Mind Brain Behavior
New Collaborative Works to Reconnect Fragmented Science
Disruptions affecting the gene CHD8 can contribute to white matter damage in the brain, which may help explain why researchers have noted a link between that gene and autism spectrum disorders. Read more on page 5.
Is Now the Time for Circadian Medicine?

The precise time you take your medicine could make all the difference in its effectiveness, say researchers here. John Hogenesch, PhD, Director, Center for Chronobiology at Cincinnati Children’s, led a team of several collaborators on two recent studies that significantly advance the science of circadian medicine. The work involved collaborators from several divisions at Cincinnati Children’s, as well as experts at Vanderbilt University, the University of Pennsylvania and Procter & Gamble.

Marc Ruben, PhD, was first author for findings published Sept. 12, 2018, in Science Translational Medicine, that found a surprising number of genes affected by circadian rhythms. The team developed the CYCLOPS algorithm (CYCLic Ordering by Periodic Structure) to analyze thousands of human tissue samples to measure the timing of gene-to-tissue interactions in 13 tissue types.

OUR BODIES HAVE MANY CLOCKS

“We identified rhythms in gene expression across the body in a large and diverse group of people,” Hogenesch says. “It doesn’t matter if you’re male, female, young or old, or what your ethnicity is, your body’s internal clock regulates half your genome.”

Says Ruben, “Overall this connects thousands of different drugs, both approved and experimental, to nearly 1,000 cycling genes.” Many of these genes code for proteins that help transport or metabolize drugs or themselves drug targets—including genes with well-known connections to the cardiovascular system.

THE ULTIMATE ‘WEARABLE’?

Next, first author Gang Wu, PhD, and colleagues published findings Oct. 30, 2018, in PNAS, concluding that a number of cycling genes in the skin function are more effective biomarkers for measuring an individual’s particular internal clock than current methods based on genes found in the blood. This study included NIH funding and other sources. Critical data was provided by Procter & Gamble, which also paid for the clinical work involved.

“We showed that human epidermis has a stronger clock than blood and developed a panel of biomarkers that can phase individuals to within three hours from a single sample,” the authors wrote.

The researchers emphasize that additional studies are needed before the findings can be applied to clinical practice. But the findings suggest that a practical method may soon become available to allow doctors to instruct patients more precisely on when to take medications at peak times for maximum effectiveness, or at trough times to minimize side effect risks.

Evidence-based Guidelines Emerge for Concussion

Healthcare providers now have consistent, evidence-based guidance for diagnosing and managing mild traumatic brain injury, or concussion. Shari Wade, PhD, Director of Research, Division of Rehabilitation Medicine, was one of the clinical experts who worked with the Centers for Disease Control and Prevention (CDC) to develop 19 clinical recommendations that cover diagnosis, prognosis, management and treatment. The guidelines were published Sept. 4, 2018, in JAMA Pediatrics.

The recommendations include several key, practice-changing guidelines, says Wade, including identifying risk factors that might contribute to slower recovery, advice on avoiding routine neuroimaging for diagnosis; and optimizing recovery by allowing children to return to non-sports activities within days, rather than weeks, of injury.

The CDC followed a rigorous process guided by the American Academy of Neurology, and the 2010 National Academy of Sciences’ methodologies for developing evidence-based guidelines. The guideline authors also reviewed 25 years of scientific research.

Improving the Odds of Bone Marrow Transplants

The experimental drug CASIN improved the harvest of donor blood stem cells and lessened toxicity in transplant recipients, according to two preclinical studies led by our researchers, both recently published in Leukemia.

Both studies were led by senior investigator Yi Zheng, PhD, and a team of experts at the Cancer and Blood Diseases Institute.

In June 2018, Zheng’s team reported using CASIN to mimic the action of the gene Cdc42, which helps regulate blood stem cells. Tests showed that CASIN effectively mobilized blood-making stem cells and promoted their exit from the bone marrow. The harvested stem cells also were harder following transplant than cells harvested with current clinical regimens.

Then in September 2018, researchers used CASIN to make the mouse bone marrow more receptive to healthy blood stem cells, lessening the chemotherapy needed prior to transplant.

The researchers caution the procedure remains in preclinical testing and results from such studies may not translate to human patients.

Left: This heat map of clock gene expression in skin from 238 donors shows robust population-based clock function in humans. Red means correlated, blue indicates anti-correlated. Right: This CYCLOPS display shows conservation in timing of clock gene expression in mice and humans. Moving clockwise from 0 (~10PM), the outer circle shows when human genes peak, while the inner circle depicts mouse genes.

A donor stem cell harvested from a mouse treated with CASIN (bottom) is depolarized and shows several colorized polarity markers. This cell has better mobilization potential than the untreated stem cell in the top image.

Dr. John Hogenesch (left) and Dr. Shari Wade (right).
Deleting an RNA-Silencing Protein Speaks Volumes About Obesity

Researchers here say that blocking an RNA-silencing protein in the livers of mice keeps the animals from getting fat and developing diabetic conditions. Findings appeared Sept. 10, 2018, in Nature Communications.

Takahisa Nakamura, PhD, and colleagues genetically deleted a protein called Argonaute 2 (Ago2) from the livers of mice. Ago2 slows energy metabolism and the liver’s ability to process a high-fat diet. When the scientists deleted the protein, it stabilized energy metabolism, staved off obesity and prevented the mice from developing diabetes and fatty liver disease.

“Although this is still basic science, our findings may have important translational implications for metabolic disorders like diabetes, fatty liver diseases, and other obesity-associated illnesses,” says Nakamura, a member of the Division of Endocrinology. “This allows us to explore the potential of finding a novel therapeutic approach that alters energy balance in obesity and modulates the associated diseases.”

Scientists Grow First Human Esophagus in Lab

Researchers here have grown a human esophageal organoid entirely from pluripotent stem cells (PSCs). Scientists in our Center for Stem Cell and Organoid Medicine (CuSTOM) reported the breakthrough Sept. 20, 2018, in Cell Stem Cell.

This is the first success at growing human esophageal tissue entirely from pluripotent stem cells (PSCs), which can form any tissue type in the body. The latest advance follows previous successes at using PSCs to bioengineer human intestine, stomach, colon and liver organoids. The long-term goal: develop all the organoids needed to create an entire human gastrointestinal system on a chip.

“In addition to being a new model to study birth defects like esophageal atresia, the organoids can be used to study diseases like eosinophilic esophagitis and Barrett’s metaplasia and metabolize organoids to individual patients,” says lead investigator Jim Wells, PhD. “Many esophageal conditions need better treatments, be they congenital defects like esophageal atresia or conditions that appear later in life such as esophageal cancer, gastroesophageal reflux disease (GERD), or achalasia, a rare disease that prevents the esophageal muscle contractions needed to pass food.

All of these conditions need more precise understanding of the genetic and biochemical mechanisms causing them. The ability to grow organoids based on a person’s own cells provides a powerful opportunity for finding such causes—and targeting treatments accordingly.”

The CuSTOM center, launched in November 2017, will continue its efforts to develop organoids and investigate their therapeutic potential.

When a Cancer Suppressor Becomes a Driver

The protein AMPK (AMP-activated protein kinase) is best known as a cancer suppressor. But in a study published online June 18, 2018, in Nature Cell Biology, scientists here report that the protein actually drives growth of certain deadly brain cancers.

“AMPK is considered to play a suppressive role in cancer because it inhibits cancer-promoting enzymes like mammalian target of rapamycin (mTOR) and acetyl Co-A carboxylase (ACC),” says senior investigator, Biplab Dasgupta, PhD, who collaborated with first author Rishi Raj Chhipa, PhD, and others.

“Our study uses analysis of the Cancer Genome Atlas to show that AMPK proteins are expressed in lethal human glioblastoma, and inhibiting AMPK by genetic means shrinks brain tumors and prolongs survival in mice.”

The researchers say they hope the study will encourage pharmaceutical companies to search for AMPK inhibitors.

Findings Explain Gene’s Role in Autism

Scientists here have clarified how mutations in the gene CHD8 harm the brain and contribute to autism spectrum disorders. They reported their findings June 18, 2018, in Developmental Cell.

Previous studies had linked CHD8 mutations to autism and abnormalities in the brain’s white matter, but the underlying biology has been a mystery.

This study showed that disruption of CHD8 hindered production and maintenance of nerve insulation, harming the brain’s neuronal connections and contributing to white matter damage. Mice engineered to lack CHD8 protein in the oligodendrocytes—cells that produce the protective nerve sheath—exhibited behavioral anomalies and seizures, according to lead investigator Q. Richard Lu, PhD, Division of Experimental Hematology and Cancer Biology.

Although study results are early, Lu says the work could lead to treatments that restore function to faulty CHD8-dependent processes.

This micrograph shows the presence of basic myelin protein and normal oligodendrocyte cell differentiation in the brain of a mouse. The cells form a protective sheet of insulation around nerves in the outer layers of the brain.
In 2004, Cincinnati Children’s physician-scientist Michael Jordan, MD, led a study in mice that identified what appeared to be molecular drivers of the mysterious and fatal immune disorder hemophagocytic lymphohistiocytosis (HLH). That discovery led Jordan and a corps of parents, advocates and fellow researchers on a nearly 15-year journey to the first approved treatment specifically for HLH. The U.S. Food and Drug Administration gave the drug, Gamifant (emapalumab-izsg), the green light in November, 2018. Jordan calls the approval “amazing.”

“My goal for our work over all these years has been to use scientific exploration and practical medical approaches to make a difference in the lives of these children,” he says. “It’s been a privilege to help develop this idea from an unexpected laboratory discovery to an approved medicine.”

Jordan’s 2004 mouse study, published in the journal Blood, showed that elevated levels of the protein interferon gamma (IFNg) are essential to the HLH disease process. Gamifant, made by Sweden-based Sobi, specifically targets and blocks IFNg. Reaching this point included patient families and advocacy groups working closely with Jordan and colleagues at Cincinnati Children’s HLH Center of Excellence. Fundraising efforts included more than $1 million raised in seven annual “700 Miles to Hope” marathon bicycle rides from Jackson, MS, to Cincinnati.
Human DNA in Mice Sheds Light on Causes of Preterm Birth

Inserting just enough human DNA into mice allowed researchers to study an important contributor to the problem of human preterm birth.

In September 2018, scientists in our Perinatal Institute and the Department of Pediatrics at the University of Cincinnati College of Medicine reported in PLoS Biology that they hope to discover what controls expression of corticotrophin-releasing hormone (CRH) in the placenta. CRH expression is linked to birth timing.

The precise biology of preterm birth in humans has been difficult to study in animal models. Having transgenic mice with the human DNA to express CRH in the placenta should help researchers learn about how CRH works, says senior investigator Louis Muglia, MD, PhD.

Muglia and his team plan to explore whether manipulating placental CRH levels can alter the timing of birth. Transgenic mouse models that mimic key aspects of human pregnancy also should help researchers learn more about how epigenetics affect birth timing.

In Some Cancers Flawed Gene Translation Can Hinder Immunotherapy

Emerging immunotherapies appear to be a major advance in cancer treatment. But on Oct. 23, 2018, study in Nature Communications, led by scientists here, highlights a potential limitation.

Immunotherapies work by disabling the molecular cloaking abilities cancer cells use to evade the body’s immune system. Removing these abilities allows immune cells to attack the cancer and helps make chemotherapy and other treatments more effective.

However, a study led by Kakajan Komurov, PhD, and colleagues in the Cancer and Blood Diseases Institute discovered that kidney cell carcinoma, metastatic melanoma and some other cancers have transcription elongation defects. This defective genetic process impairs pro-inflammatory response in the cancer cells, which in turn limits the effectiveness of immunotherapies that rely on pro-inflammatory signals.

Although the study points to some potential limitations for immunotherapy, the findings suggest it also may be possible to test cancer patients to determine whether they are candidates for immunotherapies.

Statins Effective in Treating Lung Disease PAP

Cholesterol-busting statins can effectively treat pulmonary alveolar proteinosis (PAP), a disease that causes air sacs in the lungs to clog with surfactant, according to a new research led by Bruce Trapnell, MD, Director of our Translational Pulmonary Science Center.

Years ago, Trapnell and colleagues showed that PAP is linked to disrupted cell regulation by the molecule granulocyte-macrophage colony stimulating factor (GM-CSF). On Aug. 7, 2018, Trapnell and first author Cormac McCarthy, MD, PhD, reported in Nature Communications that the disruptions caused by GM-CSF reduce the ability of macrophages to process and clear out cholesterol. This contributes to the accumulation of surfactant that causes PAP and hinders breathing.

The discovery “will change thinking in the PAP field,” Trapnell says. “Now that we know cholesterol in macrophages is a target for therapeutic development, repurposing statins is a straightforward pharmacological approach for treating people with PAP.”

The findings are expected to lead to a larger clinical trial to test statin therapy.

Common Genetic Variant Found for Fatal Lung Condition PAH

Pulmonary arterial hypertension (PAH) is a rare disorder caused by blockage of the pulmonary arteries, resulting in heart failure and premature death. Treatments have advanced in recent years, but PAH remains a devastating disorder.

Now, an international team of scientists that included investigators from Cincinnati Children’s has advanced our understanding of PAH genetics through genome-wide association studies that analyzed data from 11,744 people of European decent.

The study, published in Lancet Respiratory Medicine, is the largest genetic analysis to date for PAH. It reports that PAH is associated with two genes, SOX17 and HLA-DPA1/DPB1. Although many genes with rare variants have already been identified in PAH, this is the first study identifying common variants in a large population of patients.

“This is the first finding of common variation associated with PAH and all of the U.S. patients in the study are enrolled in the National Biobank and Data Repository for PAH at Cincinnati Children’s,” says William Nichols, PhD, Director of the PAH biobank here and a senior investigator on the study. “The biobank is the world’s largest sample and genetic data repository in the world for patients with this disease.”

Michael Pauciulo, MBA, Division of Human Genetics, was a co-first author on the study.
Experts at Cincinnati Children’s are advancing two powerful projects that could sharply reduce the harm caused by sickle cell disease: one that could accelerate the use of a life-saving, low-cost treatment in Africa, and another to evaluate a potential gene therapy that could someday reverse the disease.

**Reaching Out to Africa**

Sickle cell disease affects more than 90,000 people in the United States, but it affects millions more in sub-Saharan Africa. In a groundbreaking study published online in December, 2018, by The New England Journal of Medicine, researchers report that daily hydroxyurea pills reduced rates of sickle cell pain by an average of 55 percent, infections by 38 percent, malaria by 51 percent, transfusions by 67 percent, and deaths by 70 percent.

The findings came from the REACH multinational clinical trial, in which more than 600 African children in four nations took hydroxyurea daily for six months. “Hydroxyurea was safe and offered many benefits to these young patients, including improved anemia, fewer sickle cell pain events, less malaria, and better survival,” says Russell Ware, MD, PhD, the study’s senior investigator.

Now, Cincinnati Children’s is working with the National Institutes of Health and partner organizations in Africa to continue the work to expand access to this low-cost therapy while monitoring longer-term outcomes.

**Early Clinical Data for Gene Therapy Shows Promise**

In December 2018, Purnom Moisik, MD, presented preliminary data from a Phase 1-2 clinical trial involving a gene therapy that has been under development at Cincinnati Children’s for more than a decade. The therapy uses a modified lentivirus to carry a healthy fetal hemoglobin gene into a patient’s blood stem cells.

“One year after treatment of our first patient, and six months after treatment of our second patient, both have seen a remarkable improvement in the quality of life due to remarkable reduction in disease symptoms. This includes near elimination of chronic pain and sickness events and improved anemia,” Moisik said at the American Society of Hematology’s (ASH) annual meeting in San Diego. “Although it’s still early post-treatment, these preliminary results are quite promising.”

While other research teams also are developing gene therapies for sickle cell disease, this approach requires a less intense pre-treatment conditioning regimen, which could make the therapy more practical for hospitals in developing nations.

Cincinnati Children’s also recently partnered with Revivant Sciences to create Aruvant Sciences, a joint venture that will make the therapy more accessible to hospitals in developing nations.

The REACH clinical trial (Realizing Effectiveness Across Continents with Hydroxyurea) involved more than 600 children in four nations. Co-investigator Leon Thibault, MD, PhD, Centre Hospitalier Monkole, said the project lived up to its name.

**Ebola Vaccine Clinical Trial Launched at Cincinnati Children’s**

As the Ebola virus continues to cause deadly outbreaks in other nations, a Phase 1 clinical trial has started here to test a combination vaccine that researchers hope will help protect first responders and others who encounter infected people.

Cincinnati Children’s has a long history of vaccine research, from developing the Sabin oral polio vaccine in the 1950s to more recent advances against rotavirus, norovirus and respiratory syncytial virus. Cincinnati Children’s also evaluates annual flu vaccines and others as one of nine Vaccine and Treatment Evaluation Units funded by the National Institute of Allergy and Infectious Diseases (NIAID).

“Researchers are looking for new ways to stop these outbreaks and to treat people who become infected and develop Ebola virus disease. The development of preventive vaccines for Ebola is a top global public health priority,” said Paul Spearman, MD, lead investigator and Director of the Division of Infectious Diseases. Laboratory evaluations will be led by Karnail Singh, PhD, on Ebola expert here.

The clinical trial is recruiting up to 60 healthy volunteers to determine immune response to a combination of two vaccines, the ChAd3-EBO-Z vaccine and the MVA-BN®-Filo vaccine. Participants will be followed for six months. For more information, visit ClinicalTrials.gov or use the identifier NCT03583606. To enroll, follow this link or call 513-636-7699.

**Cincinnati Children’s Develops Most Accurate Tool Yet for Predicting Asthma**

The new Pediatric Asthma Risk Score (PARS) outperforms the current gold standard and 29 other methods as a tool for predicting which children with signs of allergy face elevated risk of developing asthma, according to data published online in December 2018 in the Journal of Allergy and Clinical Immunology.

“PARS is superior to the Asthma Predictive Index (API) in its ability to predict asthma in children with mild to moderate asthma risk, with 11 percent increase in sensitivity,” says Gurjit Khurana Hershey, MD, PhD, director of Asthma Research at Cincinnati Children’s and senior author of the study. “Children with mild to moderate risk may be the most likely asthma patients to respond favorably to prevention strategies.”

The study found that the API missed 43 percent of asthmatic children identified by PARS as mild to moderate risk. PARS and the API equally predicted asthma risk for children in the most risk factors. A notable achievement of the PARS over the API is that it delivers a personalized asthma risk score to the patient. While useful for predicting which children will not develop asthma, the API test “leaves much room for improvement in terms of identifying children who will,” says Jocelyn Biagini Myers, PhD, lead author of the study.

The PARS tool is available for download at no cost. A PARS web application, which provides fast and easy calculation, is accessible here. Apps also are being developed for the iPhone and for Android phones.
Reimagining
How We Think About Our Brains

Collaborative Effort Seeks to Forge Stronger Bonds Between Bright Minds Across Many Fields

by Tim Bonfield

The brain is the body’s most complex organ, so complex that its study and treatment over the years has required breaking down the work into smaller pieces. This fragmentation has allowed researchers and clinicians to concentrate on different functions controlled by the brain—movement, cognition, emotion, mental health, behavior, and so on. However, this narrow approach has tended to limit the power of discovery.

Now leaders at Cincinnati Children’s are building new connections and deeper collaborations across disciplines with its Mind Brain Behavior collaborative (MBB), launched internally in 2017. The mission: to serve as a catalyst for transforming our research and clinical care models with the goal of helping all children with behavioral, mental health and neurological conditions reach their optimal quality of life.

“This has been needed for a long time,” says Tracy Glauser, MD, Associate Director, Cincinnati Children’s Research Foundation. “Our research and care delivery systems continue to fragment into more and more subspecializations as we break topics down into smaller units that we can better understand. But if we hope to make transformational advances, we need to put the parts back together and look at the brain more holistically.”

Reducing Barriers to Innovation

The concept of a Mind Brain Behavior initiative took shape as dozens of leaders at Cincinnati Children’s joined initial working groups co-chaired by Margaret Hostetter, MD, Research Foundation Director and Chair of Pediatrics, and Brian Coley, MD, Radiologist-in-Chief.

Some groups focused on the clinical side, looking for ways to drive adoption of best practices and to streamline overlapping lines of care. Other groups focused on research—basic and translational.

“Ultimately, we don’t want to just improve treatment of disease. We want to get to health and wellness. The only way to get there is to bring all these disciplines back together again.”
Glauser and Lori Stark, PhD, Director, Behavioral Medicine and Clinical Psychology, were chosen to co-direct the MBB initiative. Their goals include building a larger community of brain-focused researchers, recruiting new faculty in selected fields, assessing infrastructure needs and accelerating innovation, and building integrated models of clinical care. Much of this work will continue for months and years to come, but several initiatives are underway:

- A team led by Steve Danzer, PhD, has launched the Center for Pediatric Neuroscience to provide a “virtual home” for basic scientists working on MBB projects across divisions. (See story on page 16.)
- Another team led by Susmita Kashikar-Zuck, PhD, is building the Alliance for Clinical and Translational Science to focus on later stages of the research pipeline. (See story on page 20.)
- An internal application and funding process also has begun to support pilot projects in these areas through the Research Innovation Pilot Funding Program.

“We believe investing in infrastructure and key recruits will speed discovery,” Stark says. “We believe that building alignment and synergy across basic and translational research will help drive improvement in clinical areas.”

CLINICAL FOCUS
ON NEW MODELS OF CARE

Clinically, MBB is re-shaping multidisciplinary teams to bring new models of care to more patients, starting with traumatic brain injury, cerebral palsy, and mental health.

Mental health is a particularly challenging area. The National Alliance on Mental Illness estimates that one of every seven children aged 2-8 years, and one in five youths aged 9-17 years, experience a behavioral or mental condition. However, interventions often can be delayed by a decade or more with only 15 to 25 percent of children receiving the care they need.

MBB is addressing this crisis in our community by developing an early intervention model that places psychologists in primary care clinics to address emotional and physical health needs as they emerge, in one seamless system.

“This integration will make behavior services available to substantially more children in a trusted setting—their primary care home. This reduces barriers of stigma and the inconvenience of extra visits that can occur in a subspecialty system of care,” Stark says.

Likewise, we are building alternative management models to help children and adolescents in mental health crisis with the goals of preventing emergency room visits and reducing unnecessary hospitalizations.

Similar integrated care models are being developed for other clinical conditions within MBB.

A LONG-TERM EFFORT

With so much to be done, it will take several years for the MBB initiative to bear its most important fruits.

“Ultimately, we don’t want to just improve treatment of disease. We want to get to health and wellness. The only way to get there is to bring all these disciplines back together again,” Glauser says. “And because of our strong resources, because of our culture of collaboration, we really believe we can do this here.”

MIND BRAIN BEHAVIOR INITIATIVES

Center for Pediatric Neuroscience

With hundreds of neuroscience studies and related projects underway at Cincinnati Children’s and the University of Cincinnati, the new Center for Pediatric Neuroscience will serve as a clearinghouse to help basic scientists and clinicians find each other. “Our hope is that we get to a point where we can understand the bigger questions about behavior, emotion and consciousness,” says center Director Steve Danzer, PhD. (See page 16.)

Alliance for Clinical Translational Science

How can a behavioral scientist learn from an expert in sports medicine? And how might such a partnership provide insights into controlling chronic pain? Forging these kinds of cross-cutting collaborations is the mission behind the MBB’s new Alliance for Clinical and Translational Science.

“Teens love having a trainer, they do not love having a therapist,” says alliance leader Susmita Kashikar-Zuck, PhD. “And the results indicate that there might be something about exercise that changes the tone of the brain, the way pain is perceived and reduced.” (See page 20.)

Internal Seed Funding

Through 2021, Cincinnati Children’s plans to provide internal seed funding grants of up to $75,000 each to accelerate Mind Brain Behavior collaborations. Projects to be funded will emphasize translational work that builds clinical and basic science teamwork across specialties.

Inviting Experts

The Mind Brain Behavior collaborative invites speakers from within Cincinnati Children’s and brain science experts from other research centers to share their knowledge. The program is inspiring faculty and students at multiple levels to find new ways to apply their skills to neuroscience and related fields.

Topics range as widely as brain science itself, including ways to apply imaging technology, genomics, computer algorithms and other methods to deepen understanding of autism, pain, seizures, tumors, maternal depression, and more.

Enhancing Care, Expanding Reach

As many as one in five children aged 9 to 17 experiences a behavioral or mental condition, but only 15 to 25 percent get the care they need. Cincinnati Children’s is addressing this crisis by embedding more psychologists in pediatric primary care clinics. Leaders also are hiring more Mind Brain Behavior experts in autism and other fields while working to enhance patient and family experiences at the hospital, and to streamline services that involve multidisciplinary clinic care.
As far as we know the human brain is the most complex structure in the universe. That’s what Cincinnati Children’s neuroscientist Steve Danzer, PhD, tells his students at the University of Cincinnati College of Medicine (UC), where he’s an associate professor of Anesthesiology. However, while the brain’s complexity makes the jobs of these future doctors and scientists more difficult, the brain’s ability to restructure and rewire itself creates opportunities for developing entirely new therapies.

About the size of two clenched fists, this oblong globe of tissue fits 200 billion electrically sensitive neurons and glia cells and more than 100 trillion synapses into our heads. The components all work together inside that relatively small space to help make us what and who we are. It controls the function of our organs and limbs, is capable of logic, reason, love, hate and fear and can burst forth with brilliant creativity.

Danzer’s challenge—and that of his colleagues in the Center for Pediatric Neuroscience—is to figure out more about how it works and why. Scientists and physicians see great potential to use the brain’s abilities to improve medicine and human health. To some extent medicine already does this, but there is still far more about the brain that we don’t know than we do.

“Neurology and neuroscience affect almost everything,” says Danzer, center director and a neuroscientist in the Department of Anesthesia. “We know the brain has tremendous adaptive capabilities—like restructuring itself to recover the ability to walk or speak after stroke—but these endogenous processes often are insufficient. We need to learn more about how the brain repairs itself so that we can help these processes to work better, and prevent them from going wrong and producing pathological outcomes, like chronic pain.

That journey is still relatively early, according to Danzer. A lot more foundational science work is needed.

“We are getting a good understanding of how neurons and individual cells work and how neural networks work,” Danzer explains. “Our hope is that we get to a point where we can understand the bigger questions about behavior, emotion and consciousness. We’re not there yet and the answers are still kind of wide open.”

ENDLESS FORKS IN THE ROAD

Hundreds of studies and related projects focused on the neurosciences are underway at Cincinnati Children’s and its research affiliate, UC. They point in a multitude of different and often complementary directions.

The Center for Pediatric Neuroscience serves as a centralized scientific clearing house. It helps basic scientists in laboratories and physicians in patient clinics find each other.

“Numerous skill sets are involved in neurosciences—all the way from psychology and psychiatry where people work with
patients to studying gene mutations and subcellular structural changes in neurons,” Danzer says. “We have a very strong neuroscience group at Children’s and UC. The center makes it easier for clinicians and basic scientists to coordinate our research and overall efforts.”

So far about 60 basic scientists and physician-scientists have joined the center’s expanding lineup.

Some teams study the molecular processes underlying the formation of neural circuits in the spinal cord. Others study neuroplasticity—the ability of the brain to use its muscle-like characteristics to adapt and recover from injuries and illnesses. Other studies seek to identify the molecular processes that cause brain and central nervous system diseases—including epilepsy, autism spectrum disorders, cancer, hydrocephalus, sleep disorders and more. Still others specialize in biomedical informatics, where computer algorithms and systems biology concepts can be applied to analyze massive amounts of biological data.

CHASING TSUNAMIS

One study underway at the new center explores the mysteries of spreading depolarizations (SDs), popularly referred to as “brain tsunamis.”

Scientists know these fluctuating waves of neural activation can spread throughout brain’s cortex, but no one knows exactly what they mean. Are SDs a symptom or biomarker of brain problems, or a cause? Do they have diagnostic potential? Some of these tsunamis appear linked to the strange dizzy feeling or “aura” that some people feel before agonizing migraine headaches. Depolarizations also can occur after traumatic brain injuries and among people with epilepsy or other kinds of brain seizures.

“There is still a debate in the field over whether spreading depolarizations are good or bad and if they should be prevented or stopped,” explains Candi LaSarge, PhD, a neuroscientist working with Danzer and pediatric neurosurgeon Jesse Skoch, MD, to find out.

Basic research about SDs has lagged in part because current technologies allow viewing them only to a limited degree. To change that, LaSarge, Skoch and Danzer worked with Matt Batie in our 3-D Printing and Design Engineering service to develop a tiny stereotaxic frame that lets researchers measure SD intensity with high clarity in living mice.

The 6- by 4-inch black box is equipped with optical imaging and anesthesia access ports that allow a confocal electron microscope to record SDs in mice with brain tissues tagged to “light up” as the waves spread. The team plans to use the tool to map SDs in real time while modeling seizures, brain injury, and other conditions.

“Clinically we don’t have highly effective or sensitive ways to observe and monitor brain activity during spreading depolarizations in people,” says Skoch, who operates on children with epilepsy and other neurological conditions. “This research will eventually give us a diagnostic tool for injured brains or those with disease. Being able to visualize activity with the device gives us a sensitivity that electrodes cannot, which allows us to study SDs in ways that we could not before.”

MORE TO COME

The SD project highlights a key goal of the new center—to meet the challenges of advancing neuroscience in the 21st century by bringing together basic scientists, clinicians, engineers, bioinformatics specialists and other experts.

“Our combined efforts will be essential if we are to gain an understanding of the most complex structure in the universe,” Danzer says.

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“Our combined efforts will be essential if we are to gain an understanding of the most complex structure in the universe,” Danzer says.
I n creating a semi-structured strategy to improve collaboration among researchers of mind, brain, and behavior, Susmita Kashikar-Zuck’s approach provided a dash of simplicity—add art to science and stir.

The clinical psychologist decided to bypass the siloed, meeting-heavy mentality of many large research institutions. She wanted to engage faculty on the cross-pollination of ideas in small groups, emphasize overarching themes over narrowly defined topics, and keep it short.

Her secret ingredients included conversation, cookies, crayons, and craft paper. It was a winning recipe.

The Discovery Café concept is part of the Alliance for Clinical and Translational Science (ACTS), an initiative launched as part of the larger Mind Brain Behavior Collaborative at Cincinnati Children’s. The café was born from a listening tour Kashikar-Zuck undertook in fall 2017. Researchers told her they wanted communication and culture, not more lectures, especially long ones.

In its first year, ACTS has grown into an impassioned group of scientists in 16 divisions who share data, grant opportunities, resources and insights. Kashikar-Zuck likens the process to a qualitative study.

“The goal was to identify synergies, to galvanize research across Cincinnati Children’s,” says Kashikar-Zuck, PhD, Research Director in the Division of Behavioral Medicine and Clinical Psychology (BMCP). “That’s how it was different. Some researchers were working together, some were not, but generally there were many clinical and research silos. It’s one of the mind/brain areas where we could show how people can cross-cut their ideas.”

Its name is borrowed from the World Café, a similarly informal approach that has gained traction at the Centers for Disease Control and Prevention, the United Nations, and in the corporate and governmental worlds.

The Mind Brain Behavior (MBB) initiative at Cincinnati Children’s has two arms: basic research, headed up by Steve Danzer, PhD, of the Department of Anesthesia (page 16), and the translational arm that Kashikar-Zuck leads.

Creating ACTS was suggested by MBB directors Lori Stark, PhD, Director, BMCP and Tracy Glauser, MD, Associate Director of the Cincinnati Children’s Research Foundation.

“I told Lori and Tracy, this novel approach to bring faculty together could really flop,” she recalls with a smile. “But, I said, let’s see how people react to the full idea of getting together under this umbrella. I was, frankly, a little concerned.”

She needn’t have been.

“We needed a catalyst,” says Greg Myer, PhD, Director of Research in the Division of Sports Medicine. “Crayolas are not part of our usual tool box, but I think they were critical to our expanded thinking.”
Dean Beebe, PhD, Director of the Neuropsychology Program in BMCP, put it this way: “I didn’t know what to expect going in. I had no doubt about the goals, and I do think it’s the right thing to do. I open to the idea of trying things out. Besides, preconceived notions kind of defeat the whole purpose, don’t they?”

**CONNECTING THE PARALLEL ROADS OF RESEARCH WITH SIDE STREETS**

In the first two sessions of the Discovery Café, Kashikar-Zuck, who specializes in pediatric pain research, saw common methodologies used in different ways.

“For example, pediatric migraine, fibromyalgia, and functional abdominal pain are conditions treated by neurology, rheumatology and GI specialists,” she says, “and what they all have in common is that the pain is brain-based.”

From Beebe, café participants learned about research using a mobile device called an actigraphy sensor, a wristwatch-like unit that assesses children’s rest/activity cycles. He also was awarded MBB’s first Research, Innovation and Pilot grant for his clinical-translational project on sleep and traumatic brain injury.

“In the first two sessions of the Discovery Café, Kashikar-Zuck, who specializes in pediatric pain research, saw common methodologies used in different ways.”

“The tone of the brain, the way pain is perceived and reduced.”

Kashikar-Zuck says. “Once they decide to participate, we’ve had no trouble at all.”

In September 2018, the team published results from a pilot study in The Journal of Pain, reporting that FIT Teens outperformed CBT-only treatment, even in pain reduction.

“Can this kind of sharing also extend beyond the campus?” says Beebe, who studies the impact of childhood sleep pathology on neuropsychological functioning. “And I’ve done really interesting research in simulation work. We’re not a classic collaborative, so the question is, how do we harness that? That’s when you realize how cool these things are.”

**NEW INSIGHTS ON PAIN, MOVEMENT**

Research teams had Kashikar-Zuck’s patients do things Myer’s patients do: climbing stairs, resistance exercises, jumping off boxes of varying heights, and so on.

“People have tried and ran smack dab into organizational types of issues. Institutions are set up in different ways, so you think, OK, that’s not going to work,” Kashikar-Zuck says. “But there’s so much interest in improved approaches, whether it’s for pain, epilepsy or migraine. And as researchers, we’re trained to be persistent.”

Co-authors Susmita Kashikar-Zuck, PhD, Jeffry and Greg Myer, PhD, have led several recent studies examining the efficacy of neuromuscular exercise training.
Clinicians describe chronic migraine as having at least 15 days per month of headache for more than three months with at least two aggravating symptoms. The pain tends to come with a pulsating quality. Sufferers often feel nausea, an aversion to light, or other discomfort severe enough to disrupt normal activity.

Nearly 2,000 children and teens visit the Headache Center at Cincinnati Children’s each year seeking help to relieve misery that often keeps them out of school, off the field and curled up in a dark room. Many families hope that doctors can simply prescribe a pill to make the pain stop. Many are surprised to find out that medications—especially by themselves—are not necessarily the right answer.

Experts in the field say a seismic shift is occurring in migraine pain management. While one surprising study reports that two of the most frequently prescribed migraine medications show no better results than placebo, other studies suggest promising results from non-medication approaches such as cognitive behavioral therapy (CBT).

Now, a team of scientists at Cincinnati Children’s is working to learn more about why. They are combining expertise in brain imaging technology, neurology, behavioral therapy, and other fields to lay the foundation for a new set of best practices in migraine control.

Bringing varied skill sets to bear in the hunt for better solutions for migraine pain is no accident. Forging working partnerships from bench to bedside is a prime mission of the Mind Brain Behavior Collaborative, say co-leaders Lori Stark, PhD, Director of Behavioral Medicine and Clinical Psychology, and Tracy Glauser, MD, Associate Director of the Cincinnati Children’s Research Foundation.

“One of our strengths over the years has been our collaborative nature. But collaboration can either occur passively, or we can...”

“So now we're going back to the bench and asking, 'When we attempt a treatment, what parts of the brain are being affected? What mechanisms are involved? Why is the placebo effect so powerful?'”
A surprising study of teens with migraines, published in 2017 in The New England Journal of Medicine, helped spark a fundamental reexamination of pain treatment. The study, led by Cincinnati Children’s investigators Scott Powers, PhD, and Andrew Hershey, MD, PhD, reported finding no statistical difference between the two most-prescribed migraine medications—amitriptyline and placebo.

The study did not conclude that the medications offered no value. Instead, the co-authors reported that the expectation of benefit from taking any pill, including a placebo, was powerfully real. “Then as we find those connections, we can design treatments that intentionally trigger those parts of the brain.”

**CAN PSYCHOLOGICAL TREATMENTS FOR PAIN BE IMAGED?**

With the nation facing an epidemic of opioid abuse, safely and effectively managing pain has become a more complex challenge.

In previous research, Powers and colleagues have reported significant success in controlling migraine pain through cognitive behavioral therapy (CBT). Instead of medication, CBT components focus on cognitive modification and distraction, and behavioral change strategies such as relaxation training, biofeedback, activity pacing, and adherence plans.

Clinical trial data reported as far back as 2013 shows that CBT helps reduce headache frequency and disability. And yet, many physicians remain reluctant to trust CBT over medication. To some providers, if pain can be controlled without a pill, then maybe the pain isn’t real. With many young patients already facing doubts and questions about exaggerating their suffering, some tell doctors that having a prescription medication provides validation.

But what if CBT produces detectable, measurable changes in brain function? Robert Coghill, PhD, an expert in using brain imaging techniques to determine how cognitive behavioral therapy (CBT) influences how the brain reacts to pain. Early data indicates that CBT affects several brain regions.

“Brain Activation Related to Headache Reduction After CBT”

“Brain Activation Related to the Mean Effect of CBT”

“His technology can help in a number of ways,” Stark says. “It can help convince people that the pain a child feels is real. It also can show that a treatment that does not involve medication can affect the parts of the brain that can inhibit headaches just as much as a chemical can. Obtaining that kind of result is only possible through collaboration across disciplines.”

Robert Coghill, PhD, is working with colleagues at Cincinnati Children’s to use advanced brain imaging techniques to determine how cognitive behavioral therapy (CBT) influences how the brain reacts to pain. Early data indicates that CBT affects several brain regions.
Japan’s Royal Family Honors Takebe for Excellence in Research

Takasori Takebe, MD, was one of six young Japanese researchers to be presented with the JSPS PRIZE at a February ceremony that included the Imperial Prince of Japan. The Japan Society for the Promotion of Science (JSPS) offers this annual award to recognize supradipe researchers under 45. Recipients have the potential to become world leaders in their fields. Takebe is a physician and researcher in our Division of Gastroenterology, Hepatology & Nutrition and the Center for Stem Cell & Organoid Medicine. His team is using stem cell technologies to develop liver “buds” for potential use as transplants for patients with rare congenital metabolic disorders. If successful, the approach could be expanded to other diseases like liver cirrhosis.

Whitsett Receives Trudeau Medal

Jeffrey Whitsett, MD, Executive Director of the Perinatal Institute and Chief of the Section of Neonatology, Perinatal and Pulmonary Biology, has received the Edward Livingston Trudeau Medal from the American Thoracic Society. The award recognizes lifelong major contributions to lung disease research, education and clinical care.

Marilyn Goske, MD, Radiology, retired, won a Gold Medal from the American College of Radiology for her work in founding and chairing Image Gently®, a campaign dedicated to making imaging safer for children worldwide.

Andrew Hershey, MD, PhD, Neurology, was elected as a Fellow of the American Academy of Neurology, and to serve as Chair of the Academy’s Headache Section.

Neil Johnson, MBBS, MMed, Radiology, was recognized as the 2018 Janet Patiti Scholar by the Association for Vascular Access and the Pediatric Special Interest Group.

Jeffrey Whitsett, MD

Theodosia Kaffe, MD, PhD
Cancer and Blood Diseases Institute and 2017 Schmidlapp Scholar, will receive continuing support from the Fifth Third Bank/Charlotta R. Schmidlapp Women Scholars Program for her research in developing new therapies for serious blood disorders in children.

Steve Muehling, MD, Chief Quality Officer, has been named as the only pediatrician to serve on the Institute for Healthcare Improvement’s National Steering Committee for Patient Safety. Cincinnati Children’s is one of 25 organizations taking part.

Victoria Wurster Oaveille, MD, Emergency Medicine, was one of seven experts to be selected for the 2018-19 Visiting Scholars Program by the American Board of Medical Specialties. The honor recognizes her research in physician assessment and professional development.

David Pruitt, MD, Physical Medicine and Rehabilitation, received the Corbett Ryan Pathways Pioneer Award from the American Academy for Cerebral Palsy and Developmental Medicine. He also recently served as the featured speaker at a National Cancer Institute workshop on disruption of children’s physical activity during and after cancer.

Laura Ramsey, PhD, Clinical Pharmacology, received the inaugural Darrell Abernethy Early Stage Investigator Award from the American Society for Clinical Pharmacology and Therapeutics.

Daniel Schumacher, MD, MEd, Chief, Education Research Group, was named a Macy Faculty Scholar by the Josiah Macy Jr. Foundation. The program fosters the potential of forward-thinking medical educators.

Samie Shah, MD, Hospital Medicine, has been named Editor-in-Chief for the Journal of Hospital Medicine.

Van Ginkel Named Great Living Cincinnati

Judith Van Ginkel, PhD, President of Every Child Succeeds (ECS), was recently honored as a Great Living Cincinnati for her role in spearheading the $16 million home visitation program in 1999 with three founding partners — Cincinnati Children’s, United Way of Greater Cincinnati and the Hamilton County Community Action Agency.

The program serves first-time, high-risk mothers and their infants from the prenatal period until the child is 3 years old. To date, ECS has made over 600,000 home visits, seen 26,000 families, and become a national reference program.

Says Michael Fisher, President and CEO, Cincinnati Children’s, “Judy is one of the most driven people I’ve ever come across. Whether you’re talking about the advocacy front, the philanthropic front or the entrepreneurial front, Judy is all in, all the time, and she motivates others to join her. She has had a huge impact in Cincinnati.”

Robert Wood, PhD, MD, Director, Pulmonary Bronchoscopy, received the American Thoracic Society’s Founder’s Award at the 2018 International Conference in San Diego in recognition of a lifetime of achievement in pediatric respiratory medicine. Wood has played a major role in developing instrumentation and techniques for flexible bronchoscopy in pediatric patients and in teaching endoscopic techniques to a generation of clinicians.

Akihiro Asai, MD, PhD, Gastroenterology, Hepatology and Nutrition, received a Pinnacle Research Award in Liver Disease from the American Association for the Study of Liver Diseases for his work with induced human hepatocytes to model genetic cholestasis.

Robin Cotton, MD, Director, Aerodigestive Center, was recently elected a Fellow of the Royal College of Surgeons of England. Cotton served as Cincinnati Children’s first full-time director of Pediatric Otolaryngology – Head and Neck Surgery from 1973 to 2012, and was instrumental in developing the Airway Management Unit, which evolved into the renowned Aerodigestive Center.

Neil Johnson

Robert Wood, PhD, MD

Theodosia Kaffe, MD, PhD

Akihiro Asai, MD, PhD

Jeffrey Whitsett, MD

Judith Van Ginkel
From June 1 through Dec. 31, 2018, researchers at Cincinnati Children's were awarded 325 grants valued at approximately $133 million in total costs. This list reflects grants near or above $1 million.

Theresa Alenghat, VMD, PhD, Immunobiology, received a four-year, $14 million grant from the National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK) to study host integration of commensal and pathogenic bacterial-derived signals.

Jorge Bezerra, MD, Gastroenterology, received a five-year, $2.2 million grant from the National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK) to renew support for ongoing research of immunologic dysfunction in biliary atresia.

Lee Denson, MD, Gastroenterology, Hepatology and Nutrition, received a three-year, $2.4 million grant from several co-sponsors including the Bill & Melinda Gates Foundation to study environmental enteropathy and malnutrition in Pakistan. Denson also received a five-year, $1.7 million grant from the National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK) to study development of neonatal innate lung defenses.

Prasad Devarajan, MD, Nephrology and Hypertension, received a five-year, $2 million grant from the National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK) to conduct translational studies in pediatric nephrology.

Hitesh Deshmukh, MD, PhD, Neonatology and Pulmonary Biology, received a five-year, $2.1 million grant from the National Heart, Lung, and Blood Institute (NHLBI) to study development of neonatal innate lung defenses.

Matthew Flick, PhD, Experimental Hematology and Cancer Biology, received a five-year, $3.8 million grant from the National Heart, Lung, and Blood Institute (NHLBI) for cooperative research targeting the plasminogen activation system to limit pancreatic fibrosis during myoblast fusion.

Robert Franck, MD, Infectious Diseases, received a two-year, $1.9 million grant from the National Institute of Allergy and Infectious Diseases, to renew support for the Vaccine and Treatment Evaluation Unit at Cincinnati Children’s.

Douglas Millay, PhD, Molecular Cardiovascular Biology, received a five-year, $1.6 million grant from the National Heart, Lung, and Blood Institute (NHLBI) to study molecular pathways controlling cardiac gene expression.

Taosheng Huang, MD, PhD, Human Genetics, received a five-year, $17 million grant from the National Institute of Child Health and Development to study the genetic basis and molecular mechanism for paternal mitochondrial DNA inheritance.

Edith Janssen, PhD, Immunobiology, received a five-year, $21 million grant from the National Institute on Aging to study metabolic alterations in age-associated dendritic cell dysfunction.

Peter Mangolic, MD, Anderson Center, received a $14 million grant from ImproveCareNow to build the capability of the network in patient-centered outcomes research.

Jeffery McKerren, PhD, Molecular Cardiovascular Biology, received a five-year, $1.6 million grant from the National Heart, Lung, and Blood Institute (NHLBI) to study molecular pathways controlling cardiac gene expression.

Louis Muglia, MD, Neonatology and Pulmonary Biology, received a five-year, $5.1 million grant from the National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK) to study the role of skeletal muscle stem cell fusion and fibrosis during myoblast fusion.

Scott Powers, PhD, Behavioral Medicine and Clinical Psychology, received a four-year, $1.4 million grant from the National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK) to support the personalized cystic fibrosis research center.

Nancy Ratner, PhD, Developmental Biology, received two grants from the National Heart, Lung and Blood Institute (NHLBI); one for $2.8 million to study pulmonary macrophage transplantation.

James Wells, PhD, Developmental Biology, received a five-year, $2 million grant from the National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK) to study mechanistic models of congenital heart valve disease; another for $3 million to study mechanisms of congenital heart valve disease in postnatal development and adult injury response.

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GRANTS

GRANTS
Steve Danzer, PhD, Director of the Center for Pediatric Neuroscience at Cincinnati Children’s, uses a multiphoton confocal microscope to generate high-resolution whole-brain images of mice to study the basic mechanisms of epilepsy. In this image, bright green dots show activated neurons in the cortex and hippocampus. Read more about basic brain research happening at Cincinnati Children’s. Read more on page 16.

KINGSGATE MARRIOTT, CINCINNATI, OH

The region’s largest genomics conference features talks by thought leaders in research, clinical, and translational genomics, plus a vendor fair showcasing the field’s leading-edge products and services.

KEYNOTE SPEAKERS:

Matthew Porteous, MD
Associate Professor, Department of Pediatrics and Institute of Stem Cell Biology and Regenerative Medicine, Stanford University.

Bing Ren, PhD
Professor of Cellular and Molecular Medicine, University of California San Diego (UCSD), and Director of the UCSD Center for Epigenomics.

For event details and registration information: www.cincypgm.com
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Stirring Thought at the Discovery Café
Imaging the Invisible

To receive research updates from Cincinnati Children’s by email, sign up at www.cincinnatichildrens.org/email-rh