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Review

Cellular therapy for traumatic neurological injury

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Neurological injury is the primary lethal mechanism of injury in children, and the primary etiology of long-term disability after trauma. Laboratories and clinical/translational teams have sought to develop stem/progenitor cell therapies to improve recovery in a clinical setting in which there is no significant reparative option. While none of these treatments are currently standard therapeutics, phase IIb clinical trials are underway in both adults and children in severe traumatic brain injury (TBI) and phase I/IIa trials in spinal cord injury. This review will characterize the cell therapy strategies: cell replacement and tissue integration vs. immunomodulation/enhanced endogenous tissue repair. TBI is somewhat different from other central nervous system injuries (spinal cord injury and stroke), in that TBI is a diffuse injury, whereas spinal cord injury and stroke are anatomically discrete. Importantly, this drives cell therapy approaches, as TBI is less apt to be treatable with a local cell replacement intervention. More localized injuries may be more amenable to local approaches and cell replacement to bridge focal gaps. This review focuses on a few reports in the field that highlight areas of progress, but is not intended to be a comprehensive survey of the state of regenerative medicine for neurological injuries.

BACKGROUND

Traumatic Brain Injury

Approximately 1.5 million people (40,000 pediatric emergency department visits, 30,000 pediatric hospitalizations, and 3,000 pediatric deaths) suffer traumatic brain injury (TBI) yearly in the United States. The annual mortality approaches 50,000 with the remaining patients suffering from varying levels of long-term impairment. Overall, 6.5 million patients are burdened by the physical, cognitive, and psychosocial deficits associated with TBI, leading to a total economic impact of ~60 billion dollars (1). There is currently no effective pharmacologic therapeutic for TBI (2). Since the 1970s, TBI has been described as "primary injury" and "secondary injury." The primary injury is the immediate result of energy dissipation within the substance of the brain, and occurs within milliseconds of impact. Primary injuries include direct neuronal, glial, and vascular disruption. Secondary injuries are the result of the reactive biochemical events that occur after the primary injury. These reactive biochemical events may accelerate or exacerbate initial cellular injury or cause "new" injury (3,4). Current TBI management strategies are designed to minimize secondary injury and their consequences (5–7). The current treatment paradigm focuses on the evacuation of extra-axial fluid collection(s), and the management of cerebral hemodynamics by reducing intracranial pressure (ICP) or increasing mean arterial pressure (MAP) to optimize cerebral perfusion pressure (CPP) (8,9). There are currently no proven treatments to prevent secondary brain injury after TBI, which can be manifest acutely as elevated intracranial pressure as a consequence of increased blood–brain barrier (BBB) permeability and cerebral edema. Elevated ICP has been correlated with poor clinical outcomes. Clinically, secondary brain injury associated with TBI is associated with neuroinflammation and the subsequent cerebral edema, leading to an increase in ICP and a subsequent decrease in cerebral perfusion. If poorly controlled, elevated ICP will impair cerebral perfusion and exacerbate the primary injury. Significant additional advances in reducing the disability associated with TBI are unlikely using the current management strategies alone (2). For pediatric patients suffering a severe TBI, there is an ~30% chance of a bad outcome-defined as death, vegetative state, or severe disability (10).

Spinal Cord Injury

Spinal cord injury (SCI) continues to be a significant cause of disability despite extensive research and supportive clinical care. Similar to TBI, no reparative therapies exist for SCI. There are ~11,000–20,000 new cases/year (~1,500 pediatric) in the United States, and 250,000 patients live with SCI. SCI consists of both the kinetic primary injury and the biochemical secondary injury, characterized by inflammation, cytotoxic depolarizations, which can lead to further neuronal loss, and oligodendrocyte apoptosis at a distance from the primary lesion. The loss of oligodendrocytes results in myelin loss and subsequent poor action potential conduction. This pathophysiology is the foundational concept of neural stem cell (NSC)/oligodendrocyte precursor cell (OPC) replacement strategies to restore function after SCI.

Overview of Cell Therapy for Neurological Injury

Over the past 10 years there has been a growing body of literature supporting the use of various progenitor cell types

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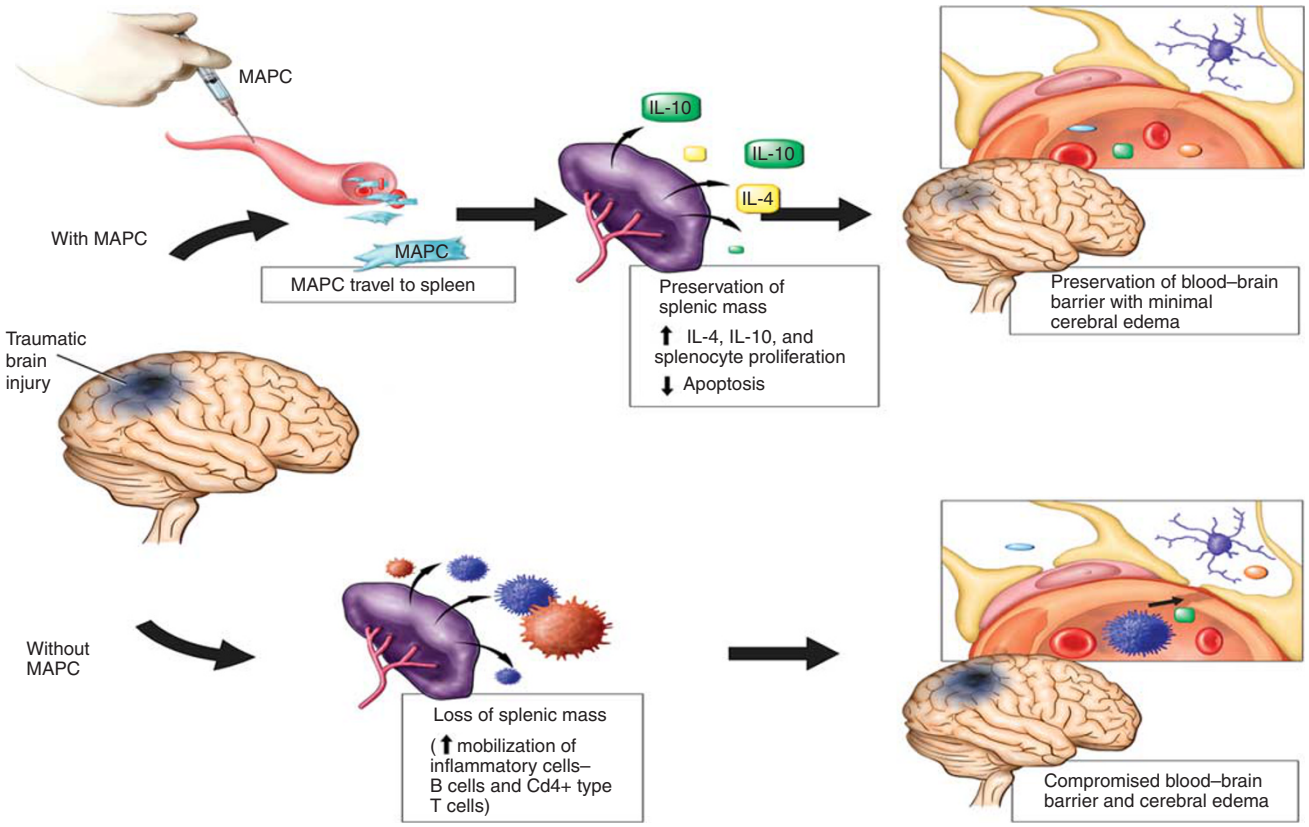


Figure 1. Systemically injected multipotent adult progenitor cell (MAPC) interact with splenocytes to exert anti-inflammatory effect. This cartoon demonstrates the concept of peripheral immune interactions that influence central nervous system (CNS) inflammatory responses to injury. Through cell-labeling experiments, we demonstrated that these cells sequester in the spleen and lung, resulting in an efflux in anti-inflammatory cytokines, and T-regulatory cells. This correlated with polarization towards an M2 predominant microglial phenotype and functional improvements. This figure was adapted from our original publication in *Experimental Neurology* (16).

to treat acute neurological injuries such as TBI and stroke. NSCs (adult and embryonic), mesenchymal stromal (MSCs) and multipotent adult progenitor cells (MAPCs), and bone marrow mononuclear cells (from which MSC and MAPCs are derived) have all shown efficacy in preclinical models of TBI/stroke through various mechanisms; however, few groups believe that true neural replacement and integration are the mechanisms involved in the observed efficacy. More likely is that the progenitor cell populations are modifying the regional response to injury (inflammatory/reparative vs. regenerative), resulting in improved functional outcomes.

Bone marrow–derived adherent/expanded cells: MSCs (auto and allogeneic ± modified) and MAPCs. MSCs are a similar cell type relative to MAPC, in that they are an adherent, bone-marrow–derived cell, but they differ in terms of ultimate product profile in terms of potency, size, and expansion characteristics. There are numerous publications that report the efficacy of MSCs in animal models of TBI, and this was reviewed in a meta-analysis of preclinical models of TBI using a cellular therapeutic (11). A reported mechanism of action is that cells migrate to the site of injury and exert a paracrine effect by secreting growth factors that preserve at risk neurons. We could not reproduce those data nor could we confirm reports of cell engraftment (12). Our findings of lack of MSC survival/engraftment in the central nervous system (CNS) have been confirmed by others (13). Finally, we noted that the degree of growth factor production and MSC distribution within the CNS as reported could not produce a clinically meaningful concentration of the putative mediators of the observed improvements (14). Preclinical data using MAPC in a rodent model of TBI demonstrated improved functional outcome at 120 days after TBI, as well as preservation of the blood–brain barrier in the acute phase of injury (15). Mechanistically, these cells upregulate the anti-inflammatory response to injury via interactions with splenocytes (16). Ultimately, there is an alteration in the microglial activation status to a reparative *vs.* inflammatory phenotype (14). (**Figures 1 and 2**) All of these data support the working hypothesis that MAPC infusion produces the observed functional benefit by altering the innate immune response to TBI (secondary brain injury), and that engraftment is neither required nor desired for the effect to occur.

Nonexpanded/noncultured bone marrow mononuclear cells contain MSCs/MAPCs in small numbers as well as a host of hematopoietic progenitors and monocytes/lymphocytes. These bone marrow mononuclear cells have similar characteristics to umbilical cord blood mononuclear cells and both

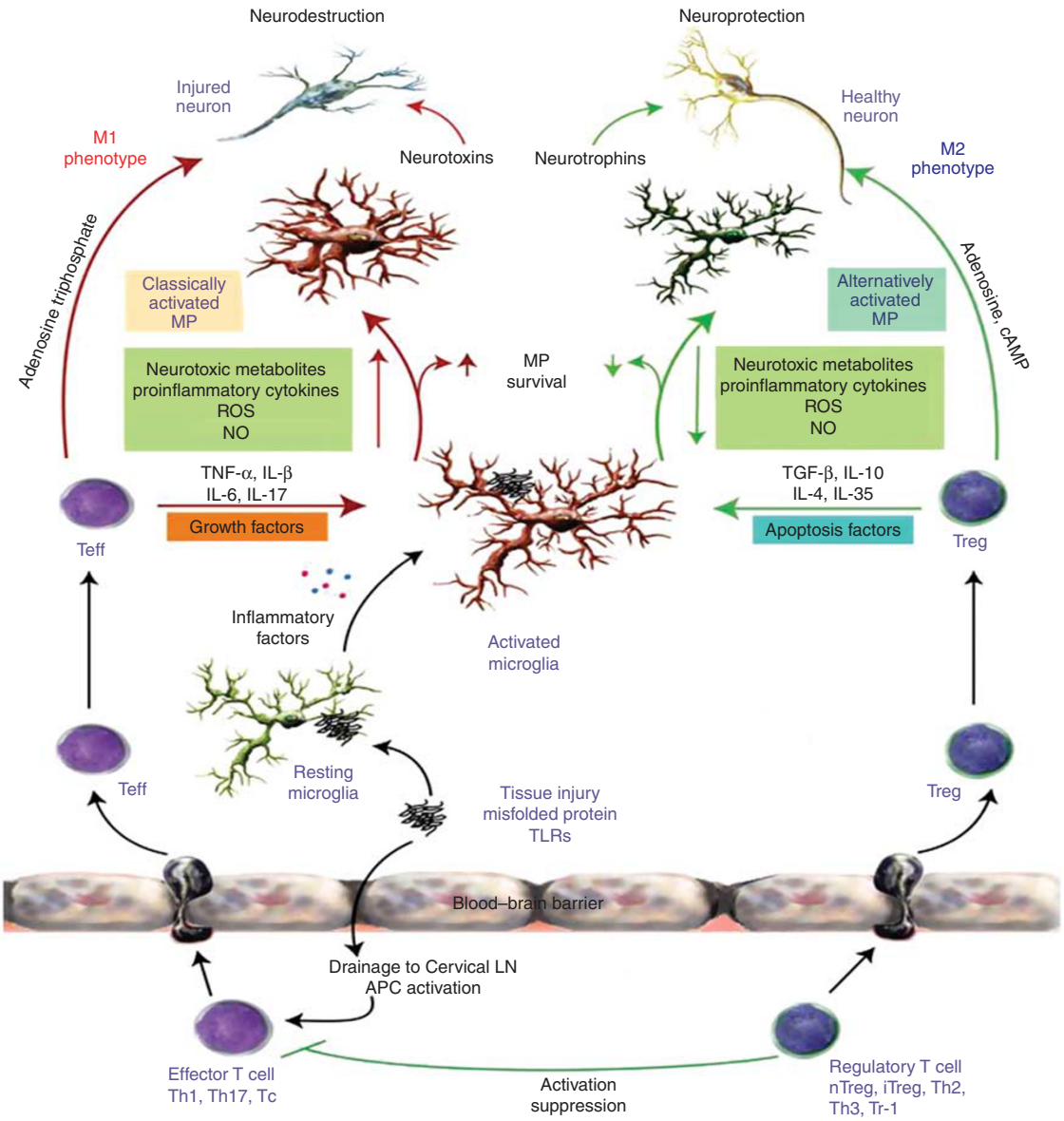


Figure 2. Cellular therapies polarize the microglia to an anti-inflammatory M2 phenotype via pleiotropic mechanisms of action. Microglial polarization is important as these are the primary effector cells of the neuroinflammatory response to injury.

cell populations have proven efficacious in proof of concept studies treating TBI (15,17). Similar work, with parallel results, have been done in stroke with both cell types (18–20).

ESC–derived NSC or oligodendrocyte stem cell/OPC. This paradigm uses a starting bank of embryonic stem cell (ESC) to expand a large number of cells, and then they are differentiated in culture to the proposed neural precursor cell. The use of NSCs or OPCs to replace damaged neurons and supporting cells is conceptually attractive, but difficult due to a host of practical issues and barriers. Primarily, TBI is a multifocal disease, thus targeted delivery of a cell product or even a cell/scaffold composite is hampered by the numerous areas of injury. While there may be a dominant contusion visible on initial imaging, this may not be the primary lesion of clinical significance. These cells do not migrate in the adult brain to any clinically relevant distance, so this requires multiple, stereotactic injections. In the clinical setting of diffuse injury/multiple lesions, it can be difficult to discern the specific lesion responsible for the clinically dominant pathology. This is easy to model in animal experiments, but difficult to translate into heterogeneous contusion/diffuse axonal injury patterns that occur in patients. Secondarily, the issue of immunosuppression to ensure engraftment is potentially problematic in a trauma population, but has proven feasible in the chronic patient. Finally, the complication of ectopic tissue development can be especially problematic in the CNS as opposed to many other potential sites. This concern is real, but probably overstated with current approaches for cell selection. However, the concern is that even a very small number of residual nondifferentiated ESCs

(in theory only one is required) can result in teratoma development (21). These barriers will make this approach a more distant possibility, and even if successful, could be complementary to systemic, immunomodulatory approaches.

Cell-derived proteins. Supernatants or conditioned media have been used successfully in preclinical models of TBI with striking success. In a mouse model of TBI, we have shown an effect on BBB permeability, and enhancement of neurogenesis due to TIMP-3 (tissue inhibitor of metalloproteinases-3) production by MSCs (22). Similarly, Prockop's and co-workers (23) has shown that TSG-6 production from MSCs produces similar early neuroprotective effects and late functional behavioral improvement in mice. One of the primary barriers in translation of using the protein alone is the scale-up to produce the proteins in a clinically relevant volume (DJ Prockop, personal communication). While this is ultimately a solvable problem, it could make the cost of this therapy beyond the reach of any practical application. The use of exosome-derived proteins from stimulated MSCs or other adherent, bone marrow–derived cell types may also be a useful, next-generation approach. Zhang *et al.* (24) have shown that MSC–derived exosomes improve functional recovery in rodent TBI, and the putative mechanism is via transfer of specific miRNAs. Limitations of this approach hinge on the identification of the most effective molecule/protein, while cell-based therapies affect multiple mechanisms of action for an overall pleiotropic effect.

PRECLINICAL DATA

Traumatic Brain Injury

There is extensive preclinical data studying stem cell–based therapies in models of TBI. Conceptually, the field started in the 1990s with the concept of neural replacement with claims of transdifferentiation of MSCs into neurons when directly implanted into the brain. This was later disproven, and it is now well established that MSCs and similar cell types do not engraft in any relevant amount (13). Of the systemically infused cell types used to treat TBI (umbilical cord blood mononuclear cells, MSCs, MAPCs, bone marrow–derived mononuclear cells, adipose- and placental tissue-derived MSCs, and others), there are striking similarities in the functional outcome improvements (15,25–28). Similar results have been obtained with direct perilesional injections of these cell types as well as various NSCs (29). These commonalities demonstrate that there are probable conserved, pleiotropic mechanisms of action of various cell populations after injury. It is less likely that each cell type has a unique mechanism of action to produce similar functional improvements. The field has come to agree that the likely multiple actions are related to the cell secretome, infused cell-innate immune cell interactions that ultimately serve to polarize the microgila/infiltrating macrophage populations to a reparative vs. inflammatory phenotype, and a downregulation of proinflammatory cytokine signaling. Engraftment/replacement has not been demonstrated.

Spinal Cord Injury

A number of cell therapy approaches have been explored as a therapeutic strategy for SCI repair. In broad terms, these can be classified as neural replacement or supporting cell replacement to augment neural repair/salvage. A NSC strategy (with differentiation into neurons, as well as supporting cells such as astrocytes, oligodendrocytes, and other glial elements) using NSCs derived from ESCs or fetal subventricular zone NSCs directly implanted into the perilesional area of the injury was developed in various laboratories. A different conceptual approach using an ESC–derived OPC was pursued by the Steward laboratory (30), Cao *et al.* (31), and others. The OPC approach is appealing owing to the demyelination away from the central lesioned area. The preclinical data demonstrate that when OPCs are directly implanted into the lesioned spinal cord, they can remyelinate damaged (but viable) neurons and serve to improve locomotion. While many in the field have made substantial progress in this area, two labs developed the large portfolio of data that allowed the NSC and OPC approaches to be translated into clinical trials (28,32). Both groups did exhaustive safety, proof of concept, scale-up, confirmatory efficacy and dose ranging studies that were compelling enough to allow a relatively high risk procedure to move forward (cervical spinal cord direct injection of stem cells).

EARLY CLINICAL TRIALS

Traumatic Brain Injury

Pediatric phase I BMMNCs. One of the first cell therapy trials for TBI was completed in children, but not adults (33). The reason for this is the leading cause of trauma-related deaths is severe TBI. Further, there are no reparative therapies, so the barrier to developing any potential therapeutic is lower. Three major findings were noted in this trial: (i) acute bone marrow harvest/infusion in the acute injury setting is safe and logistically feasible, (ii) there was none of the expected post-TBI progressive CNS tissue loss (8–12%) with cell therapy (34,35), and (iii) there was progressive improvement in clinical outcome after 6 months (**Figures 3 and 4**).

PILOT: After completion of the phase I pediatric clinical trial and the observations in preclinical studies that bone marrow mononuclear cells (BMMNCS) may reduce BBB permeability and the neuroinflammatory response to TBI, our group retrospectively evaluated the therapeutic intensity level (PILOT score) required to treat elevated intracranial pressure (36). This served as a surrogate for inflammation-associated cerebral edema and BBB dysfunction. Case- and time-matched controls were compared WITH the treatment group that was reported in the initial trial. Recognizing all of the limitations of *post hoc* analysis and retrospective data collection, there was a clear reduction in therapeutic intensity in patients treated with autologous BMMNC relative to controls. Further, there was a reduction in the average maximum daily ICP burden, which has been definitively correlated negatively with outcomes (37). Importantly, these data supported the preclinical findings that were the proof of

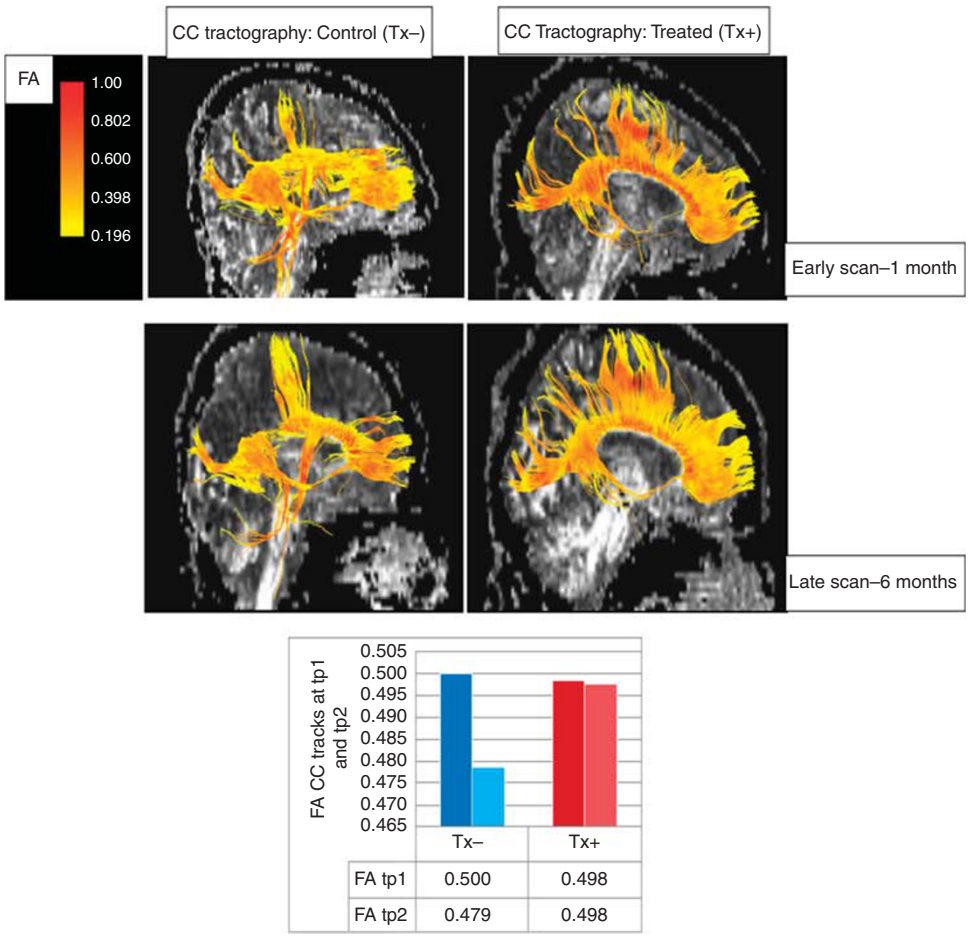


Figure 3. Central nervous system (CNS) structural preservation with bone marrow mononuclear cell (BMMNC). Since our phase I trial in children, we have focused on structural preservation as a viable surrogate outcome in traumatic brain injury (TBI). This figure shows the diffusion tensor imaging magnetic resonance imaging (DT MRI) focus on the corpus callosum, and the volumetric measurement as well as the fractional anisotropy (FA) and the underlying table (**Table 1**) shows how these measures correlate with neurocognitive outcomes. These data were presented in Stem Cells(38).

concept driving the translation of the approach in terms of dosing regimen.

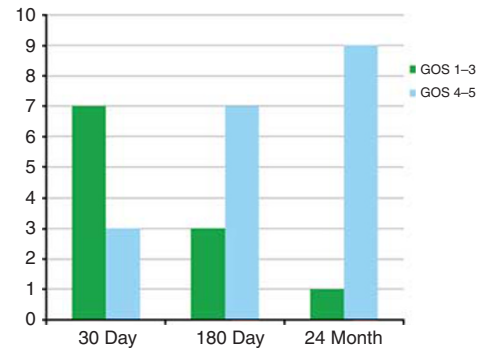
Adult phase I/IIa trial of BMMNC for severe TBI. Using the same cell type and dosing paradigm, 25 patients were enrolled in a trial evaluating safety and potential structural preservation of CNS after severe TBI (38). The adult study confirmed the logistical feasibility and safety of the autologous approach, and demonstrated a treatment effect in terms of structural preservation of key regions of interest (corpus callosum, corticospinal tract) that correlate with neurocognitive outcomes. Further, there was a dampening of the proinflammatory cytokine response to injury. These data provided/confirmed a treatment effect size based upon structural preservation outcome measures of ~50 patients. There was no difference in the Glasgow Outcome Scores between groups.

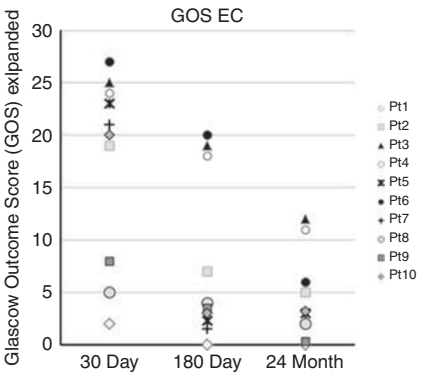
Follow-on studies: Currently there are two (adults and children, separately) phase IIb trials using a Bayesian adaptive design comparing two doses of BMMNC vs. controls in a prospective, double-blind, randomized trial that uses imaging end points as the putative biomarker for efficacy. Specifically, there is a global hypothesis that by reducing the neuroinflammatory response to injury that the typical 8–12% total volumetric loss noted after severe TBI at 6–12 months after injury will be attenuated. As of this writing, the pediatric trial has enrolled 33 of the planned 50 total number of patients. The adult trial has enrolled 11/55 planned patients as of this writing.

Chronic TBI (SanBio). SanBio is sponsoring a clinical trial to treat patients with chronic TBI and isolated motor deficits using sterotactically implanted, genetically modified MSCs. A handful of patients have been enrolled as of the time of this writing, and no interim results are available. These cells are being implanted at perilesional sites with a presumed paracrine mechanism of action. They have a similar trial in chronic stroke and have demonstrated mixed results, depending upon the outcome measure considered.

Spinal Cord Injury

OPCs (Geron-Asterias: SCiStar study). The SCiStar trial seeks to test three sequential escalating doses of AST-OPC-1 up to 20 million total cells in as many as 35 patients with





	30 Day	180 Day	24 Month
Pt 1	2	0	0
Pt 2	19	7	5
Pt 3	25	19	12
Pt 4	24	18	11
Pt 5	23	2.3	3
Pt 6	27	20	6
Pt 7	21	1.5	2.2
Pt 8	5	4	2
Pt 9	8	3.5	0.3
Pt 10	20	3	3.2

Figure 4. Evidence of progressive improvement in functional outcomes in children after 6 months, and these data were originally published there without the longer term follow-up data(33) Conventionally, the Glasgow Outcome Score (GOS) is measured at 6 months as there is little probability of changing a category after that time(42). In this phase I trial, there was a 70:30% dichotomized good:bad outcome at 6 months, which was consistent with the literature in severe traumatic brain injury (TBI) in children. However, at 2 years after injury, there was continued improvement such that the dichotomized GOS was 90:10% good:bad. In one of the few trials with 2-year long-term GOS data in children with severe TBI, the Thomale study(43)showed a 73%:27% good:bad outcome, without progressive improvement. This phenomenon of progressive improvement past standard time windows was also observed in the MASTERS trial in adult, ischemic stroke using multipotent adult progenitor cells infused intravenously. They observed a progressive, statistically, and clinically significant improvement in the treatment group relative to controls at 1 year relative to the traditional 90-day end point in stroke trials(44).

subacute C5–C7, motor complete cervical SCI. The direct injection will be at 14–30 days after injury and the patients will be followed by neurological exams and imaging follow-up. AST-OPC-1 is an ESC–derived oligodendrocyte precursor cell line that has reparative function that focuses on remyelination of demyelinated axons in the spinal cord. In preclinical testing, the remyelination was associated with improved extremity function and reduction in the size of the injury cavity. In a previous phase I trial, 2 million cells were administered in the thoracic position at 7–14 days after injury accompanied by immunosuppression for 60 days. There were no concerning safety events, but the study was not designed to evaluate for efficacy—and importantly, none was seen. This has been attributed to a dosing issue, as 2 million cells is a small number that was felt to have a lower probability of success in terms of efficacy. The 10 million cell dose cohort has not been reported outside of press releases (Asterias-biotherapeutics.com/inv_news_releases.php), but they have noted a one-level motor improvement in all six patients at 6 months, without safety concerns.

Fetal brain-derived NSCs (Pathway Trial—Stem Cells). Recently, Stem Cells halted a clinical trial (A single-blind, randomized, parallel arm, Phase 2 Proof of Concept Study of the safety and efficacy of Human Central Nervous System (HuCNS-SC) Transplantation in Cervical Spinal Cord Injury) for presumed futility. Although there was a press release of initial modest clinical improvements, the effect was not durable, and may have been associated with the planned withdrawal of the immunosuppression theoretically resulting in graft loss. This trial sought to determine the efficacy of intramedullary transplantation of fetal-derived NSCs into the cervical spinal cord in patients with C5–C7 motor levels with American Spinal Injury Association Impairment Scale Grades B or C at 12 weeks after injury. They excluded patients with complete cord transection. A recent series of publications raised significant questions regarding the translation of the preclinical data (32,39–41). The reports focused questions on either the poor predictive value of the animal models or a loss of potency in the cell product when translated into cyclic guanosine monophosphate production of the clinical grade cells for the trial. Serious questions arose after the publication by the Anderson lab that could not replicate any benefit of the clinical grade cells as used in the trial. Importantly, there was some improvement in the animals treated with the research grade cell line; however, even though the results with the research grade cells were positive, they were not compelling.

Table 1. Correlation of fractional anisotropy of corpus callosum region with outcomes, *r* (*P*)

Outcomes	*CC1*	CC2	CC3	CC4	CC5	Whole CC
Functional						
Glasgow Outcome Scal—Extended[a]	0.238 (0.299)	0.300 (0.187)	0.196 (0.394)	0.373 (0.096)	0.747 (0.000)	0.583 (0.006)
Disability Rating Scale[a]	−0.133 (0.567)	−0.310 (0.172)	−0.320 (0.158)	−0.325 (0.151)	−0.556 (0.009)	−0.471 (0.031)
Mayo-Portland Adaptability Index—Composite	−0.238 (0.298)	−0.120 (0.603)	−0.133 (0.565)	−0.212 (0.356)	−0.461 (0.036)	−0.381 (0.088)
Neuropsychological						
Motor and Processing Speed						
Grooved Pegboard—Dominant Hand[a]	0.330 (0.145)	0.655 (0.001)	0.679 (0.001)	0.509 (0.018)	0.637 (0.002)	0.761 (0.000)
Trail Making Test B[a]	0.253 (0.268)	0.512 (0.018)	0.520 (0.016)	0.488 (0.025)	0.594 (0.005)	0.687 (0.001)
WAIS Processing Speed Index	0.168 (0.468)	0.679 (0.001)	0.771 (0.000)	0.611 (0.003)	0.692 (0.001)	0.767 (0.000)
Memory						
WAIS Working Memory Index	0.411 (0.064)	0.657 (0.001)	0.564 (0.008)	0.303 (0.182)	0.378 (0.091)	0.626 (0.002)
Rey Auditory Verbal Learning Test—Trials 1–5[a]	0.559 (0.010)	0.539 (0.012)	0.376 (0.093)	0.292 (0.199)	0.304 (0.180)	0.548 (0.010)
Rey Auditory Verbal Learning Test—Delayed Recall[a]	0.320 (0.157)	0.488 (0.025)	0.504 (0.020)	0.482 (0.027)	0.414 (0.062)	0.572 (0.007)
Verbal fluency						
Controlled Oral Word Association Test[a]	0.205 (0.374)	0.575 (0.006)	0.558 (0.009)	0.321 (0.155)	0.260 (0.255)	0.475 (0.030)

Bolded values significant at $P < 0.05$
[a]Spearman's ρ.

Further complicating the issue, there was the assertion in the publication that warnings from the preclinical team were not considered fully during the translation process. Specifically, there was a claim that the clinical cell line did not meet the predescribed milestones for efficacy, and these data were communicated (but not acted upon) with the company. The trial went forward after consideration of those data, ultimately failing to demonstrate durable efficacy. This issue highlights a few critical issues in translating cellular therapies for neurological injuries. First, although the animal models are instructive, they do not necessarily have a strong positive or negative predictive value in terms of translation into a clinical outcome—an issue rigorously described in Narayan's overview published in 2002 (2). This has been well established in the TBI literature, and it is made more problematic when using immunologically deficient animals to enhance engraftment. Second, clinical Good Manufacturing Practice processing of a cell product may require alteration of particular reagents or processes that may change the ultimate cell product potency. Third, cell identity assays that function as a surrogate for potency are inadequate, especially when relying upon engraftment as a mechanism of action.

CONCLUSIONS

Since the early proof of concept data that is now over 20 years old, there has been progressive movement of cell-based therapies to treat neurological injuries—including translation into pediatric patients. The early data point to hints of efficacy, but clearly there are not miraculous "cures" noted in these phase I–II trials. The future will undoubtedly build upon these early results to refine the cellular products (focusing on potency and cell types) and identify the dosing regimens that will further improve upon this early foundation of work.

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