imaging with positron emission tomography, or functional imaging with functional magnetic resonance imaging. By identifying patients who are most likely to respond to stem cell therapy, the appropriate population can be selected for enrollment in clinical trials. Identifying specific predictive biomarkers would decrease the sample size needed to power clinical trials, thus decreasing risk to subjects, time to complete accrual, and cost. Biomarkers are dynamic measurements that show a biologic response occurred after stem cell therapy, including neuroimaging to measure effects on neuroprotection, neurorecovery, and neuroinflammation, or biochemical biomarkers of oxidative stress, inflammation, and neuronal integrity. Clinical trials would greatly benefit from biomarkers, which allow for the measurement of the effect of the stem cell therapy on the putative mechanism of a specific phenotype of cell's action, thus providing evidence of engagement of the target tissue by the therapy. To achieve stem cell repair, regeneration and protection after traumatic brain injury, each of the six points identified is critical for advancing the field, and efforts to address the points should be conducted in parallel to ensure ultimate success in improving clinical care and outcomes for individuals with traumatic brain injury. We are still faced with the need to formulate hypothesis both at experimental and clinical epidemiologic level and implementing these into clinical practice while the translational researchers serve to collaborate and coordinate all these strategies to yield rapid results.

Indeed, communication and dissemination shown in Fig. 2.3b which is patient centredness will not only impact on the public, but will also help to tame the ethical issues in this field. Communication will involve both patients and clinicians involve in conducting randomized clinical trials. With strong feedback on outcomes, pharmacovigilance, and health promotion. Education of the populace in form of scientific advocacy is so paramount as this will impact on improved scientific collaboration, quality public control, and increased transparency among researchers and may improve funding of research work (Keramaris et al. 2008).

Research in neural stem cells is still a grey area and much knowledge needs to be gained at the bench in order to actually close the knowledge gaps in stem cell therapy. There is inadequate understanding of the secondary brain injury process after traumatic brain injury, insufficient preclinical testing in diffuse axonal injury models, species differences, and lack of understanding of the mechanism of drug-receptor interactions. It has been suggested the need to use gyrencephalic models for proper translation of stem cell therapy in traumatic brain injury (Loane and Faden 2010). Academic and biotech researchers should address how to make their stem cell therapy products more feasible for commercial-scale production (Eaker

et al. 2013). There is need for increased linkages and networking between academician, researchers, and clinician for greater reward of what is being generated.

Methodological disparities between experimental models of traumatic brain injury and clinical studies cannot be overemphasized. The intent to treat models, differences in statistical analysis as a result of different sample size, and different behaviours between human and animals. Animal research is a rapid, well-controlled, and cost-effective means to initially verify hypothesis. However, limitations exist in animal models of traumatic brain injury and their application in stem cell therapy. First, because no single animal model accurately mimics all of the features of human traumatic brain injury, individual investigators have appropriately refined experimental approaches to better fit their specific research goals. However, the resulting variability in experimental approaches among studies makes comparison of results across laboratories and models difficult, limiting the confidence that results can be translated into successful clinical trials. Advancing preclinical research in animal models requires that results are comparable across studies and can translate into human studies. This requires standardization of available animal models and introduction of new models when scientifically necessary. Second, some of the popular current models do not correspond well with the human condition. Injury severities in animals differ from humans; while they are well defined in animals, it could take any direction in human. Third, preclinical studies should use the same level of rigor required for clinical trials. Specifically, assignment of animals to treatment conditions should be randomized, assessments must be conducted by blinded examiners, the primary outcome measure must be pre-determined, and statistical assessment of secondary outcome measures should utilize appropriate corrections for multiple comparisons. Fourth, the transplantation of stem cells into animal models should mimic the timing, delivery route, and equivalent mass of cells feasible in humans. Last, the neurobehavioral outcome measures most widely used in preclinical models are not sufficiently sensitive to long-term behavioral and cognitive deficits, and more sensitive rodent behavioral tasks that discriminate injury severity beyond 12 weeks after injury are needed. The need to improve study quality score has recently being called for by stroke therapy academic industry roundtable, which was recently updated and this include the following recommendations: (1) Elimination of randomizations and assessment bias, (2) Use of a priori definitions of inclusion/exclusion criteria, (3) inclusion of appropriate power and sample size calculations, (4) full disclosure of potential conflict of interests, (5) evaluation of therapies in male and female animals across the spectrum of ages, and with comorbid conditions, such as hypertension and/or diabetes. Furthermore, some researchers has expanded on these proposed recommendations for improved clinical trials in brain injury with special focus on neuroprotective therapies in traumatic brain injury (Loane and Faden 2010; Fisher et al. 2009). Nonadherence was the single most important determinant of trial failure in the past.

Finally, the International Mission on Prognosis and Clinical Trial Design in traumatic brain injury proposed ways of overcoming the above disparities and challenges. The recommendations include a robust inclusion criteria and recommendations for general research in traumatic brain injury (Loane and Faden

2010). The six point schema is an overview recommendation with the public, patient or the society as the core and the fulcrum of all activities of research and if implemented may yield quality research outcome in neural stem cells therapy in traumatic brain injury (Ugoya and Tu 2012).

2.6 Conclusion

Mortality and long-term disability from traumatic brain injury is projected to rise globally. Neural stem cell therapy is a strategy that offers hope for the future in treatment of brain injury. In addition, we are now able to monitor autologous neural stem cells *in vivo*, cell migration, and clearly demonstrate that neural stem cells could selectively target injured brain or spinal cord tissue and undergo neurogenesis. Finally, the proposed six points cyclical schema should be implemented with determined effort of all stakeholders for effective bench to bedside translation of neural stem cell therapy in traumatic brain injury.

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http://www.springer.com/978-3-319-33719-7

Neurological Regeneration
Pham, P.V. (Ed.)
2017, IX, 258 p. 30 illus., 26 illus. in color., Hardcover
ISBN: 978-3-319-33719-7