Stem Cells for spinal cord injury (SCI) repair

By Qilin Cao, M.D.

Abstract: Stem cells have shown great promise for spinal cord injury repair. Stem cells have been used to approach four different therapeutic repair strategies in SCI. These include replacement of lost neurons; replacement of oligodendrocytes to promote remyelination of demyelinated and/or regenerated axons; providing a permissive substrate for axonal regeneration to overcome the intrinsic inhibition of surface molecules; and engendering host repair. Although obstacles need to be overcome for clinical application, the rapid progress in the stem cell field makes their use to treat SCI as well as other neurological disorders more feasible than ever.

Each year, over 10,000 people in the United States, and hundreds of thousands worldwide, suffer a traumatic spinal cord injury (SCI) with about 300,000 of these SCI patients now living in the US. Economic costs for SCI approaches $10 billion per year. Besides the heavy familial, social, and economic burden, the patients’ physical and emotional suffering is immense. Unfortunately, despite extensive research, clinical advancements, and improved rehabilitation strategies, SCI continues to be a significant cause of disability and mortality. Therefore, there is an urgent need to develop novel therapeutic strategies that will bring significant functional recovery after SCI. Stem cells have shown great therapeutic potential for SCI repair in several experimental models and may represent one of the effective novel therapies. In general, stem cells have been used to approach four different therapeutic repair strategies in SCI: 1) replacement of lost neurons, 2) replacement of oligodendrocytes to promote remyelination of demyelinated and/or regenerated axons, 3) providing a permissive substrate for axonal regeneration to overcome the inhibition of intrinsic surface molecules, and 4) engendering host repair. The first two strategies involve cell-specific differentiation of engrafted neural cells and the latter two may involve grafted neural or non-neural cells. Grafted cells can facilitate host repair by suppressing secondary injury to preserve more neural tissue and/or enhance plasticity of spared circuitry or intact spinal motor units below the level of injury. My laboratory focuses on using stem cells to promote axonal remyelination and regeneration after SCI.

Non-embryonic progenitor cell therapies for traumatic brain injury

By Charles S. Cox, Jr., M.D.

Abstract: Adult stem/progenitor cells are currently undergoing intense study in preclinical trials and early Phase I clinical trials for the treatment of traumatic brain injury (TBI). Initial results pointed to a mechanism of neural replacement/cellular trans-differentiation into neurons as responsible for the observed improvements in outcomes. Recent evidence suggests that the cellular therapeutics may be functioning to down-regulate neuron-inflammation and promote endogenous neural recovery.

Despite aggressive clinical management, neurons have little ability for repair with no therapeutic modality currently available to reverse the injury on either a cellular or subcellular level. Based on pre-clinical research, adult stem cells may offer a potential therapeutic avenue to treat TBI. While preliminary evidence has identified a potential role for cellular therapy in the treatment of TBI, careful examination of the pre-clinical data also reveals barriers to interpreting and translating potential treatment options. Determining the ultimate mechanism of action has implications in terms of cell delivery strategies, that is, if neural replacement is not the mechanism of action, direct cell delivery to the injury site may not be required.

By definition, all stem cells are capable of self-renewal and are multipotent as they can develop into a variety of cell lineages. This review will focus on non-embryonic or adult stem/progenitor cells in the treatment of TBI. Adult stem cell populations currently under investigation for potential therapeutic use in TBI include: the bone marrow mononuclear fraction, the brain subventricular zone, the umbilical cord blood mononuclear fraction, and adipose tissue. The availability, multipotency, and capability for self-renewal make adult stem cells theoretical prime candidates for

Continued on page 5; Cox

The University of Texas
Health Science Center at Houston
Neuroscience Research Center

Continued on page 4; Cao
Aging Research and Age-Related Activities at UTHSC-Houston

From the director, John H. Byrne, Ph.D.

It has been a busy and productive year for activities and research about aging at the University of Texas Health Science Center at Houston (UTHSC-H). In Fall, 2009 the George and Cynthia Mitchell Center for Research in Alzheimer’s Disease and Related Brain Disorders was opened at the University of Texas Medical School in Houston (UTMS-H). This is a $2.5 million Center that was established by the George and Cynthia Mitchell and their children in honor of Mrs. Cynthia Mitchell, who was afflicted with Alzheimer’s Disease. While Mrs. Mitchell lost her fight with her death in late fall, this great Center will bring together people working in clinical areas with those in basic sciences and imaging to advance our knowledge about the processes of Alzheimer’s Disease. The Center’s Director is NRC member Claudio Soto, Ph.D.

The Center opened with a symposium entitled “Alzheimer’s Disease Therapy: In Quest of Hope”, which was sponsored jointly by Dr. Larry Kaiser, president of UTHSC-Houston, and Dan Wolterman, president and CEO of Memorial Hermann Hospital. The presenters included the NRC’s Claudio Soto, Ph.D., UTMS-H; Rachelle Doody, M.D., Ph.D., Baylor College of Medicine; Paul Aisen, M.D., UC San Diego; Norman Relkin, M.D., Ph.D., Weill Medical College of Cornell University; and Sam Gany, M.D., Ph.D., Mt. Sinai School of Medicine. They discussed new cooperative studies for treating and understanding the disease, as well new treatments utilizing antibodies and recently developed drugs.

The Cheves Smythe Distinguished Lecture in Education and Geriatric Medicine also dealt with aging and was another highlight of the Academic year. It featured Dr. Cynthia Kenyon (Director, Hillblom Center for the Biology of Aging, UC San Francisco) who spoke on March 10, 2010 about her studies on genes associated with longer lifespan in C. elegans. Her talk also included comparative studies on rhesus monkeys and diet and how these studies combined with hers and others to provide a more complete picture on the aging process.

In keeping with the aging theme, the NRC Distinguished Lecturer was Dr. Roger Rosenberg from UT Southwestern at Dallas, who spoke on “DNA Aβ42 Vaccine Therapy for Alzheimer’s Disease” on April 8, 2010. Dr. Rosenberg also had the chance to discuss his findings with many of the NRC faculty, including Dr. Claudio Soto, Dr. Joshua Breier, and Dr. Thomas Caskey. NRC members are well-represented in studies on aging, stroke and injuries and disease.

The new state-of-the-art Behavioral and Biomedical Sciences building was opened and occupied in March of 2010 and houses the new Center for Excellence on Mood Disorders. While not specifically associated with aging, this Center has a specialty clinic that treats a wide range of brain disorders, including those associated with aging. The Center is comprised of an active research team whose specialties include clinical neurosciences (neuro-imaging, neurophysiology, cognitive neuroscience, and genetics) as well as interventional research. NRC members, Dr. Jair Soares and Dr. Alan Swann, are co-directors of the Center.

The Brain and Behavior Research Fund of NARSAD (National Alliance for Research on Schizophrenia and Depression), in cooperation with UTMS-H and UTMB-Galveston, recently hosted a symposium on “Healthy Minds Across America: Discovering Hope through Science”. NRC member and former NARSAD Investigator Dr. Jair Soares chaired the symposium with Dr. Robert Hirshfeld of UTMB, who also is a member of the NARSAD Scientific Council. Featured speakers included NRC member Dr. Alan Swann of the Department of Psychiatry and Behavioral Sciences, and Dr. Lauren Marangell, clinical professor of Psychiatry at Baylor College of Medicine.

Looking ahead, the NRC will sponsor the 16th Annual Public Forum in the Spring of 2011. The moderator with be Dr. Jair Soares, Chairman, Department of Psychiatry and Behavioral Sciences, and the topic will be “Mental Health”. The Neuroscience Research Center is proud to be a part of the effort to support the discovery and intervention of brain disease processes and the promotion of mental health research at UTHSC-Houston.
NRC members Rowen Chang, Ph.D. and Chuantao Jiang, M.D. Ph.D., both of the Brown Institute for Molecular Medicine for the Prevention of Human Diseases, received a 2-year award from the NINDS of the National Institutes of Health to develop a therapeutic vaccine for Parkinson’s disease.

Valentin Dragoi, Ph.D., Department of Neurobiology and Anatomy, received a four-year grant through EUREKA (Exceptional, Unconventional Research Enabling Knowledge Acceleration) from the National Institutes of Mental Health of the NIH. His research involves measuring networks of neuronal brain cells in nonhuman primates during normal decision-making, rather than the single cell recordings that have been performed in the past.

James C. Grotta, M.D. Head of the Department of Neurology, has received a grant for a large clinical trial for brain cooling (hypothermia) for the treatment of stroke in elderly patients from the NINDS of the NIH. This trial will specifically look at the efficacy of localized cooling of damaged brain tissue rather than the more conventional overall body cooling.

Jerry Wolinsky, M.D. is the principal investigator in a multi-institutional study to study chronic cerebrospinal venous insufficiency in multiple sclerosis, a program jointly sponsored by National MS Society and the MS Society of Canada for a two-year period. These studies at present are trying to identify if there is a relationship between CCSVI and multiple sclerosis by testing different screening techniques (ultrasound, magnetic resonance imaging) both to confirm previous findings and determine the best method for detection.

F. Gerard Moeller, M.D., Department of Psychiatry and Behavioral Sciences, UT Medical School at Houston, has been elected to member status of the prestigious American College of Neuropsychopharmacology (ACNP).

Pedro Ruiz, M.D., professor of Psychiatry and Behavioral Sciences at The University of Texas Medical School at Houston, received the Irving Blumberg Award for Humanitarian Services from the American Association of Psychosocial Rehabilitation.

Susan H. Landry, Ph.D., has been appointed to the Albert and Margaret Alkek Chair in Early Childhood Development.

John O’Brien, Ph.D., was recently appointed to the Frederic B. Asche Chair in Ophthalmology at UT Medical School at Houston.

Nicole Gonzales, M.D., received the Young Investigator Award for her work on intracerebral hemorrhage. The award was presented by Dr. James C. Grotta, Head of the Department of Neurology.

Octavio Pinell, M.D., Professor of Psychiatry and Behavioral Sciences, is the recipient of this year’s John P. McGovern Award, an award given to the outstanding clinical faculty member which is chosen by the Medical School senior class.

Han Zhang, M.D., senior lecturer in the Department of Neurobiology and Anatomy, is this year’s winner of the John Freeman Faculty Teaching Award which is given annually by the senior class to recognize the Medical School’s outstanding basic science faculty member.

## Biochemistry & Molecular Biology
- Michael R. Blackburn, Ph.D.
- Henry W. Strobel, Ph.D.

## Diagnostic & Interventional Imaging
- Clark W. Sitton, M.D.

## Integrative Biology & Pharmacology
- Carmen W. Dessauer, Ph.D.
- Jeffrey A. Frost, Ph.D.
- Gary C. Rosenfeld, Ph.D.
- William A. Weems, Ph.D.

## Internal Medicine
- Philip R. Orlander, M.D.

## Neurobiology & Anatomy
- Leonard J. Cleary, Ph.D.
- Nachum Dafny, Ph.D.
- David W. Marshak, Ph.D.
- Carla S. Rogers, Ph.D.
- Han Zhang, M.D.

## Neurology
- Parveen Athar, M.D.
- Erin Furr-Stimming, M.D.
- Omotola A. Hope, M.D.
- Ernesto Infante, M.D.
- Sean I. Savitz, M.D.

## Ophthalmology & Visual Science
- Judianne Kellaway, M.D.
- John O’Brien, Ph.D.
- Nan Wang, M.D.

## Pediatric Surgery
- Stephen A. Fletcher, D.O.

## Pediatrics
- Ian J. Butler, M.B.B.S.
- Pedro Mancias, M.D.
- Hope Northrup, M.D.

## Psychiatry & Behavioral Sciences
- R. Andrew Harper, M.D.
- Iram Kazimi, M.D.
- Kenneth J. Krajewski, M.D.
- Octavio C. Pinell, M.D.
- Sonja L. Randle, M.D.
- Nurun N. Shah, M.D.
- Adel A. Wassef, M.D.
Continued from page 1; Cao

Stem cell grafts to replace oligodendrocytes after SCI. Oligodendrocytes (OLs) are particularly susceptible to oxidative stress, glutamate excitotoxicity, and the immune responses associated with the secondary injury cascade after SCI. OL death and/or apoptosis occur at the injury center as early as a few hours post-injury and significantly increase for several days thereafter. Because each OL myelimates multiple axons, their death leads to demyelination of many axons which are left intact following the initial injury. Consequently, the electrophysiological conduction of these axons is lost or delayed. Dysfunction of these demyelinated axons in the injury epicenter and also in the areas distant to this epicenter may contribute further to long-term neurological deficits after SCI. Furthermore, OLs may provide trophic support to its myelinated axons by both contact-mediated and soluble mechanisms. Demyelinated axons are more vulnerable to the insults in the injured spinal cord and undergo secondary degeneration. Therefore, promoting remyelination is an important therapeutic strategy to enhance functional recovery by restoring the electrophysiological conduction of the demyelinated axons as well as preventing its degeneration.

Cells with capacity to differentiate into mature OLs, such as neural stem cells (NSCs) or oligodendrocyte precursor cells (OPCs), persist in the adult spinal cord. They become active and significantly increase their proliferation after SCI. Although OL differentiation and remyelination from endogenous adult OPCs occur, spontaneous remyelination is limited and incomplete after SCI. Electrophysiological experiments show the persistent deficits of axonal conduction following SCI in humans and rodents. There is also ample anatomical evidence showing the presence of demyelinated axons in both the acute and chronic phases of SCI in both experimental animals and human. More recent studies showed demyelination following traumatic SCI in chronic and progressive. A limited number of precursor cells, the presence of inhibitory factors for OL differentiation, and/or the lack of growth factors for OL survival and myelination in the injured CNS may all contribute to this failure of endogenous remyelination. Therefore, strategies to promote significant functional recovery after SCI by remyelination from endogenous NSCs or OPCs may prove feasible in the future once mechanisms that regulate NSC and/or OPC proliferation, differentiation and maturation are better understood. Stem cell transplantation is still considered to be a more effective approach to enhance the remyelination and locomotion functional recovery after SCI.

Multiple types of NSCs or glial precursor cells including glial-restricted precursors (GRPs) and OPCs have been transplanted into the injured spinal cord. The multipotent NSCs, isolated from fetal or adult CNS, mainly differentiate into astrocytes with a few into OL and almost none into neurons after transplantation into the injured spinal cord. However, neuronal differentiation is observed after similar cells are transplanted into the hippocampus, an area in the adult CNS where neurogenesis persists throughout life. These studies suggest that the micro-environment in the injured spinal cord favors the astrocyte differentiation, but inhibits the neuronal as well as OL differentiation from the grafted NSCs. Importantly, the astrocyte differentiation from grafted NSCs enhance the plasticity of pain fibers and promote alldynia, a condition in which a pain response is observed from a stimulus that normally does not elicit pain, after SCI. In my laboratory, several strategies are employed to increase the remyelination from grafted stem cells. First, we induce embryonic stem cells or NSCs to differentiate into OPCs before transplantation by combining small chemicals in the defined culture medium with over-expression of transcription factors critical to OL differentiation during development. OPCs are not only more effective for remyelination but also do not differentiate into astrocytes and thus limit the onset of allodynia after transplantation into the injured CNS. Second, we combine OPC transplantation with delivery of neurotrophic factors, such as sonic hedgehog, D15A, or a mixture of multiple factors further enhance the OL differentiation and survival of the grafted OPCs. We have used our established in vitro model to screen the optimal growth factor for OL differentiation and myelination, D15A and cilary neurotrophic factor (CNTF). We have genetically modified OPCs to over-express D15A or CNTF prior to transplantation. Our results showed that expression of D15A or CNTF increase OL differentiation and survival of grafted OPCs. Importantly, transplantation of growth factor-expressing OPCs significantly increases the number of remyelinated axons and partially restores the axonal conduction as shown by electrophysiological recording after SCI. More importantly, functional recovery of locomotion is accompanied with the improved axonal conduction and increased remyelination of axons. Therefore, the anatomical, electrophysiological and behavioral evidence demonstrate that enhancing remyelination by OPC transplantation is an important strategy to promote functional recovery after SCI. Thirdly, we study the mechanisms by which OL differentiation and remyelination of endogenous and transplanted OPCs or NSCs are inhibited in the injured microenvironment. We have found that reactive astrocytes in the injured spinal cord are a major inhibitor for remyelination by increasing expression of Jagged 1 and bone morphogenetic proteins (BMPs). We are studying how signaling like Jagged and BMPs inhibit OL differentiation and remyelination. Such understanding may lead to novel strategies to promote remyelination and functional recovery after SCI. We are investigating whether combinatorial strategies including OPC transplantation, increasing expression of growth factors and blocking inhibitory signaling will work synergistically to further promote more extensive remyelination and functional recovery after SCI.

Stem cell grafts to enhance axonal regeneration. In addition to demyelination, axonal degeneration significantly contributes to functional deficits after SCI due to the interruption of axonal pathways carrying sensory information to the brain and of descending motor control pathways to the spinal cord distal to the injury site as well as the loss of local neuronal networks at the injury site. Therefore, it is critical to develop strategies to promote long distance axonal regeneration for sensory and motor recovery after SCI. Unfortunately, most axons in the adult mammalian CNS fail to regenerate after injury. This has been attributed not only to the intrinsic indolence of mature neurons but also to the non-permissive environment encountered by the injured axons. Axons in the adult CNS can regenerate if a permissive environment is provided and/or the inhibitory factors are removed. To promote axonal regeneration in the injured spinal cord, several promising repair strategies have received particular attention. These include: 1) enhancing the intrinsic regenerative capacity of the injured neuron, 2) providing permissive factors such as administered neurotrophins, and transplantation of regeneration-permissive cells into the injured CNS, 3) removing the inhibitory factors in the injured CNS, such as blocking the inhibitory activities of OLs and CNS myelin and removing inhibitory molecules such as the chondroitin sulfate proteoglycans (CSPGs) produced by reactive astrocytes. Because the mechanism of action for each of these strategies may be different, one would expect that combining multiple strategies would bring about greater axonal regeneration following SCI. My laboratory focuses on the
combinatorial approaches based on stem cell transplantation for axonal regeneration.

NSCs and glial precursor cells can promote axonal regeneration after SCI. NSCs constitutively secrete neurotrophic factors into the injured spinal cord to promote axonal growth following transplantation into the transected spinal cord. The NSCs may also provide the permissive substances for bridging the regenerating axons across the injured gap. After transplantation into the transected rat spinal cord, human NSCs promote regeneration of the corticospinal tract across the injury site to reach the caudal spinal cord where the regenerating axons reform synapses. Glial precursor cells (GPCs) or the young astrocytes from GPCs are also an alternative candidate to promote axonal regeneration. However, NSCs and GPCs may cause allodynia after transplantation into the injured spinal cord, which may prevent their use clinically. Combination of biomaterial scaffolds with NSCs or GPCs may provide a solution. The scaffolds may provide structural support for the attachment of grafted NSCs in the injury site to guide the axonal regeneration after SCI. They could also provide a controlled microenvironment to induce the differentiation of NSCs to desired cell lineages and to prevent the unwanted side effects of grafted NSCs to the host spinal cord outside the scaffolds. My laboratory is testing whether a combination of novel nano-engineered multi-channel scaffolds with stem cells as well as the delivery of growth factors will promote axonal regeneration and functional recovery after SCI.

In addition to promoting axonal remyelination and regeneration, stem cells also exhibit great potential for neuronal replacement and engendering host tissue repair. However, although stem cells may hold great promise for SCI and other neurological diseases, there is currently no consensus as to what type of stem cell is optimal to facilitate repair in specific injuries.

We expect that the cells that will be grafted will be autologous as grafting cells isolated from the patient will eliminate all problems with immunological rejection and immunosuppressive drugs. In any of these approaches, we believe that neural cells derived from autologous induced pluripotent stem cells (iPSCs) will be the cells of choice. iPSCs can now be readily generated from fibroblasts or keratinocytes and recently developed methods have not only obviated the need for viral derivation but the inserted genes can be efficiently removed once the iPSCs are generated. The major concern with iPSCs and ESCs is the potential for tumorigenicity as it has not been shown conclusively that the uncontrolled proliferative potential is completely eliminated from neutralized ESCs or iPSCs. The fact that the transforming genes needed to isolate iPSCs can be removed once they are formed may lessen or reduce the chances of this potentially devastating complication. We are attempting to establish standard protocols to induce and purify the lineage restricted precursors, such as OPCs from viral vector-free iPSCs. We are testing the long-term therapeutic efficacy and safety of iPSC-derived OPCs or NSC for SCI repair. Although there are a number of clinical and technical obstacles to be resolved before its clinical application, we firmly believe that stem cell grafting will ultimately prove effective as one aspect of a combinatorial therapy to treat SCI. The rapid progress in the stem cell field makes its use to treat SCI as well as other neurological disorders more feasible than ever.

**About the Author**

Dr. Qilin Cao earned his MD from Hunan Medical University in 1990. Following his postdoctoral training in University of Freiburg, Germany and University of Louisville, he started as an assistant professor in the Kentucky Spinal Cord Injury Research Center at University of Louisville in 2004, where his focus was stem cells and spinal cord injury. In 2008 he joined the faculty in the Department of Neurosurgery at the University of Texas Medical School at Houston where he is currently an associate professor.

Continued from page 4; Cao

Continued from page 1; Cox
Adipose derived stem cells (ASCs) represent a promising source for large amounts of stem cells. There are several terms that have been used to describe these cells, including adipose derived stem/stromal cells, adipose derived adult stem cells, adipose derived stromal cells, adipose stromal cells, processed lipoaspirate cells, and adipose mesenchymal stem cells. These cells probably represent the pericytes in the capillaries of the fat tissue, and they functionally behave in manners very similar to MSCs.

Umbilical cord blood is an abundant source of hematopoietic stem cells (HSCs). However, further investigation has shown a subgroup of cells contained in cord blood that do not express the hematopoietic cell marker CD45 and do not differentiate into hematopoietic cells in vitro. When used as a mononuclear cell fraction, these cells have demonstrated marked anti-inflammatory effects making them a potentially attractive therapeutic agent even without the isolation of MSCs.

Transplantation of human umbilical cord blood (HUCB) mononuclear fraction into the subventricular zone of neonatal rats showed up to 20% engraftment with human cells positive for both GFAP, a marker of astrocytes and class III beta-tubulin (TUJ1), a marker of neurons, one month after transplantation. In addition, the Chopp laboratory at The Henry Ford Hospital infused HUCB into the tail veins of rats 24 hours after cortical impact injury. The specimens were followed with serial rotarod testing and neurologic severity scoring to assess neurological functioning. Results showed reduced motor and neurological deficits as well as cell engraftment positive for GFAP as well as other neuronal markers. Despite the evidence of neuronal differentiation, more recent studies have failed to show engraftment of HUCB after intravenous infusion in a rat middle cerebral artery occlusion model.

Although previous in vivo research has shown therapeutic benefit from stem cell transplantation, the exact mechanism of action has yet to be delineated. Tissue specific stem cells such as MSCs and NSCs have the ability to proliferate into loco-regional progenitor cells that enable tissue specific regeneration. Additional studies investigating MSC cell therapy have shown differentiation into multiple cell lineages including cardiomyocytes, hepatocytes, keratinocytes and neurons. The concept of stem cell plasticity or transdifferentiation would explain the capacity of adult tissue stem/progenitor cells that enable tissue specific regeneration. Additional benefit from stem cell transplantation, the exact mechanism of factor production by MSCs could stimulate the resident tissue, VEGF, and hepatocyte growth factor (HGF). Increase in growth factor production by MSCs could stimulate the resident tissue cells to repair and may account for the functional benefit seen with stem cell therapy.

Stem cells are known to migrate towards sites of inflammation and mediate the expression of inflammatory markers thereby reducing the amount of overall inflammation and edema. Co-culture of MSCs with purified immune cells such as natural killer cells, dendritic cells, and both naïve and effector T cells demonstrated an increase in production of the anti-inflammatory interleukins IL-4 and IL-10, while decreasing the amount of TNF-α and IFN-γ. An increase of IL-4 in accordance with decrease in IFN-γ promotes a shift from cytotoxic TH1 cells to TH2 helper T cells. In addition, decrease in TNF-α with increase in IL-10 could lessen maturation of dendritic cells while increasing regulatory T cells promoting an anti-inflammatory or tolerant response. Additional studies have shown treatment with MSCs to suppress proliferation of T cells. Decreased overall inflammation and immune response could correlate with possible decreased cell damage associated with stem cell therapy.

Recent investigation of a rat model of stroke showed decreased splenial mass with concomitant reduction in CD8+ T cells after ischemic accident. Transfusion of systemic HUCB after stroke showed homing towards the spleen with stabilization of both splenic mass and CD8+ T cell count. In addition T cell proliferation was decreased in accordance with increased levels of IL-10 and decreased IFN-γ. The reduction of peripheral inflammatory response was associated with up to an 85% decrease in cerebral infarct volume.

It has also been theorized that stem cell therapy induces angiogenesis, accounting for tissue repair. Intravenous injection of MSCs after induced ischemic stroke in a rat model showed increased levels of endogenous VEGF and VEGF receptor 2, as well as increased angiogenesis in the transition zone. Further investigation has shown combination therapy with MSCs and a nitric oxide donor to significantly increase vessel diameter and endothelial cell proliferation compared to MSC therapy alone.

Promising pre-clinical data has led to the initiation of several clinical trials to study cell therapy in neurologic diseases. Current FDA guidelines state that research of all new cell therapeutics must be completed in accordance with an investigational new drug protocol (www.fda.gov). Following these guidelines, we recently completed a Phase I clinical trial using autologous, intravenous bone marrow derived mononuclear cells as an adjunct in treatment for children (ages 5-14) with isolated severe acute TBI (Glasgow Coma Score of 5-8). The study recently completed enrollment and follow-up and represents the sole clinical trial examining cellular therapeutics for TBI in the US. The results of the initial Phase I clinical trial using bone marrow derived cells to treat TBI in children will be published in Neurosurgery in the coming months. The study showed that the technique is safe, with no infusion related toxic effects. The study was not designed to demonstrate efficacy, and a larger Phase 2 study is in the planning stages. A similar Phase I study has been approved by the Department of Defense in adults with severe TBI.

About the Author
Charles S. Cox, Jr., M.D. is the Children's Fund Distinguished Professor of Pediatric Surgery and Pediatrics at the University of Texas Medical School at Houston. He directs the Pediatric Trauma Program at Children's Memorial Hermann Hospital and the Pediatric Translational Laboratories. The multi-disciplinary research group focuses on progenitor cell based therapeutics for the treatment of traumatic brain injury. The group tackles the barriers to translating potentially promising pre-clinical studies into early phase studies for children with TBI.
Dr. Valentin Dragoi is the recipient of one of the prestigious NIH Directors Pioneer Award

Dr. Dragoi was awarded a 5 year grant to utilize telemetric recording systems implanted in key visual cortical areas to study neuronal populations and their impact on behavior in freely moving nonhuman primates. Phenomena that have been inaccessible, such as learning in natural environments and sleep, will become accessible, and will present a more realistic measure of cortical activity during real time in freely behaving monkeys. This research is truly innovative and we congratulate Dr. Dragoi on this achievement.

NRC 2009 Poster Session

Graduate students and postdoctoral fellows participating in the NRC sponsored Poster Session on December 5, 2009.

Ernst Knobil Lecture

The Ernst Knobil lecture featured Dr. Ron Evans from the Salk Institute. Left to right, Dr. Giuseppe Colasurdo, Dr. Peter Davies, Ms. Julie Knobil, Dr. Evans and Dr. John Byrne.

Children at Brain Night

Children explore brains at “Brain Night at the Museum” on March 18, 2010 at the McGovern Museum for Health and Medical Science.

Distinguished Lecture Series

Dr. John Byrne, Dr. Roger Rosenberg and Dr. Mya Schiess at the NRC Distinguished Lecture series, April 8, 2010.

Public Forum Panel

Panel and moderator for the NRC’s 15th Annual Public Forum on Childhood Brain Diseases which was held on February 6, 2010. The moderator was Pedro Mancias, M.D. (standing with Dr. John Byrne) and the panelists were Drs. Pauline Filipek, Deborah Pearson, Nehal Parikh and Anne Sereno.