In the Lab

Steady Progress
Parkinson’s research center focuses on fall prevention

Up to 70 percent of Parkinson’s patients fall each year, often leading to injuries such as hip fractures and long-term hospital stays. Now, U-M researchers and physicians are discovering that the solution for this debilitating problem may lie in a previously unexplored chemical system in the brain.

The research team has launched a five-year study focusing on the cholinergic system, which plays a role in our concentration on tasks such as walking. Traditionally, Parkinson’s disease research and treatment has focused on the brain’s dopamine system, which helps control movement and is damaged in the disease. But research by Nicolaas Bohnen, M.D., Ph.D. (Residency 1998), a U-M professor of radiology and neurology, suggests that the loss of cholinergic nerve cells robs patients who are already having trouble walking safely of the ability to pay close attention to their movements. The involvement of the cholinergic system likely explains why current treatments — focused on dopamine replacement — are ineffective.

“Understanding the role of the cholinergic system... will allow us to go beyond the limits of current practice, so we can create better therapies to suppress the terrible symptoms of the disease that affect balance, walking and overall independence,” says William Dauer, M.D., who directs the UMHS Movement Disorders Program and is the Elinor Levine Professor of Dementia Research and an associate professor of cell and developmental biology at the U-M Medical School. This research is funded by an $11.5 million grant from the National Institute of Neurological Diseases and Stroke. With this grant, U-M is now home to a Morris K. Udall Center of Excellence — one of only nine in the country — of which Dauer will serve as director. Udall Centers bring together researchers from many fields to tackle big questions in Parkinson’s disease, to educate the next generation of researchers and to serve as a vital resource for patients with the disease. The U-M Udall Center team includes Medical School physicians who treat Parkinson’s patients at both the U-M Health System and the VA Ann Arbor Healthcare System and study the disease in their labs. A neuroscientist in the College of Literature, Science & the Arts and biostatisticians from the schools of Nursing and Public Health also contribute to the center.

The team will conduct three projects to better understand the role of the cholinergic system in falls, focusing on the effect of lost cholinergic neurons in brain areas called the basal forebrain, which regulates attention, and the pedunculopontine nucleus, or PPN, which controls balance. The team will study this effect in both rats and people to determine if it’s possible to increase cholinergic traffic in the brain using a drug that targets acetylcholine receptors on the surface of brain cells. That drug, varenicline, or Chantix, is already available to help people stop smoking.

Additionally, researchers will work to develop personalized medicine approaches to Parkinson’s disease using specialized brain scanning and varenicline, an effort led by Dauer and Roger L. Albin, M.D. (Residency 1986, Fellowship 1988), the Anne B. Young Collegiate Professor of Neurology and Udall Center associate director. The center will partner with the Michigan Alzheimer’s Disease Center for minority outreach efforts, and run a Udall Center Fellows program, co-funded by the Medical School and the Department of Neurology, allowing physicians and physician-scientists to receive two years of intensive training and participate in center research. -KG
Kresge Researchers Repair Hearing in Noise-Deafened Mice

Researchers from the University of Michigan’s Kresge Hearing Research Institute and Harvard University have restored hearing in mice deafened by noise, paving the way for therapies to treat human hearing loss caused by noise exposure and aging. Their findings, published in the online journal eLife, zero in on a key protein in the ear called NT3. This protein is crucial to the body’s ability to form connections between hair cells in the ear and the nerves that carry sound signals to the brain. This special type of connection is called a ribbon synapse.

“There is growing consensus that damage to the ribbon synapses by noise or normal aging is an important contributor to hearing loss,” says Gabriel Corfas, Ph.D., director of the Kresge Institute and professor and associate chair in the U-M Department of Otolaryngology-Head and Neck Surgery, who began the research at his former institution, Harvard University.

Using a special genetic technique, the researchers made it possible for some mice to produce additional NT3 in cells of specific areas of the inner ear after they were exposed to noise loud enough to reduce hearing. Mice with extra NT3 regained their ability to hear much better than the control mice. Corfas says the next challenge is to study NT3’s role in making and maintaining ribbon synapses in human ears, and to look for drugs that can work like NT3 does. Boosting NT3 production through gene therapy in humans could also be an option, he says, but a drug-based approach would be simpler and could be administered as long as it takes to restore hearing. –KG

MORE ON THE WEB

Study: Brain Wiring Differs in ADHD

A Study from the U-M
Department of Psychiatry found that connections between brain networks are slower to develop in children and teens with attention deficit hyperactivity disorder.

The new findings, and the methods used to produce them, could bring doctors closer to using brain scans to help diagnose ADHD—and track response to treatment.

Using advanced computer techniques, the researchers analyzed brain scans that were publicly shared for scientists to study. Lead author Chandra Sripada, M.D., Ph.D. (Residency 2009), assistant professor of psychiatry, and research computer specialists in his lab, Daniel Kessler and Michael Angstadt, found lags in the development of connections between brain networks that underlie internally directed thought and networks that support externally focused tasks in youths with ADHD.

“We want to examine this phenomenon in a more fine-grained way that might lead us to a true biological marker, or neuromarker, for ADHD,” Sripada says. He has embarked on follow-up research to develop such a neuromarker, recruiting children, teens and young adults with ADHD. Anyone interested in these studies can contact psych-study@med.umich.edu or 734-232-0353. –KG

MORE ON THE WEB

This microscope image of tissue from inside a normal mouse ear shows how ribbon synapses (red) form the connections between the hair cells of the inner ear (blue) and the tips of nerve cells (green) that connect to the brain.
In the Clinic

A One-Two Punch for Tumors?
Trial tests new gene therapy

UNIVERSITY OF MICHIGAN DOCTORS are testing a unique approach to fighting brain tumors — one that delivers a one-two punch designed to knock out the most dangerous type of brain cancer.

The experimental approach, based on U-M research, delivers two different genes directly into the brains of patients following the operation to remove the bulk of their tumors. The idea: trigger immune activity within the brain itself to kill remaining tumor cells — the ones neurosurgeons can’t take out, which make this type of tumor so dangerous.

One of the genes is designed to kill tumor cells directly and is turned on when the patient takes a certain drug. The other gene spurs the body’s own immune system to attack remaining cancer cells. Both are delivered into brain cells via a harmless virus.

It’s the first time this gene therapy approach is being tried in humans, after more than a decade of research in experimental models. Three patients have already been treated as part of the trial.

All patients in the study must have a presumptive diagnosis of WHO grade 3 or 4 malignant primary glioma, such as glioblastoma multiforme. Patients must not have been treated yet by any therapy. They must also meet other criteria for inclusion in the trial.

More patients will be able to enroll at a pace of about one every three weeks, through a careful selection process.

In addition to surgery and gene therapy at U-M, each will receive standard chemotherapy and radiation therapy and follow-up assessments for up to two years.

“We’re very pleased to see our years of research lead to a clinical trial, because based on our prior work we believe this combination of cell-killing and immune-stimulating approaches holds important promise,” says principal investigator Pedro Lowenstein, M.D., Ph.D., the U-M Department of Neurosurgery professor who has co-led the basic research effort to develop and test the strategy. Lowenstein is also the Richard Schneider Collegiate Professor of Neurosurgery and a professor of cell and developmental biology. Co-leader Maria Castro, Ph.D., the R.C. Schneider Collegiate Professor of Neurosurgery and professor of cell and developmental biology, notes that the patients who agree to take part in the Phase I trial will be the first in the world to help establish the safety of the approach in humans.

“Without them, and without our partners on the U-M neurosurgery team and donors to the Phase One Foundation who support our work, we wouldn’t be able to take this important step in testing this novel therapeutic approach.” —KG
New EVPMA Joins U-M

ON MARCH 1, MARSCHALL S. RUNGE, M.D., PH.D., joined the University of Michigan as executive vice president for Medical Affairs. Previously, Runge was executive dean for the University of North Carolina School of Medicine, a professor and chair of the Department of Medicine at UNC-Chapel Hill, and principal investigator and director of the NIH-funded North Carolina Translational and Clinical Sciences Institute.

An honors graduate of Vanderbilt University with a B.A. in biology and a Ph.D. in molecular biology, Runge earned his M.D. from the Johns Hopkins School of Medicine, where he was an intern and resident in internal medicine. He then completed a cardiology fellowship at Harvard’s Massachusetts General Hospital and was a faculty member there prior to moving to Emory University as an associate professor of medicine in 1989. Before joining the UNC faculty in 2000, Runge held the John Sealy Distinguished Centennial Chair in Internal Medicine and was Director of the Division of Cardiology and the Sealy Center for Molecular Cardiology at the University of Texas Medical Branch at Galveston.

“I am very pleased to be selected to lead such a highly regarded academic medical center,” Runge says. “I believe Michigan is uniquely positioned and has the best opportunity among academic health centers to not only thrive during this time of dramatic change, but also to direct change in academic medicine.” —RF

Study Shows Promise of Telemedicine

A RECENT MICHIGAN-LED STUDY HIGHLIGHTS THE potential of telemedicine to improve the management of chronic disease, while addressing problems of inequitable access to care, uneven distribution of quality of care and rising health care costs.

Rashid Bashshur (Ph.D. 1962), professor emeritus in the Department of Health Management and Policy in the School of Public Health and executive director of the UMHS eHealth Center, led a national team of clinicians and researchers in the study titled “The Empirical Foundations of Telemedicine Interventions for Chronic Disease Management.” They found that the use of telemedicine, or telemonitoring, in managing heart failure, stroke and chronic obstructive pulmonary disease, or COPD, resulted in: fewer hospital readmissions and shorter hospital stays; fewer emergency department visits; faster initiation of appropriate treatment in the case of stroke; less exacerbations in the case of COPD; and longer life expectancy. Bashshur notes that such benefits may not be fully accrued by frail elderly patients with co-morbid conditions who lack physical dexterity for electronic technology.

The team published their study in Telemedicine and e-Health, and Bashshur also presented the findings to both Houses of the U.S. Congress and the Congressional Budget Office earlier this year.
In the School

Chronicling Childhood Cancer
Medical student publishes patient stories

THE FACE IN THE DRAWING IS SPLIT down the middle. The left side is red, horned and grimacing. The right: yellow, haloed, smiling. “Cancer is half and half,” writes the artist — Jacob, age 15 — at the bottom of the page. University of Michigan medical student Trisha Paul holds out the picture.

“This patient talks about how cancer is an angel and a devil, which is very powerful,” she says.

Jacob’s story is one of 10 collected by Paul, a 2018 M.D. candidate, and published in the new book *Chronicling Childhood Cancer: A Collection of Personal Stories by Children and Teens with Cancer*. The young authors were all at different stages with cancer at C.S. Mott Children’s Hospital. Some were newly diagnosed, many undergoing treatment, some in remission, and others had relapsed. Their words and drawings present first-person perspectives on living with childhood illness.

When Paul started as a 16-year-old volunteer at Mott, she wasn’t sure what to expect. She accepted a position at the inpatient playroom, visiting weekly through her undergrad years at U-M. She became increasingly curious about the patients’ perspectives as she interacted with them. “I came to wonder how children understand and cope with this mysterious, complex illness,” she writes in the book’s preface.

Paul was a junior English major at Michigan when she came up with the idea to collect patient stories for her honors thesis in English. She shared the idea with Rajen Mody, M.D., M.S. (Fellowship 2000), a pediatric oncologist at Mott and a U-M associate professor of pediatrics and communicable diseases, who encouraged her to pursue the project and later wrote the foreword for the book. With additional assistance from Mott’s Child Life specialists, the patients’ families and her English thesis advisor, Paul interviewed over 30 pediatric patients the summer before her senior year. Paul believes studying literature helped prepare her for a career in medicine.

“As I was studying English, I could feel myself becoming more aware of how I was interacting with people,” she explains. “This project reiterated to me the importance of language, specifically within medicine, and how important it is to make space for patients to share their own stories.”

With crayons, pencils, pens and markers, the children expressed sadness, pain and loss. They also expressed pride, friendship — even playfulness. In one pencil drawing, 12-year-old Shannon smiles alongside her cousin, who accompanied her to chemotherapy. They’re wearing flowing capes and fancy hats. “We were allowed to dress up,” Shannon writes.

Reflecting upon the project, Paul says, “I think one of the biggest take-home messages for me was to realize how differently children perceive their disease. The amount of variation in how they define cancer and how they cope with cancer was just incredible to me.”

The book was published by Medical School Information Services Learning Design and Publishing and released through Michigan Publishing in September, with proceeds supporting two programs at Mott: the Block Out Cancer campaign for pediatric oncology research and the Child and Family Life Program. Paul’s book is available on Amazon and at Bookbound bookstore in Ann Arbor. Content can also be accessed online at the Open.Michigan repository. —SARA TALPOS
U-M Residency Programs Lead in National Ranking

The University of Michigan residency programs rank among the best in nation, according to a national survey compiled by the physician network Doximity and U.S. News & World Report. In this first-ever comprehensive national evaluation of residency programs, the U-M Health System was recognized as a top place for young doctors to train in their chosen field across all 20 medical specialties included in the rankings. In 12 of those specialties, the U-M ranked in the top 10. In three specialties — otolaryngology, pathology and surgery — U-M ranked No. 1 in the country for large public hospitals.

The rankings were chosen from over 50,000 physician peer nominations, based on their answers to a survey about the best residency programs in their specialty. Each could name up to five. Nearly 3,700 residency programs were mentioned. The results of these rankings are featured in Doximity’s free interactive tool called Residency Navigator designed for third- and fourth-year medical students, which launched with the release of the rankings in September. Medical students and physicians will now have access to additional data on each residency program in the 20 ranked specialties, such as the percentage of residency alumni who went on to sub-specialize and the rank of past trainees in publication of research findings. —KG

U-M Faculty Edit Top GI Journals

U-M FACULTY MEMBERS EDIT TWO JOURNALS THAT ARE QUICKLY becoming the most, trusted sources for GI research worldwide: Gastroenterology and American Journal of Gastroenterology. According to a Thomson Reuters report, the most recent impact factor, which reflects the number of times manuscripts published in a given journal are cited, has increased for both. Gastroenterology remains No. 1 of 74, with an impact factor of 13.9. AJG rose to No. 3, with an impact factor of 9.2. William D. Chey, M.D. (Fellowship 1993), professor of internal medicine, is co-editor-in-chief of AJG, while Bishr Omary, M.D., Ph.D., the H. Marvin Pollard Professor of Gastroenterology, professor of internal medicine and professor and chair of the Department of Molecular and Integrative Physiology, is editor-in-chief of Gastroenterology.

Medical School Dean Wins Flexner Award

U-M MEDICAL SCHOOL DEAN JAMES O. Woolliscroft, M.D. (Residency 1980), has been recognized with the Flexner Award for Distinguished Service to Medical Education. Presented annually, the award is considered the highest honor given by the Association of American Medical Colleges, or AAMC, and recognizes extraordinary contributions to the medical education community.

The AAMC Award citation credits Woolliscroft, the Lyle C. Roll Professor of Medicine, with being a strong leader in the transformation of medical education and a talented mentor who inspires in others a passion for educating. Woolliscroft currently leads an effort to transform the U-M medical curriculum, preparing students to be physician leaders who will be able to answer society’s call for improved systems of health care. In addition to the Flexner award, honors for Woolliscroft’s contributions to medical education include the 2008 AAMC Group on Educational Affairs Merrell Flair Award and the 2004 Society of General Internal Medicine Career Achievement in Medical Education Award. —KG
In the School

U-M Faculty Elected to Institute of Medicine

Three University of Michigan Medical School faculty members have been elected to the Institute of Medicine of the National Academies in recognition of their major contributions to the advancement of medical sciences, health care and public health. One of the highest honors in the fields of health and medicine, U-M now has 59 past and present members of the IOM, including the following most recently elected members.

CAROL R. BRADFORD (M.D. 1986, Residency 1992), chair of the Department of Otolaryngology-Head and Neck Surgery and the Charles J. Krause, M.D., Collegiate Professor of Otolaryngology, is an internationally recognized leader in the treatment of head and neck cancer. She specializes in head and neck cancer surgery and reconstruction, as well as cutaneous oncology and sentinel lymph node biopsy. During her 16-year tenure as co-director of the Head and Neck Oncology Program at the U-M Comprehensive Cancer Center, she helped to advance it from a small program with a few members to one with 30 members from 10 departments and five schools. She continues to play an active role within the program.

EVA L. FELDMAN (M.D. 1983, Ph.D. 1979, Fellowship 1988), is the Russell N. DeJong Professor of Neurology and director of the A. Alfred Taubman Medical Research Institute. An internationally renowned expert in amyotrophic lateral sclerosis, or ALS, she has devoted her career to finding new therapies and treatments for neurodegenerative diseases. Feldman treats patients and also directs a laboratory staffed by more than 30 scientists who are uncovering the mysteries of conditions ranging from diabetic neuropathy to Alzheimer’s disease.

MARK FENDRICK, M.D., is a professor of internal medicine at the Medical School, a professor of health management and policy at the School of Public Health and director of the University of Michigan Center for Value-Based Insurance Design, or V-BID. He has received numerous awards for the creation and implementation of value-based insurance design. Fendrick is a leading advocate for developing and implementing innovative health plans that align benefits with the clinical value, not just the cost, of preventive services and treatment options. He has fostered collaborations for such plans with government agencies, health plans, professional societies and health care companies, leading to the V-BID concept’s inclusion in several state and national policy initiatives including the Patient Protection and Affordable Care Act. –KG

U-M Startup gets FDA Approval for Lung-Imaging Software

IMBIO, A STARTUP COMPANY

launched at the U-M in 2007, has received clearance from the U.S. Food and Drug Administration to sell its software platform, Lung Density Analysis, or LDA.

LDA analyzes images of patients’ lungs with detailed precision, helping doctors make clearer diagnoses and more individualized treatment plans for patients. The new FDA 510(K) clearance allows doctors to use the technology in patients with chronic obstructive pulmonary disease, which affects over 60 million people worldwide. The company is also developing techniques for analyzing other lung images and images of cancerous tumors, using variations of the same technology.

The technology grew out of basic laboratory research at the U-M by Imbio’s co-founders, Brian Ross, Ph.D., the Roger A. Berg M.D. Radiology Research Professor and professor of radiology and biological chemistry, and Alnawaz Rehemtulla, Ph.D., the Ruth Tuttle Freeman Research Professor of Radiation Oncology and professor of radiology. Both are now scientific advisors to Imbio. Not only does the technology have its roots in the U-M Department of Radiology’s Center for Molecular Imaging, which Rehemtulla directs, it was also tested by a separate team of U-M lung-imaging experts. Results of their in-depth testing were published in Nature Medicine in 2012. –KG