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News & Featured Research of the Neuroscience Research Center

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The Gut's Microbiome – A Frontier for the Discovery of New Stroke Therapies

By Venugopal Venna, Ph.D., Bhanu Priya Ganesh, Ph.D., and Louise McCullough, M.D., Ph.D.



Venna



Ganesh



McCullough

Abstract: One consistent finding in aged individuals is a persistent, low level of circulating markers of inflammation, which contributes to a global reduction in their ability to cope with stress. Our research group has found that age-related changes in the gut microbiome leads to the loss of beneficial microbial metabolites, excessive growth of toxic bacterial populations, altered gut integrity, and enhanced pro-inflammatory immune responses. Stroke also leads to similar changes in the gut in both young and aged animals, but they are significantly worse in the aged. These changes contribute to the high morbidity and mortality seen in aged animals after stroke. We have found that altering the gut microbiota or microbial products even days after stroke improves recovery in aged animals, thus providing an exciting new translational direction for stroke treatment.

Advancing age is a major risk factor for stroke, now the number one cause of adult disability in the United States. After the age of 55, stroke rates double for every additional 10 years of age. With improvements in acute stroke care, many more patients live to even older ages than ever before. This has led to a growing number of stroke survivors in our communities, the majority of whom are over age 65, many with neurological deficits. Evidence from experimental and clinical studies shows chronic low grade inflammation occurs

CONTINUED ON PAGE 6; VENNA, GANESH & MCCULLOUGH

Mesenchymal Stem Cell Therapy for Parkinson's Disease

By Mya C. Schiess, M.D. and Jessika Suescun, M.D.



Schiess



Suescun

Abstract: Chronic neuroinflammation plays a critical role in the pathogenesis of idiopathic Parkinson's disease (PD), yet there are no proven therapies that address or reverse this process.

This article describes a transformative and novel therapeutic approach using mesenchymal stem cells. We report encouraging preliminary findings of the first FDA-approved Phase 1 trial of immune modulating cell-based therapy in the form of donor bone marrow-derived mesenchymal stem cells to treat idiopathic PD.

Neurological disorders are the leading cause of disability worldwide, and Parkinson's disease (PD) is the fastest growing. Neurodegeneration in PD involves the loss of dopamine producing neurons, the presence of an abnormal structural change in a neuronal protein called alpha-synuclein, and a chronic neuroinflammatory process. The mainstay of therapy is the use of dopaminergic drugs to restore dopamine concentration. In the early stages of the disease, this exogenous restoration of dopamine can nearly normalize voluntary movements. However, as the disease progresses, patients experience a wearing-off of therapeutic benefit and the emergence of motor fluctuations. Over the past decades, an armamentarium of medical therapies and surgery based neuromodulation therapies have been developed that provide highly effective symptomatic relief. In contrast, there are no FDA-approved therapies to arrest

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Director's Column

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



This issue of the newsletter departs somewhat from our usual approach to selecting topics for our two research articles. Over the 25 years that we have published the NRC Newsletter, we traditionally present in each issue a single topic, or two that are closely related, from the different perspectives of a basic scientist and a clinician. This time we instead spotlight different diseases—*ischemic stroke*, on the one hand, and *Parkinson's disease* on the other—and on new approaches to treating them that our authors are currently investigating. Although the potential treatments they envision are completely different, they share a novelty that is tremendously exciting.

Louise McCullough, M.D., Ph.D., professor of neurology and chair of McGovern Medical School's Department of Neurology, together with two of her colleagues, Venugopal Reddy Venna, Ph.D. and Bhanu Priya Ganesh, Ph.D., both assistant professors of neurology, discuss their research on the gut microbiome and the glimmer of possibilities for treating stroke. Our other article reports on a trial of a new treatment for Parkinson's disease. Mya Schiess, M.D., professor of neurology and director of the UTHealth Movement Disorders clinic, together with Jessica Suescun, M.D., a research scientist in the Department of Neurology, present their preliminary findings of the first FDA-approved Phase 1 trial of immune modulating cell-based therapy to treat Parkinson's disease. I hope you will find these two research studies interesting.

The hum of innovation in the neurosciences resounds throughout UTHealth, with reverberations in the surrounding Texas Medical Center, Houston, the state, and even beyond with the creation of the new, cutting-edge Texas Institute for Restorative Neurotechnologies (TIRN). Designed as a major research, patient care, and educational enterprise, TIRN will harness today's most advanced and rapidly burgeoning developments in neuroscience, neuro-technology, and neuroinformatics to transform the understanding and treatment of brain disorders. Close collaborations with Rice University, other UT System institutions (medical and non-medical—for example, UT Austin), as well as institutions outside the U.S. will propel the institute's leading edge research and innovation.

Initially, the primary clinical focus will be epilepsy, a disease afflicting more than 3 million Americans and some 50 to 60 million individuals worldwide. Other functional disorders (those characterized by disordered operations of brain networks with minimal or no discernible structural abnormalities) within the TIRN's purview will be movement disorders, intractable psychiatric illnesses, and chronic pain disorders, all of which lead to untold suffering. UTHealth's highly interdisciplinary, collaborative institute will provide a super structure integrating clinical programs, basic science research, technological innovation, and academic training to target these diseases. In addition to innovative therapies for functional disorders, areas

of emphasis for development include brain-machine interfaces, neuroinformatics, big data, and precision neurological therapies. The goal for TIRN, created under the leadership of an executive council of three co-directors, is to become an internationally recognized center for the treatment and the advancement of treatments of functional disorders, focusing in the first five years on epilepsy care, especially epilepsy surgery.

As a transformative clinical research center providing top quality education and training, TIRN will be a key asset for UTHealth. Its executive leadership will report directly to the office of UTHealth President Giuseppe Colasurdo, M.D. The institute will be housed largely in the renovated space of the Jesse Jones Library building adjacent to McGovern Medical School. TIRN will also lease space in Rice University's BioScience Research Collaborative building, which will house engineers engaged in this effort from Rice. TIRN will also engage with other institutions in the UT System, as well as Houston's growing entrepreneurial community, to develop neural technologies. In addition, TIRN's cognitive science program will collaborate with Rice and UT Austin departments of neuroscience and psychology.

The TIRN's executive council includes three co-directors:

Nitin Tandon, M.D. is professor and vice chair in the Vivian L. Smith Department of Neurosurgery at McGovern Medical School and chief of Epilepsy Surgery at Memorial Hermann Hospital. The Epilepsy Surgery Program is part of the Texas Comprehensive Epilepsy Program (TCEP), a collaboration between McGovern Medical School and Memorial Hermann and the leading program in the southwestern U.S. for the diagnosis and surgical treatment of epilepsy. Dr. Tandon is a co-director of TIRN, with responsibility for the Epilepsy Surgery and Neural Interfaces Division. Its research areas include outcomes research following epilepsy surgery; intracranial neuromodulation for epilepsy; imaging relevant to epilepsy surgery and pre-operative localization; and intracranial recordings and modulation of cognition.

Samden Lhatoo, M.D., F.R.C.P., is the John P. and Kathrine G. McGovern Distinguished University Professor of Neurology and executive vice chair of the Department of Neurology. A recipient of a University of Texas System STAR award, he is a recent faculty recruit to UTHealth. He serves as director of the TCEP and is a co-director of TIRN, with responsibility for the Epilepsy Monitoring Division. The division's research areas include epidemiological aspects of epilepsy; wearable (non-invasive) technologies; the interaction between epilepsy and the autonomic system; and imaging research in intractable epilepsy.

G.Q. Zhang, M.S., Ph.D., is vice president and chief data scientist for UTHealth and a professor in the Department of Neurology. He also recently received a University of Texas System STAR award and is a recent faculty recruit to UTHealth. He is a co-director of TIRN, with responsibility for the Neuroinformatics Division.

In addition to its executive council, the TIRN will have an internal advisory board, to be chaired by Michael Blackburn, Ph.D., dean of the UT MD Anderson Cancer Center UTHealth Graduate School of Biomedical Sciences and executive vice president and chief academic officer of UTHealth. An external advisory board will also be established to support the institute's vision. Chaired by President Colasurdo, it will consist of international leaders in clinical and basic neuroscience research, bioinformatics, computer science, and healthcare delivery.

As I look ahead to the many exciting developments, such as the TIRN, on the horizon, I am impressed by how far we at UTHealth have come in advancing the neurosciences. I

am grateful for the opportunities the NRC has had to partner with outstanding individuals and institutions in advancing our mission. One of the NRC's greatest supporters from its inception in 1991 through many years of membership on our executive committee and attendance at numerous NRC programs just retired last May —George M. Stancel, Ph.D., who at the time of his retirement was senior vice president for Academic and Research Affairs. The photo below shows him wearing his brain cap at the NRC's annual Brain Night for Kids last March at the McGovern Museum of Health and Medical Science. Thank you, Dr. Stancel, for your support of the NRC. What a pleasure it has been!



From left:
John Arcidiacono,
McGovern Health
Museum president &
CEO; George Stancel;
John Byrne

U.S. Rep. Lizzie Fletcher, from Houston, came by McGovern Medical School for a visit last August. As the photo shows, I enjoyed introducing her to my laboratory's Aplysia. Afterward she tweeted, "Thank you to Dr. Jack Byrne and the team at UTHealth Science Center, who gave me a tour and talked about critical neuroscience research & the role of NIH funding, as well as the overall reach of UTHealth. Incredible work happening here, and the biggest snails I've ever seen!"



news & information

Jaroslaw Aronowski, M.D., Ph.D., professor of neurology at McGovern Medical School, has received an NIH/NINDS grant for the project, "Humanin and Intracerebral Hemorrhage," to explore the role of mitochondria transfer from astrocytes to neurons and to microglia as a process leading to improved outcome after intracerebral hemorrhage. **Joo Eun Jung, Ph.D.**, assistant professor of neurology, is also a PI. In addition, Dr. Aronowski has an NIH grant to investigate tocilizumab, an FDA-approved medication for rheumatoid arthritis, as a potential treatment for acute ischemic stroke. The research is one of six studies in coordination with the Stroke Preclinical Assessment Network recently created by NIH.

Laura Farach, M.D., assistant professor of pediatrics at McGovern Medical School, received grants from the U.S. Department of Defense Medical Research and Development Program and the Tuberos Sclerosis Alliance for her project, "Developing a Genetic Risk Prediction Model for Epilepsy in Patients with Tuberos Sclerosis Complex."

Erin Furr Stimming, M.D., associate professor of neurology and director of the HDSA (Huntington's Disease Society of America) Center of Excellence at UTHealth, is the Site Investigator for Generation HD-1, a pivotal Phase 3 trial sponsored by Roche/Genentech, studying a potentially groundbreaking therapy (RG6042) for patients with manifest Huntington's disease. The multicenter, randomized, double-blind, placebo-controlled study will evaluate the safety and efficacy of intrathecally administered RG6042, an antisense oligonucleotide designed to target and destroy the mutant "huntingtin" protein (mHTT) that breaks down nerve cells in the brain. Dr. Furr Stimming also received a grant from Cures Within Reach, a nonprofit funding agency, to assess the use of dextromethorphan/quinidine (Nuedexta®) for individuals who have Huntington's disease with irritability, a common symptom with no currently approved treatment.

Ruth Heidelberger, M.D., Ph.D., Frederic B. Ashe Chair in Ophthalmology and professor of neurobiology and anatomy at McGovern Medical School, received an award from the new neuro-related joint seed grant program of the Medical School and Rice University for her project designed to combat the type of blindness that occurs in retinitis pigmentosa and age-related macular degeneration.

Ilya Levental, Ph.D., associate professor in the Department of Integrative Biology and Pharmacology at McGovern Medical School, has received a grant, together with international collaborators, of over \$1 million from the Human Frontier Science Program Organization for the project, "Regulation of Membrane Receptor Function in the Brain by Lipid Composition and Dietary Inputs." His collaborators are from the University of Helsinki, the German Center for Neurodegenerative Diseases, and the University of Akron in Ohio. The team will investigate links between dietary fats, cell

membranes, and neuronal function from the molecular to the organismal level.

Dianna Milewicz, M.D., Ph.D., professor in the Department of Internal Medicine at McGovern Medical School and director of the M.D./Ph.D. Program at The University of Texas MD Anderson Cancer Center UTHealth Graduate School of Biomedical Sciences, won the American Heart Association's \$1 million Merit Award. The award is for her proposed studies of stroke-causing mutations of the ACTA2 gene, found in some children with the rare cerebrovascular disorder, Moyamoya disease.

Rodrigo Morales, Ph.D., associate professor of neurology at McGovern Medical School, received a grant from the U.S. Department of Agriculture for his project to detect infectious prions in biological samples from feral swine.

Ines Moreno-Gonzalez, Ph.D., assistant professor of neurology at McGovern Medical School, received an award from the neuro-related joint seed grant program of the Medical School and Rice University for the project, "Photodynamic Treatment for Alzheimer's Disease Based on Directed Amyloid Photooxidation."

João L. de Quevedo, M.D., Ph.D., professor and vice chair of faculty development and outreach in the Department of Psychiatry and Behavioral Sciences at McGovern Medical School, has received an NIH/NIMH grant for a project to study plasma neural-derived extracellular vesicles in bipolar disorder patients and controls. He will also investigate the development of a machine-learning algorithm for the identification of a microRNA biosignature. The algorithm may lead to the identification of clinically relevant, peripherally measured, brain-specific biomarkers that improve knowledge of the disorder and inform the development of personalized treatments.

Kazim Sheikh, M.D., professor of neurology at McGovern Medical School, received an NIH/NINDS grant for a proof-of-concept study on a novel method of drug delivery to neurons for the treatment of different degenerative disorders. The project will examine whether a monoclonal antibody or its fragments, directed against neuronal/axonal surface glycans, can be used for the targeted delivery of an enzyme to affected neurons in the spinal cord in an animal model of Sandhoff disease.

Ching-On Wong, Ph.D., instructor in the Department of Integrative Biology and Pharmacology at McGovern Medical School, received an NIH/NIA grant for research related to APOE, which is associated with late-onset Alzheimer's disease. His project aims to define the role of a vesicular membrane protein, TTYH1, and its Drosophila homolog in regulating APOE secretion in glial cells.

Jiaqian Wu, Ph.D., associate professor in the Vivian L. Smith Department of Neurosurgery at McGovern Medical School, has received a grant for her project, "Dissecting Molecular and Cellular Constituents of Spinal Cord Injury," from Mission Connect, a collaborative funding program of the TIRR Foundation.

In Other News...

Louise D. McCullough, M.D., Ph.D., professor and chair of the Department of Neurology at McGovern Medical School, received the 2019 Landis Award for Outstanding Membership, an annual award of the NINDS/NIH. The Landis Award Steering

Committee was unanimously impressed with Dr. McCullough's "thoughtful approach to mentoring, the breadth of [her] mentorship efforts, and the notable impact" she has had on her trainees. The award provides support for the advancement of her trainees' career advancement.

David I. Sandberg, M.D., professor and chief, Division of Pediatric Neurosurgery at McGovern Medical School, is the recipient of the 2019 Humanitarian Award of the American Association of Neurological Surgeons. He was selected for his work throughout the world with children suffering from neurosurgical disorders.

Postdoctoral research fellows, graduate students, and their mentors . . .

Three postdoctoral research fellows in The BRAINS Research Laboratory Group, headed by Dr. Louise McCullough in the Department of Neurology at McGovern Medical School, received awards of over \$100,000 each for their research from the American Heart Association. **Sungha Hong, Ph.D.**, (mentored by Sean P. Marrelli, Ph.D., professor) received funds for his project, "The Role of Endothelial TRPV1 Blood Flow Restoration Following Stroke." **Michael Maniskas, Ph.D.** (mentored by Akihiko Urayama, Ph.D., associate professor) received funds for "Peripheral Mechanism Contributing to Cerebral Amyloid Angiopathy." **Juneyoung Lee, Ph.D.** (mentored by Dr. McCullough and Venugopal Venna, Ph.D., assistant professor of neurology) received funds for "Mucin as a Sentinel for the Brain-Gut Axis Following Stroke." Dr. Lee also received the 2019 Lawrence M. Brass Stroke Research Award, presented to him in May at the American Academy of Neurology

Annual Meeting in Philadelphia.

Three students at The University of Texas MD Anderson Cancer Center UTHealth Graduate School of Biomedical Sciences (GSBS) received pre-doctoral fellowships from the NIH/NEI for their research: **Natasha Kharas** for her project on how sleep improves behavioral performance; **Samantha Debes** for her project, "Optogenetic Manipulation of Cortical Feedback for Controlling Network Coding and Behavior"; and **Russell Milton** for his project to determine how processing of visual information by cortical networks is influenced by the ongoing brain state. (All three are mentored by Valentin Dragoi, Ph.D., professor of neurobiology and anatomy at McGovern Medical School). Doctoral student **George Edwards III** (mentored by Claudio Soto, Ph.D., professor of neurology at McGovern Medical School) published a first-authored paper, "Traumatic Brain Injury Induces Tau Aggregation and Spreading," in the Journal of Neurotrauma. His published research also received a best poster award at the 2019 Texas Alzheimer's Research Care and Consortium in Austin, Texas.

Ryan Cassidy, an MD/PhD student at McGovern Medical School and GSBS (mentored by Qingchun Tong, Ph.D., associate professor in the Center for Metabolic and Degenerative Disease at the Institute for Molecular Medicine) published a first-author paper on the cover of Science Advances. Cassidy's research demonstrates for the first time, neurocircuits that underlie the link between dysregulated eating behaviors and emotion, especially anxiety.

UTHealth broke ground in June for Houston's first new public psychiatry hospital in over 30 years



UTHealth leaders, government officials, and supporters celebrated the groundbreaking on June 26 of a new psychiatric hospital and campus to be built adjacent to the existing UTHealth Harris County Psychiatric Center (HCPC). Created with \$125 million in state funds in partnership with the Texas Health and Human Services Commission, the hospital and HCPC together will be the largest academic psychiatric hospital in the country.

From right: U.S. Dept. of Health and Human Services Regional Director Fred Schuster; Jair Soares, M.D., Ph.D., executive director of UTHealth HCPC and chair, Dept. of Psychiatry and Behavioral Sciences at McGovern Medical School; Giuseppe Colasurdo, M.D., president of UTHealth; Louis Faillace, M.D., founding chair, Dept. of Psychiatry and Behavioral Sciences at McGovern Medical School; Barbara Stoll, M.D., dean, McGovern Medical School; Texas Sen. Borris Miles; Peter Pisters, M.D., president of The University of Texas MD Anderson Cancer Center; Jijie Zhang, Ph.D., dean, UTHealth School of Biomedical Informatics; John Zerwas, M.D., executive vice chancellor for health affairs at The University of Texas System (at time of groundbreaking, a Texas representative); Lois Moore, former chief operating officer, UTHealth HCPC, now a board member of The Harris Center for Mental Health; current COO, UTHealth HCPC, Stephen Glazier; Mike Maples, deputy executive commissioner, Texas Health and Human Services; Michael Blackburn, Ph.D., dean of The University of Texas MD Anderson Cancer Center UTHealth Graduate School of Biomedical Sciences. Additional participants, not visible in the photo, were Executive Commissioner of Texas HHS, Courtney Phillips, Ph.D. and Texas Sen. Brandon Creighton.

with aging, which contributes to a network of changes such as impaired synaptic plasticity, enhanced microglial activation, and loss of hippocampal neurons. These changes, in turn, contribute to delayed stroke recovery. Given recent studies showing that the gut microbiota (the mixed community of microorganisms, mainly bacteria) and its secreted microbial metabolites change with age and alter host immunity, our BRAINS research laboratory at the McGovern Medical School at UTHealth is using established animal models to uncover how the gut microbiota contribute to age-related diseases, including ischemic stroke. Our work has focused primarily on understanding the communication within the microbiota-gut-brain axis. Our emerging data strongly suggest that changes in gut microbiome composition and in the metabolites that these organisms produce can influence age-associated inflammation.

Age is associated with significant alteration in the composition of the gut microbiota. One major change is the alteration in the ratio of its two largest bacterial subgroups, Firmicutes and Bacteroidetes. Aging favors a higher proportion of Firmicutes to Bacteroidetes, a ratio representing gut dysbiosis. This dysbiotic shift has been linked to the development of several age-related diseases, including hypertension, cardiovascular disease, diabetes, dementia, and cerebrovascular diseases. Ischemic stroke, accounting for over 80 percent of all strokes and the focus of our research, occurs when a blood vessel to the brain is occluded by a thrombus or embolism, causing severe loss of oxygen and glucose to the ischemic brain region. It leads to neuronal death and the activation of glial cells, including microglia, the resident immune cell of the brain. This brain inflammation triggers the influx of peripheral immune cells into the brain, leading to further damage. We, and others, have found that some of these infiltrating cells are gut-derived T cells.

Post-stroke inflammation is a critical determinant of damage and recovery after stroke—and a main cause of mortality. Clinically, close to 65 percent of the world's population who have had a stroke suffer with mild or severe impairments afterward; an additional 15 percent die shortly after stroke. Increasing evidence suggests that peripheral inflammatory responses to stroke play an important role in determining neurological outcome, and recognition of the importance of the brain-gut axis in response to stroke is increasing among researchers. We have reported that stroke elicits a vicious cycle of central and peripheral inflammation through bi-directional communication within the gut-brain axis (Spychala et al., 2018, *Annals of Neurology*. 2018; Crapser et al., 2016, *Aging*). Maintaining the integrity of the gut barrier is of utmost importance, as bacterial translocation can lead to infections, a major cause of mortality in stroke patients.

The gut is one of the largest reservoirs of lymphoid-associated tissue in the body and plays a role in nearly

all aspects of host homeostasis. Importantly, the gut also serves as a home for trillions of microorganisms that impact everything from digestion to behavior. These commensals strongly influence the production of intestinal mucus, which maintains gut barrier homeostasis and keeps the host separated from these organisms. They also can induce pro-inflammatory and anti-inflammatory responses in the host. With aging, gut epithelial barriers become more permeable, leading to increased local and systemic inflammation, even in the absence of injury. Both clinical and animal studies have shown that stroke leads to significant changes in microbial diversity in fecal samples, independent of comorbidities. Our group has shown in recent experimental studies that ischemic stroke elicits a pathological imbalance of the gut microbiome, disrupts intestinal mucus production, and impairs gut barrier integrity. This damage is much more significant in aged animals. Using a mouse middle cerebral artery stroke model, we identified a significant change in the diversity of the gut's microbiota after stroke in both young and aged mice. In aged mice prior to stroke, we altered the gut microbiota composition through a fecal transfer of the biome from healthy young animals. After the transfer and post-stroke, we observed increased anti-inflammatory Tregs (helper, regulatory T-cells) and reduced pro-inflammatory T-cells (IL-17+ $\gamma\delta$) in the intestinal lamina propria, as well as reduced leukocyte infiltration into the brain. The result was reduced mortality and improved recovery in aged mice. In contrast, we found that the transfer of aged dysbiotic microbiota from aged into young mice tripled mortality, increased the infiltration of detrimental immune cells into the brain, and led to the prolonged activation of microglia; in sum, it recapitulated the immune response seen in aged animals after stroke. This work suggests that manipulation of peripheral factors especially immune cells and inflammatory cytokines can alter outcome after stroke centrally.

Our studies suggest that an unidentified detrimental metabolite produced by the aged microbiota, or the loss of a beneficial metabolite produced by young microbiota—or a combination of both—may be important to stroke recovery. Microbiota play an important role in host homeostasis through their production of metabolites, complex signaling molecules, and other microbial components that are intrinsic to health. The gut microbiota produces and secretes an extremely diverse range of metabolites. These secreted molecules play critical roles in host function, both locally at the mucosal layer to maintain gut barrier integrity and, following their stimulation of nerves in the gut, their release into the blood stream. One important class of metabolites is short chain fatty acids (SCFAs). These include propionate, butyrate, and acetate, the vast majority of which are produced by the gut bacteria. They are highly beneficial and protective to the host in relation to their roles in G protein-coupled receptor activation and the inhibition of histone deacetylases. SCFAs help to stabilize the gut

In the Spotlight



Left: Henry Roediger, III, Ph.D., professor of psychological & brain sciences at Washington University in St. Louis, was the **UTHealth NRC's 2019 Distinguished Lecturer**. He delivered his lecture, "Making Learning Stick," on Feb. 28. During his visit to Houston, he met with former colleagues at Rice University and with UTHealth faculty, including from right: James Pomerantz, Ph.D., professor of psychology at Rice; Roediger; Randy Martin, Ph.D., professor of psychology at Rice; UTHealth professor of neurobiology and anatomy, Anthony Wright, Ph.D.; and Jack Byrne, Ph.D.

Right: Panelists for the NRC's 24th Annual Public Forum, titled *Maintaining Brain Health Across the Life Span*, on April 13 were, from left: moderator Thomas D. Meyer, Ph.D., associate professor of psychiatry & behavioral sciences at McGovern Medical School; Summer Ott, Psy.D., assistant professor in the McGovern Medical School Dept. of Orthopedic Surgery; Joy Schmitz, Ph.D., professor of psychiatry & behavioral sciences at McGovern Medical School; and Paul Schulz, M.D., professor of neurology and director of the Dementia and Memory Disorders Center at McGovern Medical School.

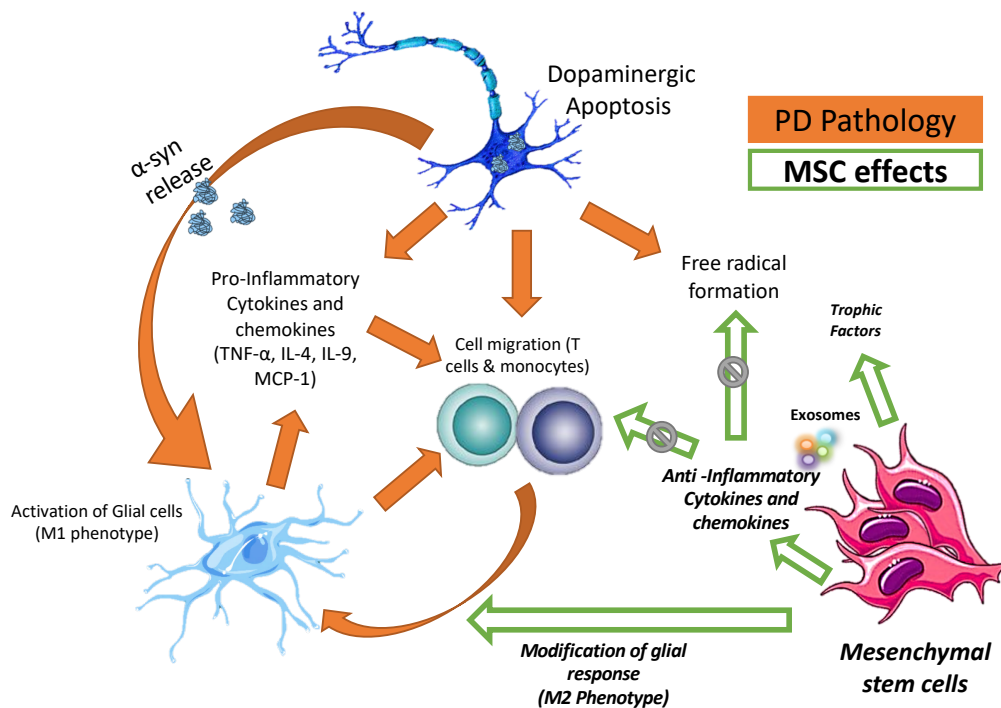


Left: Engineering students at Rice University gather with their mentor, Nitin Tandon, M.D., professor of neurosurgery at McGovern Medical School and adjunct professor of electrical and computer engineering at Rice, to discuss their project, "Axon Mobile Wireless Recorder for Intracranial Epileptic Seizure Monitoring," for the International Symposium on Circuits and Systems Conference in Japan. The students became the worldwide winners of the Institute of Electrical and Electronics Engineers Circuits and Systems student design competition in May. From left: Andres Gomez, Irene Zhang, Sophia D'Amico, Tandon, Benjamin Klimko, and Aidan Curtis. (Jeff Fitlow/Rice University)



Above: The NRC's annual **Brain Night for Kids** attracted over 1,500 children and family members to the McGovern Health Museum on March 14. With the help of UTHealth students, post-docs, faculty and staff, kids enjoyed the chance to hold a real human brain and to participate in an egg drop activity that shows the importance of wearing bike helmets.

Figure 1. Proposed Mechanisms of Mesenchymal Stem Cells in Parkinson’s Disease



PD pathology (orange): As a result of the misfolded alpha-synuclein aggregates, dopaminergic neurons are damaged early in the PD disease process, leading to activation of glial cells. As neurons degrade, a-synuclein is taken up by the microglia which activate T cells and release pro-inflammatory cytokines. This creates a self-perpetuating inflammatory process.

Proposed mechanism of MSCs (green): The potential benefit of MSC therapy relies primarily on paracrine actions, including the release of trophic and immunosuppressant factors (cytokines and chemokines), in addition to exosome activity. These can enhance angiogenesis, inhibit fibrosis and apoptosis, and suppress free radical formation. These actions can create a favorable environment for regeneration and allow a restorative process to occur.

the disease process or delay continued degeneration of neurons.

Cell-based therapy emerged as a treatment in 1979 with the first dopamine replacement efforts in animal models. Since then, the majority of cell-based approaches have focused exclusively on the dopaminergic deficit. However, cell substitution does not address the etiology of the disorder or the non-motor symptoms (including sleep disturbances, constipation, and mood disorders) that originate from other neurotransmitter systems. A completely different and novel approach instead focuses on the chronic inflammatory process widely described in PD. It takes advantage of immune-modulatory mesenchymal stem cells (MSCs).

Our research group (including investigators in McGovern Medical School’s Movement Disorders division, UTMOVE, under the direction of Dr. Schiess; the Department of Pathology and Laboratory Medicine, the

Department of Anesthesiology, the School of Public Health, the School of Bioinformatics and The City University of New York) has extensively studied the role of the peripheral immune system in PD neurodegeneration. We have conducted investigations using a lipopolysaccharide rat model of PD, human-derived cultured glial cells, and cerebrospinal fluid and plasma of patients with PD (Csencsits-Smith, Suescun, Li, Luo, Bick and Schiess, 2016, *Neuroimmunomodulation*, 23, 301-308). Our findings showed that neurodegeneration promotes a persistent inflammatory stimuli and/or a failure in immune modulation that leads to neuronal cell death.

Researchers have shown over the last decade that neuroinflammation in PD may be triggered by a variety of factors, including genetic susceptibility, toxin exposure, misfolded protein aggregates, oxidative stress, immune system aging, drugs, infectious agents, and systemic diseases. These factors, in

turn, alter the central nervous system’s homeostasis. The inflammatory state of the neuronalglial microenvironment has been well described in human post-mortem tissue and in vivo models (toxin induced models), as well as in vitro models. The neuroinflammatory response is orchestrated by interactions of glial cells (local), peripheral immune cells (B and T-lymphocytes), and signaling molecules (cytokines, chemokines, and growth factors). (See Figure 1.) Their interactions elicit a coordinated reaction between the central nervous system and the peripheral immune system. Epidemiological studies support the role of anti-inflammatory drug regimens in lowering risk for developing PD.

Mesenchymal stem cells are capable of migrating to sites of injury, where they deploy their dual ability to either suppress or activate immune responses, depending on the environment to which they are exposed. The MSC’s potential therapeutic benefit relies primarily on paracrine actions and activity of

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exosomes (extracellular vesicles). The paracrine actions lead to the release of trophic and immunosuppressant factors, development of new blood vessels, promotion of neurogenesis, and inhibition of fibrosis and apoptosis, as well as suppression of free radical formation. At the same time, exosomes, which function as intercellular communication vehicles, elicit diverse cellular responses and support the maintenance of immune homeostasis. MSCs have multiple advantages over other types of stem cells: They are easily procured on a large scale and have a low probability of being tumorigenic. MSCs also have few to no ethical issues associated with their procurement or use.

In late 2015, our group obtained an investigational new drug approval to conduct the first U.S. Phase I study of allogeneic bone marrow-derived mesenchymal stem cell therapy for idiopathic PD. We launched the trial at the end of 2017, finished in September 2019, and are currently in the process of analyzing the data. We recruited 20 patients with mild to moderate Parkinson's disease. Each individual received a single intravenous dose of MSC per kg of body weight. Donor cells were procured under Current Good Manufacturing Practices designated by the FDA. We followed the study participants at multiple time points through a full year in the UTHealth Clinical Research Unit located at Memorial Hermann-Texas Medical Center hospital.

Our preliminary findings from this encouraging proof-of-concept study show that all doses of the intravenous allogeneic MSC were safe and well-tolerated in the study participants. Clinically, there was a significant improvement in the motor scores when motor symptoms were assessed without the influence of any dopaminergic medication ("OFF" state). Scores for quality of life and activities of daily living also showed significant improvement. These findings should be interpreted with caution, as they are based on a small sample size and

on the study's purpose to assess safety (Schiess, Suescun et al. 2019, *Neurology* 92 (15 Supplement): S16.008).

Additional findings reveal an anti-inflammatory effect with a significant reduction of pro-inflammatory cytokines, like tumor necrosis factor alpha (TNF-alpha), paired with an increase in growth factors like brain-derived neurotrophic factor (BDNF). High levels of TNF-alpha have been correlated in the literature with worse motor and cognitive scores in PD. Concomitantly, BDNF, a trophic factor regulating cell survival and synaptic plasticity, increased following MSC infusion. We hypothesize that these peripheral changes lead to an anti-inflammatory profile that could enhance neuronal survival and promote angiogenesis. Because we found that the immune peripheral changes and the improved motor response were not sustained beyond six months, we also postulate the necessity of repeated dosing to maintain the effect. Overall, as a result of our promising findings, we anticipate the start of our Phase IIa trial, using multiple infusions of MSCs, by fall 2020.

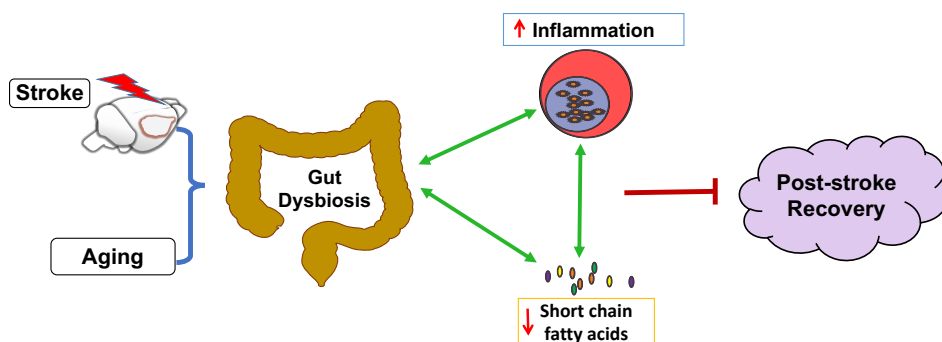
Finally, it has been predicted that by 2040, Parkinson's disease will become a pandemic affecting 17.5 million people worldwide. Our hope is that within the coming decade, clinicians will have the tools to counter this pandemic with the results of rigorously executed clinical trials that define the effectiveness of cell-based therapies to halt PD progression, restore health to the brain, and revolutionize the field.

About the Authors

Mya Schiess, M.D. is a professor of neurology at McGovern Medical School and holder of the Adriana Blood Distinguished Chair in Neurology. A board-certified neurologist and movement disorders specialist, she is the creator and director of the UTHealth Movement Disorders clinic and fellowship training program (UTMOVE). Over 20 years she has led multiple observational and interventional trials for Parkinson's disease, including development of classification criteria for subtypes and their relationships to neurotransmitters; studies of blood biomarkers for diagnosis and progression; use of structural, functional, and diffusion-weighted MRI to evaluate brain changes; and assessment of new medical and surgical interventions, with a main focus on Parkinson's disease. Dr. Schiess leads a large investigator initiated prospective longitudinal biomarker study looking at REM Sleep Behavior Disorder as a prodromal condition for parkinsonism and a pilot early Phase I study of Allogeneic Bone Marrow-Derived Mesenchymal Stem Cell Therapy for Idiopathic Parkinson's Disease.

Jessika Suescun, M.D. is a research scientist in the Department of Neurology at McGovern Medical School. Dr. Suescun has postdoctoral research training in movement disorder clinical trials and extensive experience in basic science research in both Alzheimer's and Parkinson's diseases. She has co-developed and executed multiple observational and interventional clinical trials, including the identification of blood-based and neuroimaging biomarkers for disease state and rate of progression, as well as studies of new therapies.

Figure 1. Effects of Gut Dysbiosis on Stroke Recovery



Ischemic stroke and aging, individually or together, lead to gut dysbiosis, significant increase in systemic inflammation, and reduction in short-chain fatty acids. Our recent studies identified that these changes contribute to delayed post-stroke recovery. Targeting this pathway could provide a viable therapeutic approach.

epithelial barrier, alter T-lymphocyte populations, increase the protective mucus layer, and beneficially modulate cytokine and antibody secretion. These SCFAs, as well as other metabolites, can profoundly affect the inflammatory response following stroke.

Our research has established that aging and stroke individually or together lead to a significant reduction of SCFAs in mice gut. To confirm the potential beneficial effects of SCFAs, we cultured a cocktail of selected bacterial strains (part of healthy gut microbiota) that are known to produce SCFAs. These bacteria were transplanted into aged recipients three days after stroke, when the stroke-induced changes in the gut were at their peak. This strategy led to a significant increase in the concentration of SCFAs in both the gut and the brain, implying that these donor bacteria were able to recolonize the aged post-stroke gut. Transplantation of these selected SCFA-producing bacterial strains significantly improved neurological outcomes, host immune responses, and gut barrier integrity. To test whether changes in the levels of SCFAs were evident in the systemic circulation of stroke patients, we recently analyzed levels of several important SCFAs 24 hours after stroke. We found a dramatic decrease in SCFAs in the plasma of stroke patients compared to age-matched controls. Based on these findings, we believe that enhanced SCFA production could be a viable therapeutic target for the treatment of stroke.

Based on our current work, we believe that the relationship between the microbiome and the host represents a scientific frontier ripe for the development of a wide range of clinical therapies and interventional strategies. To date, very few studies have directly evaluated the effects of changes in the gut microbiome on stroke recovery. SCFAs may not be beneficial if directly administered, due to their short half-life. However, the clinical implications of our findings are clear. Transplanting bacteria that consistently produce these

beneficial microbial metabolites could be a new, effective approach to enhancing recovery in stroke patients.

About the Authors

Venugopal Reddy Venna, Ph.D. is an assistant professor of neurology at McGovern Medical School. After receiving his Ph.D. in neurosciences from the University of Lille, in France, he completed postdoctoral training at the University of Connecticut and was recruited to UTHealth in 2015. His work in the BRAINS research laboratory focuses on the development of therapeutics for stroke. He has published in a number of prestigious journals.

Bhanu Priya Ganesh, Ph.D. is an assistant professor of neurology at McGovern Medical School. She received her Ph.D. in gastrointestinal microbiology from the German Institute of Human Nutrition, a Leibniz institute in Potsdam-Rehbruecke, Germany. She completed her postdoctoral training at the Department of Pathology and Immunology, Baylor College of Medicine and joined UTHealth in 2018. Her research in the BRAINS laboratory focuses on identifying the molecular mechanisms involved in the gut-brain axis, with specific interest in age-associated diseases.

Louise D. McCullough, M.D., Ph.D. is the Roy M. and Phyllis Gough Huffington Distinguished Chair of the Department of Neurology at McGovern Medical School. A physician-scientist and leader in the field of stroke research, she has expertise in stroke/injury models, sex differences, behavioral analysis, hormone biology, flow cytometry, and translational stroke research. One of her current projects, using preclinical models, focuses on the influence of the gut's microbiome on the onset and progression of cerebral amyloid angiopathy and on stroke recovery. Dr. McCullough received an NINDS Javitz Neuroscience Investigator Award in 2017 to study how social isolation impairs stroke recovery. She also received the prestigious NINDS Landis Award for Outstanding Mentorship this year.

Upcoming Events

26th Annual Baylor / UTHealth / Rice Neuroscience Poster Session

Saturday, December 7, 2019, 9:30 a.m. to Noon

The UTHealth Cooley University Life Center, 7440 Cambridge St., Houston, TX 77054

Graduate Student Awards

1st place prizes for one graduate student from each department/center;
2nd and 3rd place prizes for the best posters of the entire group, independent of school attended

Postdoctoral / Research Fellow Awards

1st, 2nd, and 3rd place prizes will be awarded independent of school
For information and a link to registration form visit <https://med.uth.edu/nrc/education/annual-poster-session>.
Email us at UTHealth.NRC@uth.tmc.edu

UTHealth NRC and the McGovern Health Museum present

Brain Night for Kids

Thursday, March 19, 2020, 6 to 8 p.m.

McGovern Health Museum, 1515 Hermann Dr., Houston, TX 77004

This *free* annual event is part of international "Brain Awareness Week" and packed with exciting activities for kids!

Save the Date! UTHealth NRC 25th Annual Free Public Forum: *Innovative Brain Stimulation Strategies to Treat Neuropsychiatric Disorders*

Saturday, April 4, 2020, 10:30 a.m. to noon

The UTHealth Cooley University Life Center, 7440 Cambridge St., Houston, TX 77054

Joao de Quevedo, M.D., Ph.D., professor and director, translational psychiatry program, at McGovern Medical School Louis A. Faillace, M.D. Department of Psychiatry and Behavioral Sciences, will moderate a panel of leading UTHealth physicians and researchers on new treatment strategies for neuropsychiatric disorders.

Save the Date! UTHealth NRC 2020 Distinguished Lecture in the Neurosciences

Ed Boyden, Ph.D., Y. Eva Tan Professor in Neurotechnology at MIT

October 8, 2020, 12 p.m. at UTHealth McGovern Medical School Building, 3.001

Dr. Boyden leads MIT's Synthetic Neurobiology Group (syntheticneurobiology.org), which develops tools for analyzing and repairing complex biological systems such as the brain, and applies them systematically to reveal ground truth principles of biological function as well as to repair these systems.

We welcome notices of your neuroscience seminars, grand rounds, research colloquia, and conferences (sponsored by UTHealth, the Texas Medical Center, and area institutions) for our calendar (<https://med.uth.edu/nrc/eventcal/>). Please send the event name, contact details, date, time, and place to UTHealth.NRC@uth.tmc.edu.



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Questions? Comments?

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This Newsletter is distributed by mail to individuals and groups engaged in neuroscience research within the TMC and worldwide and features research, neuroscience accomplishments and outreach efforts performed at UTHealth. Past issues are available on the NRC website.

If you prefer to receive a digital copy through email, please contact UTHealth.NRC@uth.tmc.edu with your information.

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