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# Current challenges in regenerative medicine for central nervous system disorders

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## Introduction

Regenerative medicine has propelled to the forefront of innovative treatments for a wide variety of brain illnesses, an emphasis being placed on stem cell-based therapies. Adult stem cells, in particular mesenchymal stem cells (MSCs), are spearheading the cell therapy movement, largely attributed to the growing number of studies confirming their safety, efficacy, and accumulating evidence pointing to stem cells' multipronged mechanisms of action. Disease indications of regenerative medicine have targeted many neurological disorders, such as stroke, traumatic brain injury (TBI), Huntington's disease, and peripheral nerve injury.

While several preclinical studies have delineated hope from the hype of regenerative medicine, many translational challenges accompany its transition from the lab to the clinic. Nonhuman primate (NHP) models that may better approximate the clinical outcomes of regenerative medicine in humans are likely warranted. Furthermore, regulation and standardization of cell therapy will be paramount toward transparency, validation, and reproducibility of any novel treatment. These challenges must be overcome before regenerative medicine can claim its place in the clinic.

The ten papers selected for this special volume were recently presented at the 2016 American Society for Neural Therapy and Repair meeting, focusing on regenerative medicine and its applications in prevalent brain diseases. This special volume also highlights the need for translational research to harness safe, effective, and mechanism-based clinical applications of regenerative medicine for neurological disorders.

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## Feasibility of Mesenchymal Stem Cells as Donor Cells for Transplantation in Neurological Diseases

### Tracking mesenchymal stem cells using magnetic resonance imaging

MSCs are attractive candidates for the use in tissue regeneration and cell replacement therapies due to their availability, ease of expansion, and potential for multipotency. Teng Ma *et al.*<sup>[1]</sup> of Florida State University College of Engineering, examined the efficacy of magnetic resonance imaging (MRI) of superparamagnetic iron oxide (SPIO)-labeled MSCs in their recent study "Magnetic resonance contrast and biological effects of intracellular SPIOs on human MSCs with long-term culture and hypoxic exposure." Rosenberg reports that SPIO exposure does not produce any adverse effect on crucial cellular processes, such as proliferation and differentiation. Importantly, transplantation of SPIO-labeled MSCs in rodent animal models results in stable, high-contrast MRI detectability, an improvement from the less precise histological cell tracking techniques currently used to localize MSCs. This work suggests that MRI imaging using SPIO labels may represent the future of MSC cell tracking and allow researchers to better pinpoint the migratory behavior of implanted MSCs.

### Intra-arterial delivery of mesenchymal stem cells

While stroke represents a large percentage of death and long-term disability, effective and safe treatments, other than tissue plasminogen activator, have yet to advance as viable options for stroke therapy. MSCs provide an essential alternative treatment as they are easily retrieved and do not require the intake of immunosuppressants. Dileep Yavagal *et al.*<sup>[2]</sup> of

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Cerebral Vascular Disease Research Laboratories at University of Miami, USA, advance the possibilities of intra-arterial delivery of MSCs to treat cerebral ischemia. In the investigation they conducted, they determined the maximum tolerated dose and found that administration of MSCs after 24 h more effectively facilitated neuroprotection. They go on to address the benefits of intra-arterial transport when compared to intravenous transport, in terms of improved functional recovery. The intra-arterial transport of MSCs has great potential as a stroke therapy; however, further translational studies must be conducted to confirm its efficacy and benefits.

### Therapeutic Potential of Regenerative Medicine in Experimental Models of Neurological Disorders

#### Glutamate transporter 1 reduces infarct volume following ischemic stroke

The neurotransmitter glutamate is released following ischemic brain damage, and its excitotoxic effects contribute greatly to the development of stroke. Yun Wang *et al.*<sup>[3]</sup> of the National Institute of Drug Abuse of Baltimore, Maryland, USA, investigated the effects of overexpressing a glutamate transporter (GLT-1) via gene transfer to reduce ischemic brain damage in a stroke model. They observed a dramatic reduction in brain infarction in the region of injection and improved behavioral recovery among animal models. Their findings suggest that increasing the capacity to clear extracellular glutamate offers beneficial outcomes against ischemia-induced glutamate release and associated excitotoxicity. The authors propose future development of the use of GLT-1 to make this selective gene therapy a more viable approach for neurodegeneration.

#### Characterization of oligodendrocyte precursor cells for application in central nervous system disorders

Oligodendrocyte precursor cells (OPCs) have been shown to differentiate into mature oligodendrocytes, which are cells considered to participate in white matter function maintenance. While OPCs normally exist during brain development, they persist throughout adulthood and exhibit a myelinated oligodendrocyte phenotype in the forebrain. Because of this capacity to attain a myelin-forming cell, OPCs may be a good candidate as cell source for transplantation in central nervous system (CNS) disorders associated with myelin deficiency. In the study by Nao Egawa *et al.*<sup>[4]</sup> from Kyoto University Graduate School of Medicine, Massachusetts General Hospital and Harvard Medical School, they discuss the many appealing features of OPCs, specifically their isolation and culture from cells derived from patients. They also provide compelling laboratory evidence supporting the use of OPCs for cell-based therapeutic purposes in neurological disorders.

#### A polarizing view on posttraumatic brain injury inflammatory response

TBI initiates a complex, broad-spectrum inflammatory response involving a multitude of cell types and cognate receptors. Despite this, many have adopted the categorization of the inflammatory response into a strict “M1” versus “M2” delineation as innate polarization phenotypes. However, Susanna Rosi *et al.*<sup>[5]</sup> of the Brain and Spinal Injury Center at University of California, San Francisco, USA, highlight the

clinical findings that indicate that the polarization phenotypes cannot be neatly delineated in this M1/M2 paradigm. While these findings are by no means meant to discredit previous studies exploring M1/M2 following cerebral trauma, a simultaneous differential expression of both “M1” and “M2” profiles induced by TBI suggests that this accepted dichotomous nomenclature poses too many restrictions to be viable. The authors propose an approach to define the roles of the markers by a neuroinflammatory sequela to characterize the TBI-induced inflammation going further.

#### Finding effective biomarkers for pediatric traumatic brain injury

A leading researcher in the field of TBI, Ron Hayes *et al.*<sup>[6]</sup>, at Banyan Inc., and University of Florida, justify the use of glial fibrillary acidic protein (GFAP) and ubiquitin c-terminal hydrolase 11 (UCH-L1) as effective biomarkers for the treatment of pediatric TBI. In their pediatric TBI studies, they found a direct relationship between the severity of the injury and biomarker concentration and determined that GFAP and UCH-L1 are detected while computed tomography scans reveal no issue. Their results suggest the capability of the two biomarkers to detect injuries that may have been otherwise overlooked if using other detection techniques. More accurate detection of brain injury, made possible by the biomarkers in question, will help greatly in medical decision-making.

#### Creatine supplementation improves neural progenitor cell survival in Huntington’s disease

The transplantation of neural stem cells and neural progenitor cells (NPCs) represents a potentially effective therapy to treat neurodegenerative disorders, such as Huntington’s disease. Hans Widmer *et al.*<sup>[7]</sup> of the Department of Neurosurgery at the University of Berne, recently, examined whether chronic creatine (Cr) supplementation might improve the survival, robustness, and potential for differentiation of striatal NPCs and whether these effects vary according to a cell’s developmental stage. Andres found that Cr provides beneficial effects to striatal NPC grafts, ranging from neuroprotection to improved GABAergic differentiation frequency, and that the strength of these effects depends on the treated cell’s developmental progress. Future studies exploring striatal cell replacement therapies should take into account the potential of Cr in this regard as well as the age-dependent temperament of its efficacy.

#### A therapeutic shock propels Schwann cells to proliferate in peripheral nerve injury

Damage to the peripheral nervous system poses a great burden to patients and hospitals, and while Schwann cell-based treatments have been established, they are met by significant barriers. Heinz Redl *et al.*<sup>[8]</sup> of the AUVA Research Center at the Ludwig Boltzmann Institute for Experimental and Clinical Traumatology in Vienna, Austria, advance the possibilities of extracorporeal shockwave treatment (ESWT) in treating Schwann cells to overcome their proliferative limitations. The study they conducted demonstrated that Schwann cells treated with ESWT displayed increased proliferative capabilities as well as improved isolation and culture. Schwann cells treated with ESWT present the ability to treat peripheral nerve damage with advantageous results.

Nonetheless, further investigations must be conducted to understand the underlying mechanisms of ESWT and its molecular effects on Schwann cells.

### Translational Challenges Associated with Regenerative Medicine's Transition to the Clinic

#### Nonhuman primate model is essential for clinical modeling of brain disorders

NHPs are similar to humans in size, behavior, physiology, biochemistry, and immunology, thereby offering unique opportunities for translational clinical studies. Marcel Daadi *et al.*<sup>[9]</sup> of the Southwest National Primate Research Center, USA, explore the opportunities and limitations of NHPs as animal models for translational regenerative medicine. Given their close similarities to humans, the NHP model offers exceptional opportunities to understand biological mechanisms and translational applications with direct relevance to human conditions. However, limitations of this model exist, including the expense, specialized training, and lack of reputable data characterizing the ischemic brain to justify its use for validation of stem cell therapy. Therefore, the authors highlight the importance of guidelines, such as the Stem Cell Therapeutics as an Emerging Paradigm for Stroke and RIGOR, to establish uniformity in procedures worldwide to provide a firm basis for future novel discoveries.

#### Regulation and standardization of cell-based therapies

Cell-based interventional therapies stand at the forefront of treatment for a variety of diseases and several organizations around the world are determined to establish them in a clinical setting. However, the push for cell therapies has resulted in suggested treatments with unconfirmed efficacy, safety, and scientific rationales. Massimo Dominici *et al.*<sup>[10]</sup> of the Division of Oncology at the University of Modena and Reggio Emilia, Italy, assert the necessity for increased communication among stakeholders in the field, as well as universal standards and tests to prove the legitimacy of different cell therapies. They also address the importance of communicating the necessary information to patients so that they may properly give informed consent. Cell-based therapies are the future of treatment; however, it is essential that they exist under regulations and standards to promote better patient care.

### Conclusion

Regenerative medicine has evolved as an emerging experimental treatment for CNS disorders. Recent scientific advances suggest therapeutic potential of regenerative medicine in animal models of neurological disorders, including stroke, TBI, Huntington's disease, and peripheral nerve injury, as presented in this special volume. The transition from the laboratory to the clinic will likely warrant large animal model testing, as well as regulatory and standardization protocols to fully assess the safety and efficacy of these novel regenerative medicine-based treatments for brain diseases.

### References

1. Rosenberg J, Yuan X, Grant S, Ma T. Tracking mesenchymal stem cells using magnetic resonance imaging. *Brain Circulation* 2016;2:108-13.
2. Watanabe M, Yavagal D. Intra-arterial delivery of mesenchymal stem cells. *Brain Circulation* 2016;2:114-7.
3. Wang Y, Harvey BK. Reducing excitotoxicity with glutamate transporter-1 to treat stroke. *Brain Circulation* 2016;2:118-20.
4. Egawa N, Takase H, Lok J, Takahashi R, Arai K. Clinical application of oligodendrocyte precursor cells for cell-based therapy. *Brain Circulation* 2016;2:121-5.
5. Rosi S. A polarizing view on posttraumatic brain injury inflammatory response. *Brain Circulation* 2016;2:126-8.
6. Glushakova OY, Glushakova AV, Hayes RL. Finding effective biomarkers for pediatric traumatic brain injury. *Brain Circulation* 2016;2:129-32.
7. Andres RH, Wallimann T, Widmer HR. Creatine supplementation improves neural progenitor cell survival in Huntington's disease. *Brain Circulation* 2016;2:133-7.
8. Schuh C, Hausner T, Redl HR. A therapeutic shock propels Schwann cells to proliferate in peripheral nerve injury. *Brain Circulation* 2016;2:138-40.
9. Choudhury GR, Kim J, Frost PA, Bastarrachea RA, Daadi MM. Nonhuman primate model in clinical modeling of diseases for stem cell therapy. *Brain Circulation* 2016;2:141-5.
10. Dominici M, Nichols K, Levine AD, Rasko JEJ, Forte M, O'Donnell L, Koh M, Bollard C, Weiss DJ. Science, Ethics And Communication Remain Essential For the Success of Cell-Based Therapies. *Brain Circulation* 2016;2:146-51.