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# Stem cell-based regenerative medicine for neurological disorders: A special tribute to Dr. Teng Ma

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## Abstract:

This special issue of Brain Circulation presents cutting-edge research discoveries in stem cell-based regenerative medicine. Each article highlights recent advances in the fields of neurodegeneration and regenerative medicine. The selected contributions offer the groundwork for translating stem cell therapy to the clinic for treating central nervous system disorders. This issue is dedicated to Dr. Teng Ma, who passed away on May 18, 2019. Dr. Ma devoted a significant portion of his life in advancing biomedical engineering, including the utility of 3-dimensional bioreactor and magnetic resonance imaging, as a key element of the biological and therapeutic applications of stem cells for neurological disorders. Dr. Ma's research vision is celebrated in this compilation of ten articles on stem cell-based regenerative medicine.

## Keywords:

Basic research, clinical application, neurological disorders, regenerative medicine, stem cells, translation

## Introduction

Central nervous system (CNS) disorders such as stroke, traumatic brain injury (TBI), and Parkinson's disease (PD) among various other neurodegenerative disorders pose a significant health and economic burden worldwide. Yet, these debilitating diseases possess limited viable therapeutic options, marking this as a prevailing area of research in hopes of elucidating unknown pathologies and establishing sustainable treatment strategies. Current evidence suggests that regenerative medicine holds the potential to tackle these obstacles, representing an active field of innovative research. In this special issue, we span various areas of current research, such as gene therapy, exercise, and stem cells among other novel approaches for CNS

disorders. An emphasis is placed on stem cell therapy for spearheading the field of regenerative medicine, possessing promising neuroprotective capabilities. Altogether, cell therapy necessitates a significant preclinical research to determine optimal parameters, techniques, potential combination strategies, and safety measures to establish this therapeutic potential as translatable from the bench to the clinic.

The following ten sections of this issue highlight the novel findings of each article selected from the presentation of authors who have participated in the 2018 annual meeting of the American Society for Neural Transplantation and Repair, capturing their significant research contribution in the context of regenerative medicine. Gaining a better grasp of the various underlying mechanisms of neurodegenerative diseases and optimal therapeutic options is critical in advancing these laboratory findings to clinical applications.

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This special issue is dedicated to Dr. Teng Ma, Professor and Chair of the Department of Chemical and Biomedical Engineering (2014–2019) at Florida Agricultural and Mechanical University–Florida State University, who abruptly passed away on May 18, 2019. Dr. Ma championed the technological innovation of biomedical engineering for stem cell application. He was a staunch proponent of stem cell therapy for stroke and dedicated a chunk of his research work on the three-dimensional bioreactor and magnetic resonance imaging of mesenchymal stem cells (MSCs). His research was funded by the National Institutes of Health, National Science Foundation, Department of Defense, American Heart Association, and Florida Biomedical Research Program. Dr. Ma was an outstanding professor, a visionary innovator and researcher, and a loving father and husband.

### **Chapter 1: Hyperbaric Oxygen Therapy: A New Look on Treating Stroke and Traumatic Brain Injury**

Stroke and TBI represent dominant neurodegenerative diseases that encompass similar neuroinflammatory and cell death pathologies. Hyperbaric oxygen therapy (HBOT) has been recognized for its capacity to treat injuries, but its use as a preconditioning strategy presents a fascinating potential for CNS disorders. Here, the authors examine the effects of HBOT preconditioning in attenuating the deficits associated with stroke and TBI. Specifically, the present review discusses the involvement of mitochondrial transfer and subsequent reduced cell death, as well as the neuroprotective, anti-inflammatory effects of HBOT. Finally, the authors discuss the current stroke therapies in the field and suggest that HBOT preconditioning holds promising therapeutic capacity. With few current viable treatment options, stroke remains a major cause of death, warranting future exploration of these therapeutic avenues.<sup>[1]</sup>

### **Chapter 2: Another Win for Endothelial Progenitor Cells: Endothelial Progenitor Cell-Derived Conditioned Medium Promotes Proliferation and Exerts Neuroprotection in Cultured Neuronal Progenitor Cells**

Stem cells represent a promising field that may possess therapeutic benefits in mitigating the deficits associated with a wide range of neurodegenerative diseases. Here, the review investigates the effects of endothelial progenitor cell-conditioning medium in promoting regeneration of cultured striatal progenitor cells. The authors suggest the critical function of paracrine factors secreted by EPCs, as well as the involvement of crucial signaling cascades including P13K/AKT and MAPK/ERK. The regenerative and neuroprotective capacity of EPCs and their secreted

factors marks a significant area of study in promoting cell viability and proliferation. Harnessing novel findings from the presently discussed research, future direction should investigate the potential of a cell-free treatment strategy for Parkinson's and other neurodegenerative disorders.<sup>[2]</sup>

### **Chapter 3: A Brief Physical Activity Protects against Ischemic Stroke**

Recognizing the prevailing detrimental effects of stroke, the authors examined another therapeutic avenue to attenuate such deficits: exercise. Here, the review investigates the impact of brief bouts of physical activity prior to middle cerebral artery occlusion on stroke outcome. Numerous studies suggest that exercise can contribute to enhanced cerebral blood flow, cerebrovascular structure, and angiogenesis. However, the authors note other investigations that suggest strenuous exercise during the early phase poststroke may exacerbate cell death and tissue damage. This review aims to shed light on the connection between exercise and stroke outcome, evaluating current research in the field regarding parameters such as length, difficulty, and variability of physical activity. Exercise has been noted to provide cerebrovascular benefits and exploring its promising application to stroke outcomes represents an area of research warranting further investigations.<sup>[3]</sup>

### **Chapter 4: Cerebral Circulation Improves with Indirect Bypass Surgery Combined with Gene Therapy**

Moyamoya disease (MMD) is a rare cerebrovascular disorder involving the progressive narrowing of the arterial intima, consequentially placing patients at high risk for stroke or even fatal intracerebral hemorrhage. Although direct revascularization surgeries are common for treating MMD, an indirect method known as encephalo-myo-synangiosis (EMS) is used for pediatric cases of MMD. While simpler, EMS presents a risk of insufficient collateral blood flow. Here, the authors focus on the effects of a combined therapy involving EMS with administration of DNA-binding protein high-mobility group box-1 to promote angiogenesis through a proposed vascular endothelial growth factor (VEGF)-dependent manner. The review also discusses current therapeutic endeavors in the field of MMD and upholds EMS combined with gene therapy as a promising treatment strategy for this poorly understood disease.<sup>[4]</sup>

### **Chapter 5: Microbiota and Memory: A Symbiotic Therapy to Counter Cognitive Decline?**

Memory and cognitive decline is a common affliction in the elderly. It can be extremely debilitating and is linked

to greater risk of Alzheimer's disease. The highlighted study examines a possible connection between this decline and gut microbiota. This idea originates from the observed connection between microorganisms, their production of butyrate, and butyrate's proposed activation of brain-derived neurotrophic factor (BDNF). In the study, rats were given supplements of prebiotics, probiotics, or symbiotics (both prebiotics and probiotics). Those in the symbiotic group showed greater performance on a spatial memory task and had higher levels of BDNF, lower levels of pro-inflammatory cytokines, and better hippocampal electrophysiology results. This provides clear evidence of an important connection between gut microbiome and dementia. In addition to the obvious benefits, this research may add to aging-related degenerative disorders, and this review indicates that the results may also be applied to ischemic stroke recovery.<sup>[5]</sup>

### **Chapter 6: Enhanced Survival of Human-Induced Pluripotent Stem Cell Transplant in Parkinsonian Rat Brain by Locally Applied Cyclosporin**

There is a growing research into the potential of stem cell transplants as therapy for various neurodegenerative disorders, including PD. However, most transplanted cells are rejected if not provided with systemic immunosuppressive treatment, cyclosporine-A (CsA). Unfortunately, this immunosuppressive treatment can have very detrimental side effects on the kidneys, brain, and elsewhere if administered generally and long term. The focus of the reviewed study is on a new technique of CsA administration using local co-grafting of CsA-containing nanoparticles (NanoCsA) with human induced pluripotent stem cells (iPSCs) into the striatum of rats. Compared to the control group, the NanoCsA treatment performed significantly better on a variety of behavioral and chemical measures. This study represents an important development in solving a common obstacle in using iPSC transplants for stem cell therapy.<sup>[6]</sup>

### **Chapter 7: Activity of p53 in Human Amniotic Fluid Stem Cells Increases Their Potentiality as a Candidate for Stem Cell Therapy**

Stem cells have gained great attention for their therapeutic potential for treating multiple neurological disorders. However, much is still unknown, and many stem cell sources are controversial or otherwise fraught with complications. Human amniotic fluid stem (hAFS) cells stand to solve this problem as they have no ethical issues, and knowledge of their underlying properties is growing. The study highlighted here focuses on the developing understanding of the protein p53, which regulates the genes *igf2* and *c-jun* and is found in varying

amounts in hAFS cells. Along with the other benefits of hAFS cells, p53's tumor-suppressive properties improve hAFS cells' potential as candidates for stem cell therapy applications. The review also describes another possible neuroprotective treatment related to stem cells, hyperbaric oxygen treatment.<sup>[7]</sup>

### **Chapter 8: Altered Metabolism for Neuroprotection Provided By Mesenchymal Stem Cells**

MSCs have long enjoyed the research spotlight for their speculated potential for cellular therapy for tissue repair. However, lack of understanding about the cues for their immunomodulatory functions has limited their practicality. The study highlighted here delves into the underlying factors possibly determining MSCs' outcomes. Evidence suggests that the pro-inflammatory cytokine interferon-gamma (IFN- $\gamma$ ) affects the immunomodulatory functions of MSCs by altering their metabolism. The mechanism behind this may be IFN- $\gamma$ 's increase of glycolytic activity and uncoupling of glycolysis from the tricarboxylic acid cycle. This allows glycolytic metabolites and intermediates to help the production of Indoleamine 2,3-dioxygenase and prostaglandin E2, anti-inflammatory modulators. Further work in this area may eventually yield the use of MSCs in cellular therapy for neuroprotective and neurogenerative functions.<sup>[8]</sup>

### **Chapter 9: Brief Overview: Protective Roles of Astrocyte-Derived Pentraxin-3 in Blood-Brain Barrier Integrity**

During and after an ischemic stroke, the blood-brain barrier (BBB), which helps protect the brain from various harmful agents, is especially vulnerable to leakage. Astrocytes play a key role in the daily upkeep of the BBB and the CNS at large. The study highlighted here reveals novel findings about the role astrocytes may play in stroke and recovery. Researchers demonstrate that astrocytes secrete pentraxin-3 (PTX3) which increases tight junction proteins and inhibits certain growth factors. Thus, PTX3 may have ameliorative and deleterious effects during and after stroke. Harnessing and manipulating these properties may lead to an array of new prevention and treatment strategies for combatting ischemic stroke. This review also describes the role hypoxia and conditioning may play in preventing and treating neurological disorders and a possible link to PTX3.<sup>[9]</sup>

### **Chapter 10: Circular RNAs and Neutrophils: Key Factors in Tackling Asymptomatic Moyamoya Disease**

As previously discussed, the precise pathology underlying the progression of MMD remains largely

unknown, and current diagnostic measures and treatment for the asymptomatic subtype particularly are lacking. In this paper, the authors examine current research involving potential approaches and therapeutic strategies for managing MMD, specifically uncovering the contribution of the differential circular RNA expression in this disease. Further, these findings suggest the elaborate function of neutrophils and corresponding VEGF and HIF-1 $\alpha$  signaling pathways in initiating angiogenesis and contributing to the immune response. Along with current revascularization and ischemic conditioning strategies, this review suggests that targeting neutrophils and anti-inflammatory mechanisms may represent a promising approach to combatting MMD. Overall, gaining a better understanding of the critical mechanisms underlying this currently elusive MMD pathology may provide direction for future therapeutic endeavors to reduce the risk of stroke.<sup>[10]</sup>

### Conclusion

This special issue of Brain Circulation covers innovative basic research in stem cell-based regenerative medicine with potential clinical translation. Each chapter describes an exceedingly important set of advances in the field of neurodegeneration and regenerative medicine. Taken together, this issue provides compelling evidence for greater exploration of stem cell therapy for CNS disorders. Dr. Ma shared this vision of stem cell therapy emerging as a safe and effective treatment for neurological disorders.

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### Conflicts of interest

There are no conflicts of interest.

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