Persistence in the Pursuit of Discovery

Talent, vision and education are necessary for success, but without persistence, they mean nothing. Almost eight years ago we began the initiative to develop an outstanding neuroscience group to serve the needs of the Greater Houston area. By the end of 2015, we had recruited 109 physicians, research PhDs, advanced practice providers, residents and fellows to Mischer Neuroscience Associates. Of these, the 94 clinicians are part of an expanding citywide neuroscience network. Today, the seeds we planted almost a decade ago are growing and ready to achieve full bloom, allowing us to turn to research with new intensity.

In a special research section, this issue of the Mischer Neuroscience Institute Journal explores a few of the ways in which physicians affiliated with Mischer Neuroscience Institute and McGovern Medical School at UTHealth are moving medicine forward into the future. They are developing the world’s first tele-robotic microsurgical tool and learning how the brain processes language. They’re investigating new treatments for cerebral vasospasm, Alzheimer’s disease, stroke and glioblastoma multiforme, and studying a radically new approach to chemotherapy for children that delivers agents directly to the site of brain tumors, decreasing systemic drug exposure.

This fiscal year also brought the arrival of our new chair of neurology at McGovern Medical School, Louise McCallough, M.D. As you will see in this issue, she brings with her a strong cerebrovascular research team and will be a great leader for our program.

With seed funding from generous donors, we have established two new research centers: the Will Erwin Headache Research Center and the National Center for Testing Treatments in Chronic Spinal Cord Injury and Traumatic Brain Injury (NCTT). Both centers are unique in their own way—The Will Erwin Center in its focus on cluster headaches and other intractable headaches, and the NCTT in its quest to improve the lives of people who have passed the acute phase of spinal cord injury and traumatic brain injury and are living with a lifelong condition.

We would like to take this opportunity to congratulate Dr. Arthur Day, who was recognized with the prestigious Harvey Cushing Medal; Dr. Bob Fayle, who was named physician of the year by the Texas Neurological Society; and Dr. Kimberly Monday, who was installed as the 2016 president of the Harris County Medical Society. We’d also like to welcome our new physician recruits: Wamda O. Ahmed, M.D.; Spiros Blackburn, M.D.; Angel Blanco, M.D.; Vishnu Brahmandam, M.D.; Robert J. Brown, M.D.; Mark J. Burish, M.D., Ph.D.; Sebastian Herrera, M.D.; Jeremy T. Ragland, M.D.; and Gary Spiegel, M.D.C.M.

We hope the neurosurgeons among you will join us for Grand Rounds on the Green, our 2016 Neurosurgery Symposium and Tournament, to be held in October in Sea Island, Georgia, with co-hosts Emory University School of Medicine and Washington University School of Medicine. Until then, we’ll keep moving forward in the spirit of discovery. If you would like to learn more about our services, research and programs, please feel free to contact us directly.

With best wishes,

DONG H. KIM, M.D.
Chief of Neurosurgery and Director, Memorial Hermann Mischer Neuroscience Institute at the Texas Medical Center
Professor and Chair, Vivian L. Smith Department of Neurosurgery, McGovern Medical School at UTHealth

“BY THE END OF FISCAL YEAR 2015, WE HAD RECRUITED 109 PHYSICIANS, RESEARCH PHDS, ADVANCED PRACTICE PROVIDERS, RESIDENTS AND FELLOWS TO MISCHER NEUROSCIENCE ASSOCIATES. OF THESE, THE 94 CLINICIANS ARE PART OF AN EXPANDING CITYWIDE NEUROSCIENCE NETWORK.”
After 10 years of growth, the Memorial Hermann Mischer Neuroscience Institute at the Texas Medical Center has become a strong clinical program and a leader in providing quality care. We now aim to place a strong focus on research, innovation and education of the physicians of the future.

In 2006, when the Mischer Neuroscience Institute was formed with a gift from Houston businessman and philanthropist Walt Mischer and his family, the department of Neurosurgery at McGovern Medical School at UTHealth was small with only nine clinical faculty members – of which six were neurosurgeons – and no neuroscience residency program or fellowships. Memorial Hermann’s neuroscience market share was only 12 percent. Today, the Institute has more than 100 clinical faculty and a market share that has doubled to 28 percent.

In the past eight years, the Institute has grown 150 percent in volume and reported dramatic reductions in neurosurgery mortality and morbidity, despite increasing patient acuity. A patient-centered approach to providing care has significantly improved patient satisfaction, achieving results above the 75th percentile at the hospital and 17 clinic locations.

An important component of this growth was the start of education programs. The Neurosurgery department was approved for a one-resident-a-year program in 2000, then two residents a year in 2010. Because neurosurgery training is seven years, we currently have 14 residents. In 2016, the program was allowed to match three residents. This unprecedented growth reflected a major commitment to education. Currently, one in three UTHealth medical students have a two-to-four week rotation on neurosurgery, and our ICU team sponsors eight neurocritical care fellows. This is in addition to the 23 residents and 11 fellows in the department of Neurology. “Teaching is at the heart of an excellent clinical program,” says Dr. Kim. “The best physicians want to train the next generation of physicians, so that the art continues to thrive and improve.

With this clinical infrastructure in place, with programs in every area of Houston, Dr. Kim has turned more of his focus to the discovery of new knowledge that will change the face of patient care. “We’re thinking much bigger about our future,” he says, “especially in terms of innovation that will change the standards of care,” he says. “There are many neurological diseases without effective treatments; our fondest hope is to restore function and improve lives.”

Clinical research is crucial to optimizing care and providing patients with new treatment options. A large number of clinical trials are being conducted at the Institute. In addition, the majority of our neuroscience patients participate in research by consenting to allow their tissue samples to be banked in the Institute’s Neuroscience Research Repository (NRR) for current and future research.

“We’ve found it to be incredibly beneficial to have patients collaborate with us in our research endeavors through programs like the NRR, which improves the care of future patients as well as their own,” Dr. Kim says. “And we continue this collaboration through the Innovation and Quality (IQ) Program, where researchers are testing novel treatments in clinical trials and transitioning the results of that research to clinical practice. As the IQ Program expands, we will design even more trials to help neuroscience patients reach their desired functional potential.”

“A key component of our mission is to design therapeutic intervention strategies that are successful not only in the laboratory but also have real clinical potential,” says Louise D. McCullough, M.D., Ph.D., who leads the Cerebrovascular Research Group and is professor and chair of the department of Neurology at the medical school. “To ensure that these strategies are on track from their inception through application, the Group works closely with the neurology and neuroscience services at Memorial Hermann-Texas Medical Center, as well as others at the Mischer Neuroscience Institute and The University of Texas Health Science Center at Houston. Targets identified in the lab are validated in clinical samples and translated back to animal models where manipulation in a controlled research environment is possible.”

In addition, through two new research centers created in 2014 – the Will Erwin Headache Research Center and the National Center for Testing Treatments in Chronic Spinal Cord Injury and Traumatic Brain Injury - leadership at the Institute has committed to invest in discovery in two areas that affect Americans profoundly.

“We can now track a range of outcomes across various subsets of our patient population,” Dr. Kim says. “We’re creating a rich data source that includes long-term outcomes and enables us to identify the best interventions for a particular condition. The data source is part of our ongoing efforts to improve patient care, ensuring that we are providing the best possible service and follow-up to our patients.”

Pain management is a strong focus at the Mischer Neuroscience Institute. Interventional pain management specialist Nadya Dhanani, M.D., treats a patient in her procedure room.

MEMORIAL HERRMANN-Texas Medical Center

MISCHER NEUROSCIENCE INSTITUTE APPROACHES MATURITY

MISCHER NEUROSCIENCE INSTITUTE

By the end of 2015, MNI has recruited over 100 physicians, advanced practice providers, PhDs and engineers

As physicians are recruited, expanded expertise allows a high level of support at multiple locations – including endovascular capabilities, continuous EEG monitoring, and neurosurgery

Ten new research centers created in 2013 – the Will Erwin Headache Research Center and the National Center for Testing Treatments in Chronic Spinal Cord Injury and Traumatic Brain Injury

Neurosurgery residency program started

Nationally recognized residency held appointments at McGovern Medical School at UTHealth

Focus on recruitment and program development to lay the foundation for the Institute

Neurosurgeon Dong Kim, M.D., recruited from Harvard to lead the new Houston

Gift from Houston businessman and philanthropist Walt Mischer and his family

FROM 2007 TO 2016, THE NEUROSCIENCE MARKET SHARE MORE THAN DOUBLED FROM 12% TO 28%

We’ve found it to be incredibly beneficial to have patients collaborate with us in our research endeavors through programs like the NRR, which improves the care
Louise McCullough didn’t plan on a career in medicine. As an undergraduate student at the University of Connecticut at Storrs, she changed her major several times before considering science as a profession. “I accepted a work-study job washing glassware in a research lab and found I liked the laboratory environment and the atmosphere of discovery,” says Dr. McCullough, the new co-director of the Memorial Hermann Mischer Neuroscience Institute at the Texas Medical Center and professor and chair of the Department of Neurology at the Texas Medical Center campuses. She is also an active neuroscientist and is internationally known for her work in understanding the cellular and molecular basis of gender differences in response to experimental brain injury. “Patti is the reason I became interested in sex differences in stroke,” Dr. McCullough says. “The move from residency or fellowship to your first faculty position is one of the toughest transitions you can make. When you’re establishing your practice, the burden of clinical care is high. You’re very vulnerable and need a good mentor to get your first independent research grant – someone who can help you package your ideas into successful grant proposals and give you protected time to get that first grant. In academic medicine that’s what we all worry about. Patti provided that support.”

After completing a fellowship in cerebrovascular disease/neurology and anesthesiology at Johns Hopkins, Dr. McCullough held faculty and hospital appointments at the same institution and the University of Connecticut, where she rose to the rank of professor. When she joined the Mischer Neuroscience Institute and McGovern Medical School in September 2015, she brought with her 20 people from her research group in Connecticut, including two experienced clinicians and three assistant professors with their own grant funding.

In addition to her administrative roles at the Mischer Neuroscience Institute and McGovern Medical School, she is a practicing vascular neurologist, heads the Cerebrovascular Research Group and is principal investigator on five grants from the National Institute of Neurological Disorders and Stroke. Her long-standing clinical and research interests are stroke care, acute stroke treatment, vascular physiology, neuro-inflammation, cerebrovascular disease, sex differences in stroke, aging and outcome assessment.

Dr. McCullough has been recognized with numerous awards during her clinical and academic career, and has been named to Best Doctors® continuously since 2007. She is the recipient of multiple grants from the National Institutes of Health, the National Institute of Neurological Disorders and Stroke, and the American Heart Association, and has authored more than 130 studies published in peer-reviewed journals. She has mentored many medical students, residents and junior faculty who now hold leadership roles in acute neurological programs throughout the country.

Because of her personal experience with mentors, education and mentorship continue to be a primary focus. “I want to get people who have an interest in science and technology involved in laboratory research early on,” she says. “It’s an important part of my job to make sure that people who have the capability and desire to do research are supported. We’re losing clinical investigators because of the time demands of practicing medicine and because funding is limited and very competitive. There’s quite a lot of value in translating bench research to patient care to enhance the human health and wellbeing.”

Among her long-term goals is an increase in the size of the neurology residency program at McGovern Medical School. “There are not enough neurologists practicing in Texas – or in the United States for that matter,” she says. “We’re all aging, which means that neurological conditions will become a larger societal burden. At Mischer Neuroscience Institute, we have one of the largest fellowship programs in the country, and Dr. Sean Savitz has developed a fantastic educational and research program for stroke. I’m hoping my translational program – the Cerebrovascular Research Group – will integrate well with the excellent programs that are already in place to provide the entire spectrum from the bench to the bedside and back to the lab. I want the faculty in our department to enhance the infrastructure and support they need to do the very best work, whether it’s patient care, community outreach, education or basic science research.”

“I’d also like to see integrate our efforts with other departments at the medical center and the university to enhance the experience of patients,” Dr. McCullough says. “Memorial Hermann and McGovern Medical School are providing outstanding support. Over the next year I hope to add even more to an already excellent neurological program.”

In addition to her administrative roles, Dr. McCullough is a practicing vascular neurologist, heads the Cerebrovascular Research Group and is principal investigator on five grants from the National Institute of Neurological Disorders and Stroke.
Physicians at the Memorial Hermann Mischer Neuroscience Institute at the Texas Medical Center and McGovern Medical School at UTHealth are engaged in innovative research efforts that are moving medicine forward into the future. The following studies are a few of those currently under way at the Institute.

The Will Erwin Headache Research Center Opens at the Mischer Neuroscience Institute

THE WILL ERWIN HEADACHE RESEARCH CENTER OPENS AT THE MISCHER NEUROSCIENCE INSTITUTE

The Will Erwin Headache Research Foundation has teamed up with the Mischer Neuroscience Institute and McGovern Medical School at UTHealth to fulfill its mission of bringing relief to the millions of people around the globe afflicted with debilitating headaches and facial pain syndromes, including migraines and cluster headaches. The foundation’s $20 million pledge — $2 million per year over 10 years — provided the initial funding to establish the Will Erwin Headache Research Center in the Vivian L. Smith Department of Neurosurgery.

The Will Erwin Headache Research Foundation was launched by Houston native Jimmy Erwin in memory of his son Will, who suffered from both migraines and cluster headaches. “This is a condition that impacts the lives of people all over the world,” says Erwin, president of the foundation. “It’s time for an organization to step up and fix the problem and that’s what we intend to do.”

Although debilitating headaches affect 12 percent of the American population, research directed toward finding a cure is significantly underfunded. In 2014, the National Institutes of Health earmarked $45 million of annual funding for headache research, which represents only 0.3 percent of the total $146 billion allocated to medical research. Within that small amount of funding, cluster headache research is especially undersupported.

Through its global fundraising efforts, the Will Erwin Headache Research Foundation aims to dramatically increase funding for the study of neurological disorders and, more importantly, to bring an end to the pain they cause.

“The new Will Erwin Headache Research Center has recruited a group of experts dedicated to the study of cluster headaches and conditions arising from the trigeminal nerve,” says Dong Kim, M.D., director of Mischer Neuroscience Institute and professor and chair of the Vivian L. Smith Department of Neurosurgery at McGovern Medical School. “The group will develop a national consortium of centers to identify patients with cluster headache and other debilitating types of headaches. Because of the relatively small number of patients in the Greater Houston area, a collaborative consortium is the best way to make progress in understanding and treating the disorders. The nationwide group will also work to educate other caregivers to improve diagnosis and treatment.”

The new Center is led by Mark Burish, M.D., Ph.D., a neurologist who is fellowship trained in interventional pain management. A cum laude graduate of Princeton University, Dr. Burish received his M.D./Ph.D. in the Vanderbilt Medical Scientist Training Program at Vanderbilt University School of Medicine and completed his residency in neurology at the University of California at San Francisco, where he was co-chief resident of the UCSF Moffitt-Long Service and was inducted into Alpha Omega Alpha Honor Medical Society. He completed his fellowship in interventional pain management in the department of Anesthesiology at UCSF.

Scientists and researchers working with the Will Erwin Headache Research Center include neurosurgeon Dong Kim, M.D.; researcher Georgene Hergenroeder, B.S.N., M.H.A., RN, CCRC; researcher Pramod Dash, Ph.D.; and genetic counselor Krista Qualmann, M.S.

“Cluster headache is a debilitating disease,” says Dr. Burish, an assistant professor in the Vivian L. Smith Department of Neurosurgery. “They can occur at any age but are most common in young adults, at a time when people are in school or just beginning their careers. They tend to run in families and affect more males than females, but to date, no one gene related to the disorder has been identified. We hope to make progress toward finding the cause and a cure.”

Physicians and researchers working with the Will Erwin Headache Research Center include neurosurgeon Dong Kim, M.D.; researcher Geogene Hergenroeder, B.S.N., M.H.A., RN, CCRC; researcher Pramod Dash, Ph.D.; and genetic counselor Krista Qualmann, M.S.

The Will Erwin Headache Research Foundation is a component fund of the Greater Houston Community Foundation and is a registered 501c3 organization. Donations can be made at cureheadaches.org.
“The human vocabulary is large, yet we are able to select the most appropriate words at very high speeds and assemble them in a way that conveys meaning,” says Dr. Tandon, a professor in the Vivian L. Smith Department of Neurosurgery at McGovern Medical School. “How we do so is not well understood. We do know that speech production relies on a distributed network that is disrupted in many people who suffer neurological disorders, including trauma, stroke, neurodegeneration and neoplasms, and that name production is the single most common deficit associated with speech impairment. Through our research we hope to gain real insight into how humans select the most appropriate words and put them together in a logical and understandable sequence.”

Until now, intracranial recordings have focused chiefly on the spatial and temporal characteristics of individual regions of the brain in isolation, with limited analysis of network behavior during language formation. The researchers believe that a network-based understanding of the dynamics of language regions is crucial to understanding the neural basis of word production. Using high spatial and temporal resolution direct cortical recordings, they aim to quantify the cortical dynamics involved in picture naming from early primary visual perception, through selection, to word output.

For the five-year study, which began in fall 2015, Dr. Tandon assembled a collaborative team of experts in intracranial EEG analysis, psycholinguistics and neural data modeling. They include Gregory Hickok, Ph.D., at the University of California, Irvine; Robert Knight at the University of California, Berkeley; Xuq Pitkow, Ph.D., at Rice University; and Joshua Breier, M.D., at Memorial Hermann-Texas Medical Center and McGovern Medical School.

“People often ask, ‘What does this do in the brain? What does that do?’ But nothing in the brain does anything in isolation. The areas that can load an abstract concept into a word and then tell your mouth to move are distributed throughout the brain. And they have to communicate with each other. We want the ability to intercept and translate those signals.”

While data collection will be limited to relatively few of the brain’s 100 billion neurons, it will be enough to advance knowledge of how they communicate with each other. “Each person can give us only a small sample of information, but if we get hundreds of people together, we’ll be able to gather enough data from all parts of the brain to make a composite map – an atlas – of brain function during speech production,” he says. Dr. Tandon says his motivation stems from the fact that each year 100,000 Americans suffer brain injuries that impair speech. “We hope one day to be able to provide wireless brain implants that will help these patients communicate via computer programs,” he says. “Using the incomplete language network that remains, these prosthetics could reconstruct speech and allow people to communicate their basic needs and emotions.”
Researchers in Houston – at Mischer Neuroscience Institute and McGovern Medical School at UTHealth – and at KAIST in South Korea are the frontrunners in an international race to develop the world’s smallest surgical robot. The new miniaturized tele-robotic system for microsurgery, designed in collaboration with KAIST, is small, mobile, versatile and agile – a model for the future of surgery.

"The da Vinci® Surgical System, the only medical robot in use today, is expensive and bulky," Dr. Kim says. "Designed for access through four small incisions, it lacks the small scale and flexibility needed to operate through a single port. Our new miniaturized tele-robotic system for microsurgery, designed in collaboration with KAIST, is small, mobile, versatile and agile – a model for the future of surgery."

The new miniaturized tele-robot allows physicians to move the system’s four arms to accommodate the patient and the procedure. Its frame fits on an existing operating table. Instrumentation is jointed – with wrists and elbows that allow additional degrees of motion – and miniaturized to allow for the use of four surgical instruments through a single incision. Unlike the current technology, which requires frequent replacement of expensive parts, each instrument may be removed for sterilization and reused. Dr. Kim and his team expect the robot to outperform the da Vinci in cost, stability and dexterity.

The researchers have taken the miniaturation of technology a step further and developed a steerable micro-robot that can maneuver through small spaces between organs in a snake-like motion. Only 10 millimeters in diameter, this "snake robot" has two tiny graspers, one microsurgical instrument and the world’s smallest lighted camera. The micro-snake has novel robotic clinical applications for fetal surgery, as well as for spine and cranial surgery.

"Our miniaturized robot will access sites deep in the body unreachable with other robotic devices. Tele-robotics will enable physicians anywhere in the world to treat patients anywhere in the world. This new technology is cost-effective and high impact."
A part of its growing research program, Mischer Neuroscience Institute recently established the National Center for Testing Treatments in Chronic Spinal Cord Injury and Traumatic Brain Injury (NCTT). The new Center is unique in its focus on research to improve the lives of people who have passed the acute phase of spinal cord injury (SCI) and are living with the injury as a lifelong condition.

“One once we’ve generated a database of patients whose recovery has plateaued and whose deficits are stable, we’ll be in a position to test treatment ideas systematically, one at a time in experimentally controlled circumstances. We believe our approach has the best chance of rapidly impacting patients’ lives.”

“While other national organizations focus their investigations on spinal cord injury and traumatic brain injury in the acute phase of treatment, the NCTT will focus on clinical trials for patients with chronic injury,” says Dong Kim, M.D., director of the Mischer Neuroscience Institute and professor and chair of the Vivian L. Smith Department of Neurosurgery at McGovern Medical School at UTHealth. “By freeing ourselves from the time pressure of identification and enrollment of patients in trials of potentially healing therapies. In addition to testing the hypotheses of our own researchers, we’ll be able to corroborate the discoveries of others by replicating them in the lab. Our great hope is to bring about significant functional improvement after SCI.”

Researchers at the NCTT are currently working with the Houston chapter of the National Spinal Cord Injury Association to create a database of chronic SCI and TBI patients in the Greater Houston area. “The database will include all of us in the area who are willing to be considered for trials for which we as individuals are particularly well suited based on the nature of our injury, its duration and our lifestyles,” Ogilvie says. “Once we’ve accomplished that, the NCTT will be in a position to clinically test its own discoveries and share the database with other researchers who want to replicate successes they’ve shown in their own labs. Ultimately, we’d like to find three or four other groups around the country to join us in creating their own geographic databases. There is great power in a national cross-referenced database that will allow researchers to connect with willing study participants who have been carefully selected as appropriate for a specific trial.”

The NCTT’s novel approach will complement acute intervention networks like the North American Clinical Trials Network (NACTN), of which the Mischer Neuroscience Institute is a member, and the Neurological Emergencies Treatment Trials (NETT), funded by the National Institutes of Health. Founded in 2004 with support from the Christopher and Dana Reeve Foundation, NACTN was initiated as a registry that would record the natural progression of acute SCI with the immediate goal of identifying and testing potential therapies and putting them to clinical use. To date, the network has tested only one agent, riluzole, in a safety study of 36 participants. NETT recently completed a study in acute TBI showing that progesterone was safe but provided no significant benefit to patients, despite success in numerous experiments using animal models.

Dr. Kim expects the NCTT’s plan to study chronic patients to be more cost effective by eliminating the need for on-call teams required in studies of acute SCI and TBI. “Patients can be enrolled in a small number of centers located around the country, instead of 20 or more as in NACTN and NETT,” he says. “A few researchers working systemically will be able to identify and classify many patients, allowing us to perform studies to better characterize and understand these patients. This is a huge, long-term endeavor to commit energy, talent and research dollars to help people with SCI and TBI recover and participate more fully in life.”
METHOTREXATE INFUSION DIRECTLY INTO THE FOURTH VENTRICLE IN CHILDREN WITH MALIGNANT FOURTH VENTRICULAR BRAIN TUMORS

Prior to his arrival in Houston in 2012, David J. Sandberg, M.D., FAANS, FACS, FAAP, conducted translational studies that demonstrated the safety of infusing chemotherapeutic agents directly into the fourth ventricle to treat children with recurrent malignant brain tumors in this location. The promising results of those studies led to a pilot clinical trial completed in August 2015 and a new methotrexate dose-escalation study available only at Children’s Memorial Hermann Hospital in collaboration with the Children’s Neuroscience Center at the Hermann Hospital in collaboration with the Mischer Neuroscience Institute.

“Now that we’ve determined that methotrexate can be infused into the fourth ventricle without causing neurological toxicity, and that some patients with recurrent medulloblastoma experience a beneficial anti-tumor effect both within the fourth ventricle and at distant sites, our next step is to determine the optimum dose of the agent.”

The pilot clinical trial was conducted at Children’s Memorial Hermann Hospital and The University of Texas MD Anderson Cancer Center, where Dr. Sandberg is co-director of the Pediatric Brain Tumor Program. Five patients – three with medulloblastoma and two with ependymoma – received 18, 18, 12, 9 and 3 cycles of chemotherapy, respectively, through a catheter surgically placed into the fourth ventricle and attached to a ventricular access device. No serious adverse events or new neurological deficits were attributed to treatment with methotrexate. The results were published in the Journal of Neuro-Oncology in 2015.1

The new dose-escalation study will enroll a minimum of 12 patients at Children’s Memorial Hermann Hospital. To date, three patients are participating in the clinical trial, the only such study under way in the world.

Delivering chemotherapeutic agents directly to the site of disease minimizes the side effects for children by decreasing systemic drug exposure, “Despite advances in pediatric oncology, we’re still seeing too many children die of malignant brain tumors, and the treatments currently available are not satisfactory for children,” says Dr. Sandberg, who is director of pediatric neurosurgery at Children’s Memorial Hermann Hospital and the Mischer Neuroscience Institute. “Now that we’ve determined that methotrexate can be infused into the fourth ventricle without causing neurological toxicity, and that some patients with recurrent medulloblastoma experience a beneficial anti-tumor effect both within the fourth ventricle and at distant sites, our next step is to determine the optimum dose of the agent.”


THE SEARCH FOR THE BEST INTRA-ARTERIAL TREATMENT FOR VASOSPASM

The neurosurgeon P. Roc Chen, M.D., is co-investigator of a multicenter randomized study aimed at finding the best intra-arterial medical treatment regimen for cerebral vasospasm, a devastating health problem and a major contributor to poor outcomes following subarachnoid hemorrhage (SAH). Dr. Chen is an associate professor in the Vivian L. Smith Department of Neurosurgery at McGovern Medical School at UTHealth, the lead center in the 12-site national study, which began in January 2015.

“Up to 70 percent of patients who survive the initial subarachnoid hemorrhage develop cerebral vasospasm, which if left untreated can lead to devastating strokes,” says Dr. Chen, who specializes in open cerebrovascular, endovascular and skull base neurosurgery and has expertise in the treatment of brain aneurysms, arteriovenous malformations, carotid disease, acoustic neuroma and skull base tumors. “Despite improvements in microsurgical and endovascular techniques, neurosurgeons have not made significant strides in the treatment of cerebral vasospasm.”

Endovascular treatments such as angioplasty and administration of intra-arterial drugs, particularly calcium channel blockers, are considered a standard treatment to reduce the potential for ischemic stroke from delayed cerebral vasospasm. The commonly used intra-arterial drugs are single agents: verapamil, nicardipine and nitroglycerin.

“But there is no conclusive literature suggesting which of the agents or combination of agents is the most effective, and treatment results have been generally unsatisfactory,” Dr. Chen says. “The estimated case fatality following a subarachnoid hemorrhage is 25 to 50 percent with a large proportion of these being secondary to the consequences of cerebral vasospasm. Our ability to optimize outcomes following severe vasospasm remains limited because we don’t fully understand the underlying pathogenesis.”

After a retrospective review of consecutive patients treated for cerebral vasospasm at Memorial Hermann-Texas Medical Center, the researchers concluded that treatment of cerebral vasospasm with an intra-arterial cocktail of nitroglycerine, verapamil and nicardipine provides significantly better angiographic improvement of vasospasm than single-agent therapy. The results were presented at the International Stroke Conference 2014, held in San Diego, California. Based on these results, Dr. Chen and the research team pursued their current study, a prospective evaluation of the efficacy of multi-agent vasodilator infusion therapy versus the current typical single-agent therapy. “We hope to determine the optimal intra-arterial drugs and the most effective regimen for treating cerebral vasospasm,” he says. “We also hope that combining these medications for intra-arterial infusion will lead to cerebral vasodilation and minimize the cardiovascular risks associated with a high dose of a single agent.”
Unraveling the Mysteries of Alzheimer’s Disease

Three new studies under way in the laboratory of Claudio Soto, Ph.D., are investigating potential new ways to diagnose and treat Alzheimer’s disease (AD). Dr. Soto directs a team of researchers focused on the investigation of the molecular basis of protein misfolding disorders, mainly AD, Parkinson’s disease and prion-related disorders.

“Aβ oligomers may be circulating in the body years, if not decades, before cognitive symptoms arise. We’re hoping the results generated by this project will detect them and lead to the first biochemical test for blood-based diagnosis of AD.”

“A hallmark event in AD is the misfolding of the amyloid-beta protein, which then is deposited in the brain in the form of amyloid plaques,” says Dr. Soto, a professor in the Department of Neurology at McGovern Medical School at UTHealth.

“These plaques, or some of the precursor misfolded oligomeric particles, are thought to cause neuronal death and synaptic loss, resulting finally in dementia.”

Over the past 20 years, Dr. Soto has focused his research on understanding the mechanism and factors involved in the conversion of a normal protein into the disease-associated abnormal form that accumulates in the brain to produce some of the most devastating neurodegenerative diseases. “Our studies combine basic science investigations with a permanent effort to translate these discoveries into novel approaches for early diagnosis and treatment,” he says.

With a new grant from the National Institutes of Health, Dr. Soto and his team are investigating a blood-based diagnosis for AD. A fast-track combined phase I and II Small Business Technology Transfer (SBTTR) project in partnership between Ampron, Inc. and the McGovern Medical School, the project may offer a way to diagnose AD before extensive brain damage and dementia set in.

“For this purpose we’re adapting the protein misfolding cyclic amplification (PMCA) technology invented in our lab for specific and highly sensitive detection of misfolded Aβ oligomers in human blood,” Dr. Soto says. “Aβ oligomers may be circulating in the body years, if not decades, before cognitive symptoms arise. We’re hoping the results generated by this project will detect them and lead to the first biochemical test for blood-based diagnosis of AD.”

Dr. Soto is also principal investigator in two studies funded by UTHealth Brain Initiative Awards: “Chimeric Mice Harboring Human Nerve Cells as a Model of Alzheimer’s Disease” and “Traumatic Brain Injury Promotes Alzheimer’s Disease Through Seed Formation.” The first study, conducted in collaboration with Brian Davis, Ph.D., of the Brown Foundation Institute of Molecular Medicine for the Prevention of Human Diseases, aims to develop new models of AD by grafting into the mouse brain human-derived cells from healthy individuals, as well as from AD patients affected by inherited and sporadic forms of the disease. Human nerve cells have been generated in Dr. Soto’s lab by reprogramming adult fibroblast into induced pluripotent stem cells, and were later converted into different types of neurons. “Our working hypothesis is that chimeric mice harboring human nerve cells will reproduce the complete cerebral abnormalities observed in AD patients,” he says. “As a result, chimeric mice may be more relevant and predictable models of AD and may become great tools to investigate the molecular bases of neurodegenerative processes. This model may also help us discover new pharmaceutical targets and biomarkers for the much-needed development of new drugs to treat or even prevent the onset of the disease.”

In the second UTHealth Brain Initiative study, Dr. Soto and his team, in collaboration with Pramod Dash, Ph.D., of the Department of Neurobiology and Anatomy, posit that traumatic brain injury induces the formation of the first misfolded oligomeric seeds composed of either or both amyloid-beta and Tau protein, which then spread the pathology throughout the brain by a prion-like mechanism, resulting in the development of AD. They will test the theory in various transgenic mouse models.

The research has the potential to change the face of diagnosis and treatment of AD. “Alzheimer’s disease is the most common form of dementia in late life, and at present it does not have a cure or an effective treatment,” Dr. Soto says. “It is a leading cause of death in the developed world and currently affects more than 10 million people worldwide. Its treatment is hampered by the lack of early, sensitive and objective laboratory tests. We hope to change that.”
Chromosomal and Hormonal Contributions to Sex Differences in Ischemic Stroke

Recent clinical trials have shown variable effectiveness of medications in male and female patients, suggesting that sex-specific therapeutic targets may improve physicians’ ability to treat stroke patients of both sexes. Funded by a $2.2 million grant from the National Institute of Neurological Disorders and Stroke, Louise D. McCullough, M.D., Ph.D., and her team are conducting laboratory research to determine genetic and hormonal contributions to stroke sensitivity across the lifespan. Their ultimate aim is to translate basic science findings to bedside care that improves recovery from stroke.

There is considerable evidence from both clinical and experimental studies that outcomes after stroke differ in males and females,” says Dr. McCullough, who is co-director of the Memorial Hermann Mischer Neuroscience Institute at the Texas Medical Center, professor and chair of the department of Neurology and head of the Cerebrovascular Research Group at McGovern Medical School at UTHealth.

“New experimental data has shown that outcomes after stroke differ in males and females,” says Dr. McCullough, a physician-scientist with a long-standing interest in vascular physiology, neuro-inflammation, cerebrovascular disease, sex differences in stroke, and aging. “Reproductive hormones clearly contribute to the differences, but we know that biologic sex is also a factor based on our studies of tissue damage and functional outcome after induced stroke in an animal model. In addition, emerging data have shown that the mechanisms that trigger cell death differ in males and females.”

Using genetically manipulated mice, the researchers aim to dissociate the effects of chromosomal sex from that of hormones on stroke outcome in young animals, determine the effect of manipulating neonatal hormone levels on adult infarct damage and investigate sex and hormone contributions to post-stroke inflammation in the mice using a well-established middle cerebral artery occlusion model of stroke.

“Identification of sex-selective cell death mechanisms has significant translational relevance, as neuroprotective agents that are effective in one sex may actually exacerbate the injury in the other,” Dr. McCullough says. “We hope to better define these differences and develop sex-specific therapies that will result in better outcomes in stroke patients of both sexes.”

Dr. McCullough and her team are conducting laboratory research to determine genetic and hormonal contributions to stroke sensitivity across the lifespan. Their ultimate aim is to translate basic science findings to bedside care that improves recovery from stroke.

Identifying Novel Molecular Targets for Chronic Spinal Cord Injury

Recent advances in RNA-sequencing technology make it possible to map affected regions and analyze gene expression at an unprecedented level of sensitivity and specificity.

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“The majority of patients with spinal cord injury are in the chronic phase, which remains the most difficult to treat,” says Dr. Wu, an assistant professor in the Vivian L. Smith Department of Neurosurgery and Center for Stem Cell and Regenerative Medicine at the McGovern Medical School at UTHealth. “Our understanding of how molecules that hinder axon regeneration are regulated and maintained in the chronic SCI state remains unclear. Current treatment for gliosis – the reactive change of glial cells in response to injury – is not ideal, and new molecular targets are urgently needed.”

Previous molecular studies of SCI have focused on a small number of genes in pathways at a time, failing to provide a comprehensive view of the complex mechanisms underlying SCI pathology. “Microarray studies done during the past decade have provided valuable insights into SCI, but the technique has limitations in resolution, range and accuracy,” she says. “Recent advances in RNA-sequencing technology make it possible to map affected regions and analyze gene expression at an unprecedented level of sensitivity and specificity. Based on our preliminary studies using RNA-sequencing during the acute and sub-acute phases of SCI in mouse models, we believe that investigating the intricate relationship of genes and pathways in spinal cord tissue will give us a better understanding of the progression of SCI pathophysiology.”

The researchers also believe that by using the innovative strategy of integrated network analysis, they can identify critical missing links in disease processes that have not been previously noted. “We hope that the discovery of novel molecular targets will shift the research and clinical paradigms for spinal cord injury,” she says. “We also expect to create a comprehensive data resource of SCI gene expression that will be valuable to the research community.”
with funding from the National Cancer Institute, principal investigator Jay-Jiguang Zhu, M.D., Ph.D., is leading a phase II/III clinical trial studying the efficacy of veliparib with temozolomide compared to temozolomide alone in treating patients with glioblastoma multiforme (GBM) or gliosarcoma. The trial is currently enrolling patients at the Memorial Hermann-Texas Medical Center and the Mischer Neuroscience Institute at the Texas Medical Center and McGovern Medical School at UTHouston.

**Drugs used in chemotherapy, such as temozolomide, work in different ways to stop the growth of tumor cells, either by interfering with DNA replication of the cells, by spirits from dividing or by stopping them from spreading,** says Dr. Zhu, director of neuro-oncology at the Mischer Neuroscience Institute and an associate professor in the Vivian L. Smith Department of Neurology, McGovern Medical School at UTHealth.

**“During a phase I study, DM-CHOC-PEN demonstrated the capability of high CNS penetration to inhibit or halt the development of tumors in patients with advanced cancers, including melanoma, lung cancer and breast cancer involving the central nervous system, and glioblastoma multiforme,” says Dr. Zhu, who is fellowship trained at Massachusetts General Hospital and focuses his practice on primary brain tumors and primary central nervous system (CNS) lymphomas, as well as brain metastases and leptomeningeal spread of systemic malignancies. “These findings support the preclinical responses seen in mice, and no hematological, renal or cardiovascular toxicities or cognitive impairment was noted in the phase I human trial or in previous preclinical studies.” The trial is open to patients with advanced lung, breast and melanoma cancers that have spread to the central nervous system as well as those with primary CNS malignancies. The expected study completion date is August 2016.**

Two other trials led by Dr. Zhu are ongoing but not currently enrolling participants. A phase III multicenter, randomized, controlled trial is testing the efficacy and safety of a medical device called Novo TTF-100A for newly diagnosed GBM patients in combination with temozolomide, compared to temozolomide alone. The device, which patients wear on their scalp, provides a constant, safe, low-voltage electric field that has been shown to reduce tumor cell survival and division capacity. The device was approved by the FDA for progressive GBM in April 2011. The interim analysis of the trial data showed significant improvement of progression survival time and overall survival duration in participants randomized to the treatment arm of the study. Based on this trial result, the FDA approved the device for newly diagnosed GBM in October 2015. The expected study completion date is July 2016.

In addition, he is leading an open-label phase I/II (safety lead-in) study of trans sodium crocetinate (TSC) with Connecticut treatment of fractionated radiation therapy and temozolomide in newly diagnosed GBM patients. The trial examines the safety and efficacy of TSC as a radiation sensitizer for the treatment of malignant tumors. The study is ongoing but not currently recruiting patients.

Dr. Zhu was also principal investigator in a randomized, double-blind, controlled phase IIIB clinical trial testing the safety and efficacy of the vaccine ICT-107 for newly diagnosed GBM patients following resection and chemoradiation. The trial, which began enrollment in August 2011 and was completed in December 2015, showed improved, progressive-free survival of patients who were human leukocyte antigen (HLA) A2 positive. HLA genes are key to the activity of the immune system in identifying the body’s own proteins versus proteins of foreign origin. A phase III trial for HLA A2 positive GBM patients has just opened at Memorial Hermann-TMC, and patients are now being enrolled.

Sigmund Hsu, M.D., who is fellowship trained at The University of Texas MD Anderson Cancer Center, is principal investigator in several studies, including in the trial of a novel taxol chemotherapy compound, TPI 287, which crosses the blood-brain barrier and will be administered in combination with bevacizumab, versus bevacizumab alone in adults with recurrent glioblastoma. In addition, he is leading a phase II dose-escalation study of TPI 287 in combination with bevacizumab in adults with recurrent or progressive glioblastoma following a bevacizumab-containing regimen.

Both studies are aligned with Dr. Hsu’s clinical and research interests in the discovery of new and more effective therapies for patients with primary brain tumors, treatment of metastatic cancer to the brain and spinal cord, and the evaluation and treatment of neurological problems in cancer patients.

**INVESTIGATING NEW TREATMENTS for Patients with Glioblastoma Multiforme**

**Open and Upcoming Brain Tumor Trials**

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Neurologist Louise D. McCullough, M.D., Ph.D., co-director of the Mischer Neuroscience Institute and professor and chair of the department of Neurology at McGovern Medical School, is a physician-scientist with a long-standing interest in vascular physiology, neuro-inflammation, cerebrovascular disease, sex differences in stroke, and aging. A practicing vascular neurologist, she has clinical expertise in stroke aging. A practicing vascular neurologist, she has clinical expertise in stroke

Eighty-odd years since 2007. She is the recipient of numerous academic awards, Dr. Blackburn has lectured nationally and internationally on topics in radia- oncology, and has authored three textbook chapters and 30 articles and abstracts in peer-reviewed medical journals. He serves as a reviewer for the International Journal of Radiation Oncology, Biology, Physics, Journal of Radiation Oncology, and Radiotherapy and Oncology.

WAMDA O. AHMED, M.D. Associate Professor, Department of Neurology and Vivian L. Smith Department of Neurology, McGovern Medical School at UTHealth

Eleven physicians have joined the medical staff of the Memorial Hermann Mischer Neuroscience Institute at the Texas Medical Center and the faculty of McGovern Medical School at UTHealth.

SPRIS BLACKBURN, M.D. Associate Professor, Vivian L. Smith Department of Neurology, McGovern Medical School at UTHealth

ANGEL I. BLANCO, M.D. Director, Radiation Oncology and Stereotactic Radiosurgery, Mischer Neuroscience Institute; Assistant Professor, Vivian L. Smith Department of Neurology and Department of Neurosurgery, McGovern Medical School at UTHealth

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Spires Blackburn, M.D., specializes in cerebrovascular, skull base surgery and endovascular neurosurgery. A summa cum laude graduate of Old Dominion University in Norfolk, Virginia, Dr. Blackburn received his medical degree at The University of Texas Southwest Medical School in Dallas. After concluding his residency as chief resident in neurosurgery at Washington University in St. Louis, he completed a cerebrovascular fellowship at Emory University in Atlanta and a neurointerventional fellowship at Mallinckrodt Institute of Radiology at Washington University. Prior to joining Mischer Neuroscience Associates, he held a faculty appointment as assistant professor of neurosurgery at the University of Florida in Gainesville.

The recipient of numerous academic awards, Dr. Black- burn has lectured nationally on the management of cere- bral aneurysms, surgical anatomy, arteriovenous malforma- tions and stroke, and his research has been published in peer-reviewed journals. His clinical research interests include biomarkers for cerebral vasospasm and translational research for patients with subarachnoid hemorrhage, as well as a number of clinical trials for the treatment of brain aneurysms. He is an associate professor in the Vivian L. Smith Department of Neurosurgery.

VISHNU BRAHMANDAM, M.D. Neurologist, Mischer Neuroscience Associates The Woodlands

Robert J. Brown, M.D., is a diplomate of the American Board of Psychiatry and Neurology and of the United Council for Neurologists at St. Louis. He specializes in neurocritical care and neurology.

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Joseph Martinez, M.D., is a neurological surgeon who specializes in the treatment of spine disorders. Dr. Martinez received his medical degree at the University of New Mexico School of Medicine in Albuquerque. He completed his neurological surgery training at Baylor College of Medicine and the University of Texas MD Anderson Cancer Center, followed by a fellowship in complex spine surgery at the University of Miami in Miami, Florida.

Gary Spiegel, M.D.C.M., is fellowship trained in surgical neuroangiography and diagnostic neuroradiology. His practice encompasses the full scope and breadth of adult and pediatric neurointerventional treatments for brain, spine, head and neck conditions, with a focus on endovascular treatments for brain aneurysms, brain and spinal arteriovenous malformations and stroke.

An associate professor of neurological surgery and director of neurointerventional surgery at McGovern Medical School, Dr. Spiegel earned his medical degree at McGill University in Montreal, Canada. After completing his residency in diagnostic radiology at New York University Medical Center in New York City, he completed fellowships in neuroradiology and surgical neuroangiography at the same institution. Upon entering professional practice, he initiated and directed neurointerventional surgery programs at Yale University’s Hospital of Saint Raphael in New Haven, Connecticut, and later at Hartford Hospital, where he co-directed the Stroke Center. Dr. Spiegel’s efforts led the Hartford Hospital Stroke Center to become the most active acute stroke care and endovascular aneurysm treatment center in New England. He has held teaching appointments at Yale-New Haven Hospital in New Haven, Connecticut, and at the University of Connecticut’s John Dempsey Hospital in Farmington, Connecticut.

Mark your calendars for a weekend of golf and continuing medical education at Grand Rounds on the Green, to be held Oct. 14-16, 2016, in Sea Island, Georgia. Hosted by Memorial Hermann Mischer Neuroscience Institute at the Texas Medical Center and McGovern Medical School at UTHealth, Emory University School of Medicine and Washington University School of Medicine, this intimate gathering will be held at The Cloister at Sea Island and its sister hotel, The Lodge at Sea Island.

For more information about the event, visit neuro.memorialhermann.org/events/sea-island.

Dr. Jeremy T. Ragland, M.D., is a board-certified, fellowship-trained pediatric neurosurgeon and pediatric neurocritical care specialist. He completed his neurological surgery residency and fellowship in neurocritical care at the same institution. He is a member of the American Academy of Neurology and the Neurocritical Care Society and an assistant professor in the Vivian L. Smith Department of Neurosurgery.

Dr. Ragland says: “Many world-renowned, well-respected physicians have received this award in the past, and it is deeply humbling to be added to a group with such great medical legacies.”

Dr. Day is a board-certified, fellowship-trained neurosurgeon with specific expertise in cerebrovascular and skull base neurosurgery. He also specializes in microsurgical treatment of brain tumors and minimally invasive spinal surgery.

It is an honor to be recognized with the Harvey Cushing Medal,” Dr. Day says. “Many world-renowned, well-respected physicians have received this award in the past, and it is deeply humbling to be added to a group with such great medical legacies.”

Dr. Day is an expert in cerebral and skull base neurosurgery, the microsurgical treatment of brain tumors and minimally invasive spinal surgery.
by the Texas Neurological Society. The society promotes the interest of patients with neurologic disease by supporting the development and delivery of quality medical care to these patients.

Board-certified in adult neurology and sleep medicine, Dr. Fayle is a past-president of the Texas Neurological Society and currently serves as chair of the organization’s Education Committee. He has held multiple leadership positions with the Texas Neurological Society, the Houston Neurological Society, the American Academy of Sleep Medicine, the Diagnostic and Therapeutic Neurosurgical Society, the Parkinson’s Disease Foundation, and the Texas Society of Neurological Surgeons.

Dr. Fayle received his medical degree at the University of Texas Health Science Center at Houston and completed his residency in neurology at UTHealth-affiliated hospitals in Houston. The Harvey Cushing Medal is presented to “a scientist in the field of sleep and stroke, including sleep medicine, and their role in the development and delivery of quality medical care.” Dr. Fayle, who is on the medical staff at Memorial Hermann Southeast Hospital, provides neurology consultations and care at Memorial Hermann’s Milikin-Bard and White Oak Hospitals. He has received multiple awards and honors, including being named one of the Best Doctors in America®. Dr. Fayle has published more than 170 journal articles and book chapters, and co-edited two books about neurological sports injuries.

The Harvey Cushing Medal is sponsored by the MISCHER NEUROSCIENCE INSTITUTE.
Selected Publications

July 2015 to June 2016


For more information about the Mischer Neuroscience Institute or to sign up for our communications, email us at mni@memorialhermann.org.