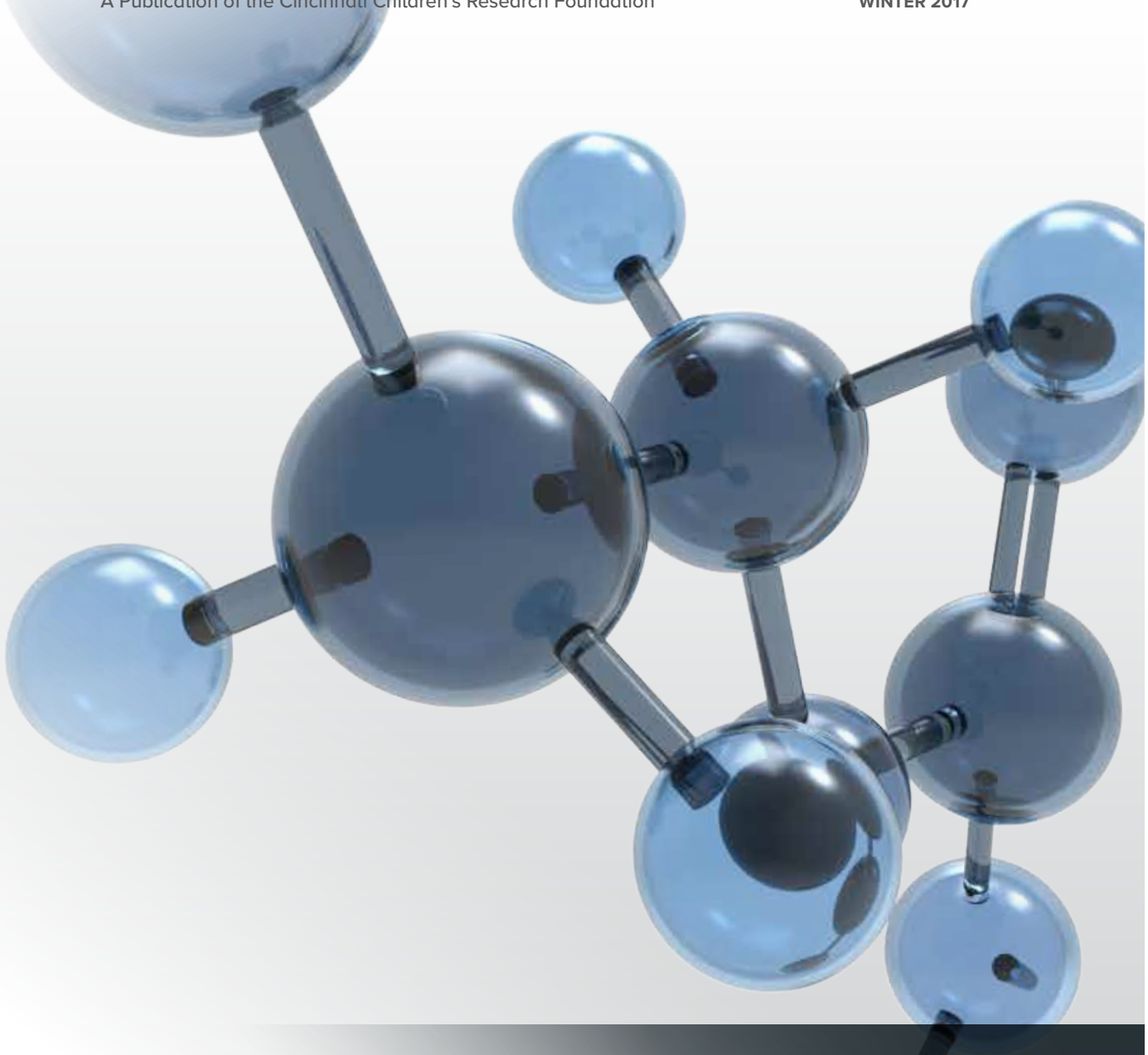
# RESEARCH HORIZONS

A Publication of the Cincinnati Children's Research Foundation

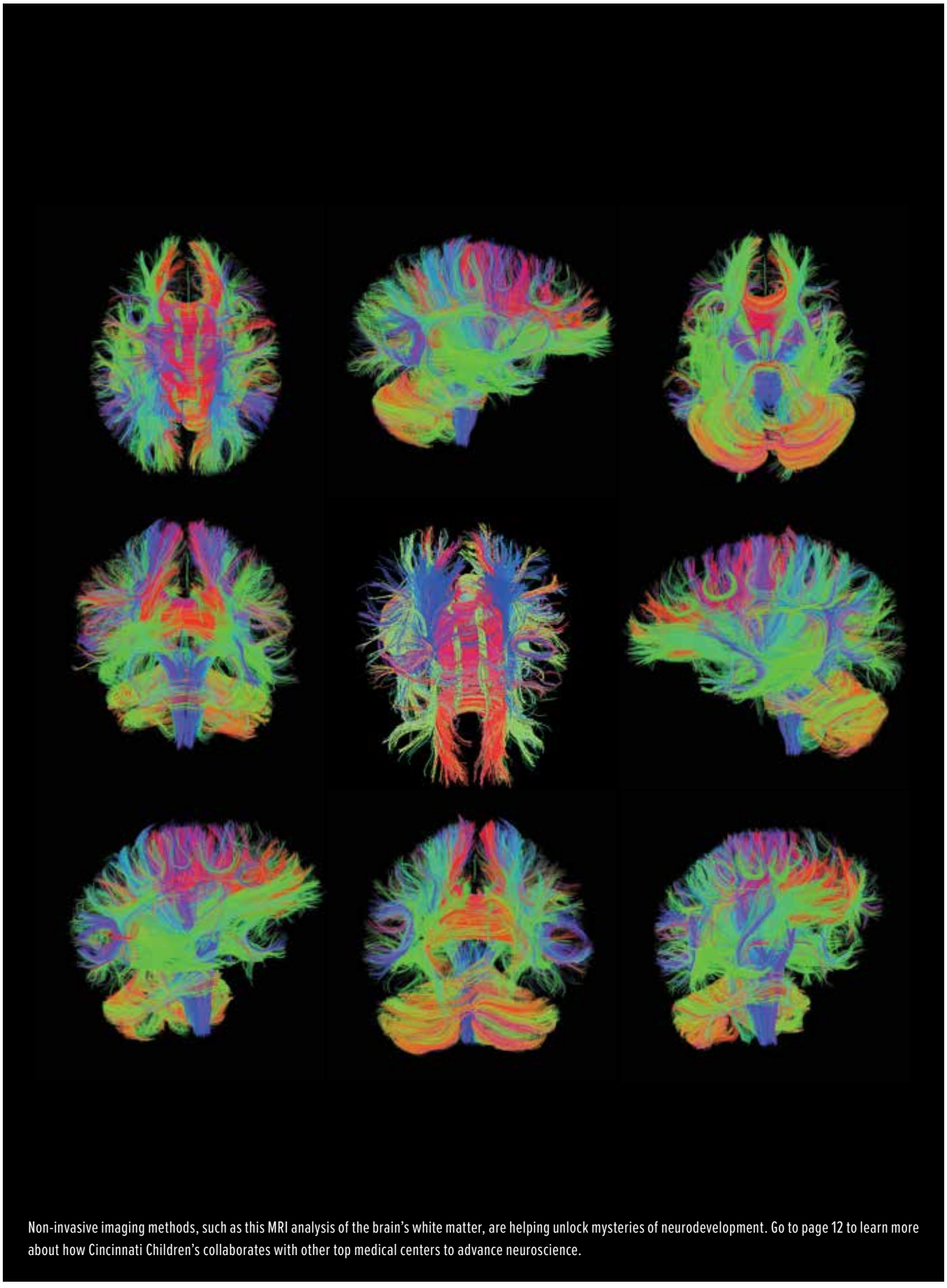
WINTER 2017



Cincinnati Children's™
changing the outcome together

## Collaboration

The catalyst that drives discovery



Non-invasive imaging methods, such as this MRI analysis of the brain's white matter, are helping unlock mysteries of neurodevelopment. Go to page 12 to learn more about how Cincinnati Children's collaborates with other top medical centers to advance neuroscience.

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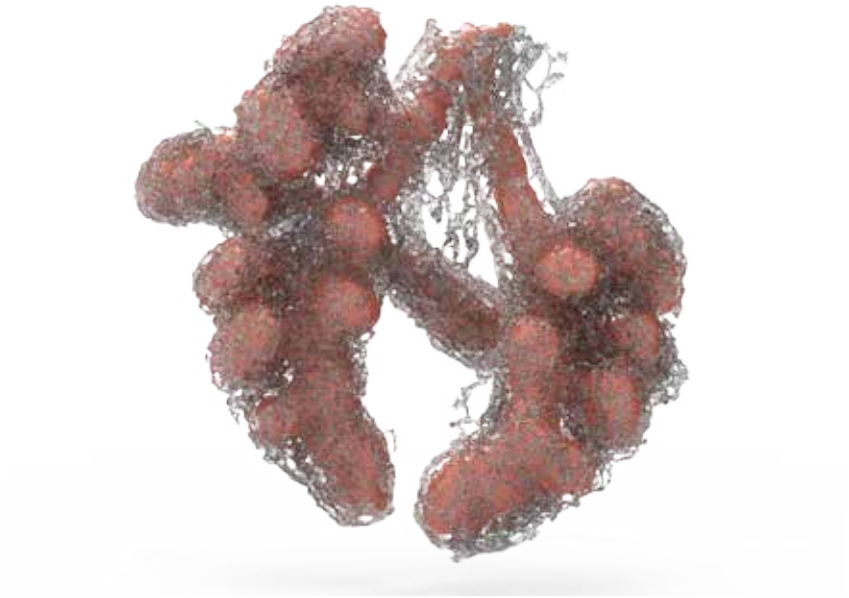
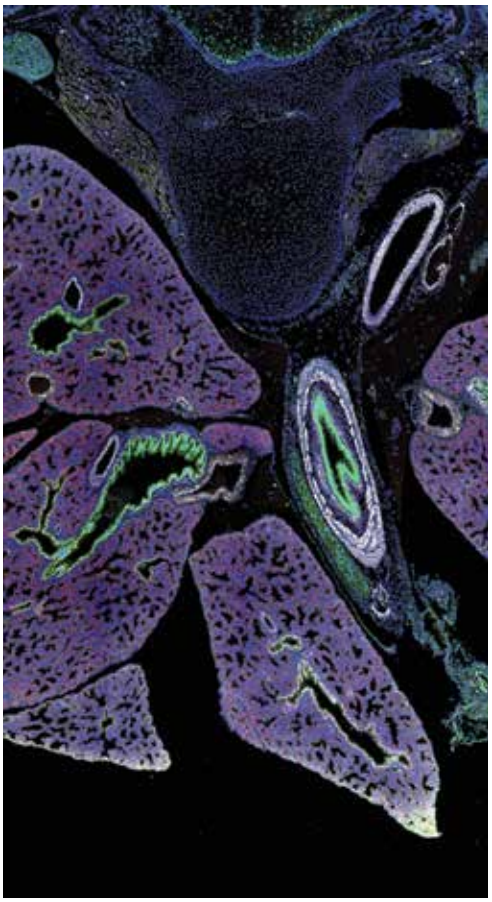




## WINTER 2017 | Collaboration

### DEPARTMENTS



### FEATURES

# Taking Teamwork to Market

## Recent acquisition of Assurex start-up underscores the value of long-term collaboration

When the news announcement came out in August, many of us at Cincinnati Children's were as proud as parents on graduation day. One of our most successful start-up companies, Assurex Health, had been acquired by Myriad Genetics. Thanks to this sale, the GeneSight test that already has helped determine the right drug and dose for more than 300,000 patients with mental health conditions is poised to benefit many thousands more.

This deal reflects a major point of pride for Cincinnati Children's. Assurex Health was founded in 2006, based on technology discovered here by three of our current faculty: Tracy Glauser, MD; John Pestian, PhD; and Alexander Vinks, PharmD, PhD. Our Center for Technology Commercialization worked closely with the spin-off company over the years, which ultimately found its home in nearby Mason, Ohio.

Although successful maturations of spin-off companies can provide funds to invest in a variety of research initiatives, the real significance of the commercialization of this technology is its demonstration of the success of the collaborative team approach we value so deeply.

The faculty team that discovered the critical drug-metabolizing pathway that underlies the GeneSight test worked across multiple specialties. The decision to launch a start-up company was supported by an entire team of leaders and managers. The financial investment to see the company through its early days involved many stakeholders inside and outside of Cincinnati Children's and reflected high-level commitment and strategic vision.

As you will see from the stories in this issue of *Research Horizons*, a commitment to team science is programmed into the DNA of Cincinnati Children's. Be it developing intestinal organoids with functioning nervous systems or serving as a national data hub to make progress against congenital heart defects, we have invested deeply in infrastructure and collaborative interactions both within and beyond our campus.

Our investigators work with partners right here in Cincinnati and around the world. Together, we anticipate that many more research discoveries will mature in the development pipeline and ultimately reach market to improve outcomes for generations of children to come.

– Margaret Hostetter, MD,
*Chair, Department of Pediatrics,*
*Director, Cincinnati Children's Research Foundation,*
*and Chief Medical Officer, Cincinnati Children's*

Greg Myer, PhD, Director of Sports Medicine Research

# Q-Collar Helps Prevent Sports Head Injuries

Scientists have shown that wearing a special compression collar may prevent or reduce trauma from head collisions in sports.

The Q-Collar device protects the brain by applying gentle pressure to the jugular vein. This increases blood volume, which helps the brain fit more snugly within the skull cavity.

Two studies published in June 2016, one in *Frontiers in Neurology/Neurotrauma* and one in the *British Journal of Sports Medicine*, reported on high school hockey and football players, half of whom wore the collar and half did not.

Imaging and electrophysiological testing revealed changes to white matter regions in the brain among athletes in the non-collar wearing group that did not occur among those wearing the collars.

"White matter essentially connects all the brain's pathways, including structure and function," says Greg Myer, PhD, Director of Sports Medicine Research and lead author of both studies. "These results demonstrate a potential approach to protecting the brain within a competitive football and hockey season."

More investigation is needed, says Myer, but this device "could be a real game-changer in helping athletes."

# Diabetes Drug Could Prevent Preterm Birth

Metformin, a medication routinely used to treat type 2 diabetes, may also play a role in blocking a significant cause of preterm birth, according to findings published July 25, 2016, in *JCI The Journal of Clinical Investigation*.

Using mice bred to be prone to premature birth, this early-stage work was led by a team of scientists at Cincinnati Children's with colleagues in France and Japan.

The study details a little-understood molecular pathway that can lead to premature birth by disrupting the function of the decidua, a membrane that lines the uterus and supports the continued growth of developing fetuses. The researchers also demonstrated two successful methods for restoring the lining's function and achieving healthy, full-term births.

"This proof-of-concept study illuminates a potential mechanism behind preterm birth," says study senior author Sudhansu Dey, MD, PhD, Director, Division of Reproductive Sciences. "It also demonstrates possible remedies that are already approved for human use."

Dey says his team has not found any human clinical trials investigating the use of metformin in preventing preterm birth. Preparing and conducting such trials could take several years.

Sudhansu Dey, MD, PhD, Director, Division of Reproductive Sciences

# How Language Might Predict School Violence

Drew Barzman, MD, Director of the Child and Adolescent Forensic Psychiatry Service

Researchers have developed a method that appears to accurately use a student's own words to assess their risk of violent behavior.

"We wanted to focus on a way to objectively analyze students at risk for getting into physical fights or other forms of violence, and who bring weapons to schools with the intent of harming others or themselves," says Drew Barzman, MD, Director of the Child and Adolescent Forensic Psychiatry Service.

The study team interviewed 25 middle- and high-school students who were quiet, withdrawn or isolated, all of which are possible warning signs of school violence.

Scientists transcribed the interviews using manual annotation, a method that extracts information from human language by identifying key words and phrases. This method also has helped identify adolescents at risk of suicide.

The work detected 13 students considered at risk for harming themselves and 11 with an elevated risk of harming others. Detailed findings appeared in July 2016 in *Psychiatric Quarterly*.

For the at-risk students, researchers recommended interventions to parents and schools.

Next, Barzman and colleagues plan to expand their evaluation to hundreds of students. If proven to be beneficial at identifying at-risk students, the testing method could become widely used by schools and clinicians across the country.

# How Heart Complications Emerge in Sickle Cell Disease

Researchers may have found what is behind the heart complications that afflict and kill many patients with sickle cell anemia (SCA).

A study published August 2016 in *PNAS (Proceedings of the National Academy of Sciences)* links malfunctioning molecular pathways to specific heart anomalies in SCA. The findings open a path to earlier non-invasive diagnosis and targeted therapies to help patients live longer with better quality of life.

Using mice bred to mimic human SCA, researchers identified changes in gene expression that resulted in hypoxia and fibrosis in heart tissues. The changes also brought about harmful electrophysiological changes. A significant number of the animals experienced sudden death.

"Sickle cell anemia is associated with significant morbidity and mortality, including a high incidence of unexplained sudden death in young adults," says Punam Malik, MD, senior author and Director of the Comprehensive Sickle Cell Program. "Our findings may provide a unifying cardiac pathophysiology that explains cardiac abnormalities and sudden death seen in humans with SCA."

Punam Malik, MD, Director, Comprehensive Sickle Cell Program

# Genetic Tug-of-War Decides Blood Cell Types

Blood cells appear to reach their final state following a competition between gene regulatory networks, say our scientists in the Aug. 31, 2016, issue of *Nature*.

As blood cells develop, they are bombarded with genetic signals that pull them into multi-lineage states. What cues them to their final type remains unknown, but research points to the instability caused by competing gene networks.

"It is somewhat chaotic, but from that chaos results order," says Harinder Singh, PhD, study co-author and Director of Immunobiology. "This helps us address the intermediate states and the networks of regulatory genes that underlie cell-type specification."

Using computer technology developed by study co-author Nathan Salomonis, PhD, Division of Bioinformatics, the team examined how neutrophil and monocyte blood cells form in mice.

With further study, the findings could provide insights into developmental miscues that cause disease, says H. Leighton Grimes, PhD, study co-author, Division of Experimental Hematology and Cancer Biology.

"How do blood cells know to become neutrophils or monocytes?" he asks. "The number of cells has to be exquisitely balanced. Too many or too few of either can kill you."

(Clockwise from top) Harinder Singh, PhD, H. Leighton Grimes, PhD, and Nathan Salomonis, PhD

# Brain Scans Suggest Gray Matter Differences in Type 2 Diabetes

Researchers here have shown that teens with type 2 diabetes have significant differences in brain gray matter volume. These differences appear to affect brain regions involved in seeing, hearing, memory, emotions, speech, decision-making, and self-control.

The study used high-resolution MRI scans to compare 40 teens of similar ages, race and gender; 20 with diabetes and 20 without. The team presented its findings at the American Diabetes Association's Scientific Sessions in June 2016.

"Previous studies suggested that youth with type 2 diabetes have differences in brain structure and poorer cognitive function scores compared to their peers," says endocrinologist Amy Sanghavi Shah, MD, senior author of the study. "Total and regional brain volume and cognitive scores had not been assessed comprehensively until now."

The findings underscore the importance of preventing type 2 diabetes during a crucial period of brain development.

"We don't know if the differences we found are the direct result of diabetes, but other studies in adults with longer duration of disease also show brain differences and cognitive decline," says Jacob Redel, MD, fellow in the Division of Endocrinology and study lead author.

Amy Sanghavi Shah, MD

Jeffery Epstein, PhD

# Online Program Helps Doctors Treat ADHD

A multi-institutional clinical trial published online July 26, 2016, in *Pediatrics* describes new software that helps pediatricians improve care for children with Attention Deficit/Hyperactivity Disorder (ADHD).

The software was developed by Jeffery Epstein, PhD, the study's principal investigator and Director of the Center for ADHD. The American Academy of Pediatrics selected the software for use in practices that joined a five-state collaborative.

The software helps community practices collect, score and interpret ADHD symptom reports from parents and teachers.

The trial involved 199 providers at 50 practices caring for 373 children with ADHD. Providers were randomized to provide care with or without the technology.

"The software not only helped improve the quality of medical care received by children, but it also improved treatment outcomes," Epstein says.

Jim Greenberg, MD, Co-Director, Perinatal Institute

# Pregnant Women Under-Report Nicotine Use

A study led by Cincinnati Children's and Cradle Cincinnati shows a significant gap between the number of women who report smoking during pregnancy and those who test positive for nicotine exposure.

The study, published online July 7, 2016, in the *Journal of Perinatology*, detected high-level nicotine exposure in 16.5 percent of women tested. The team found low-level exposure for another 7.5 percent. However, only 8.6 percent admitted to using cigarettes.

The study shows that self-reporting methods for estimating nicotine use do not capture all means of exposure, including e-cigarettes.

"We have long suspected that smoking during pregnancy is under-reported, but now we know just how many women struggle to quit when they are pregnant," says senior author Jim Greenberg, MD, Co-Director of the Perinatal Institute.

These findings underscore the need for greater public health efforts to decrease smoking among pregnant women, Greenberg says.

# Home Addresses Can Predict Asthma Risks

Helping a child with severe asthma could be as simple as knowing his home address, say authors of a study published online August 2016 in *Academic Pediatrics*.

Findings revealed that home addresses reliably identified at-risk children. In fact, a home address could guide risk assessment as soon as a family registers at the hospital or doctor's office.

"Inequalities in pediatric asthma-related illness are largely driven by socioeconomic hardships and other social determinants of health," says lead author Katherine Auger, MD, Division of Hospital Medicine. "Children hospitalized with asthma are disproportionately from disadvantaged backgrounds and neighborhoods. Bringing this information to the clinical team could be beneficial in targeting and allocating resources more effectively."

Katherine Auger, MD, Division of Hospital Medicine

# Team Science Helps Accelerate Innovation

Especially at the translational level, answering the next big questions in child health depends upon cooperation between institutions and collaboration among specialty fields

by Tim Bonfield

Tracy Glauser, MD, frames the relationship between teamwork and health science discovery as a building process.

Every house needs a strong, solid foundation. Yet as the structure rises, the complexity increases. Stone and concrete give way to plumbing, wiring, roofing, and windows. Bringing the components into a cohesive, healthy whole requires seeing the relationships between them, and understanding the systems involved.

"Thirty or 40 years ago, our understanding of the human body and our understanding of science was such that the unit of research as an individual made a lot of sense," Glauser says. "An individual researcher, with a lab support team, could take on many of the questions being asked."

In this fashion, decades of brick-by-brick foundation building has amassed today's understandings of human development and disease.

"Now, however, as discovery has accelerated over the last 30 years, the questions have become bigger. We are beginning to realize the interplay and integration between systems. We are seeing these processes at work between molecules, cells, and organisms," Glauser says. "There is a parallel to this in how science advances, between individuals, divisions and institutions."

## CHANGING QUESTIONS, SHIFTING APPROACHES

Cincinnati Children's, over many years, has built a strong culture of collaboration between researchers and clinicians. In pediatrics, such teamwork is a necessity.

Unlike the powerful driving forces of heart disease and cancer in adult medicine, a constellation of more than 7,000 rare diseases shapes pediatric science. For many scientists, simply finding enough cases to begin gathering information requires cooperation far beyond their own laboratories.

A similar dynamic plays out on the national level.

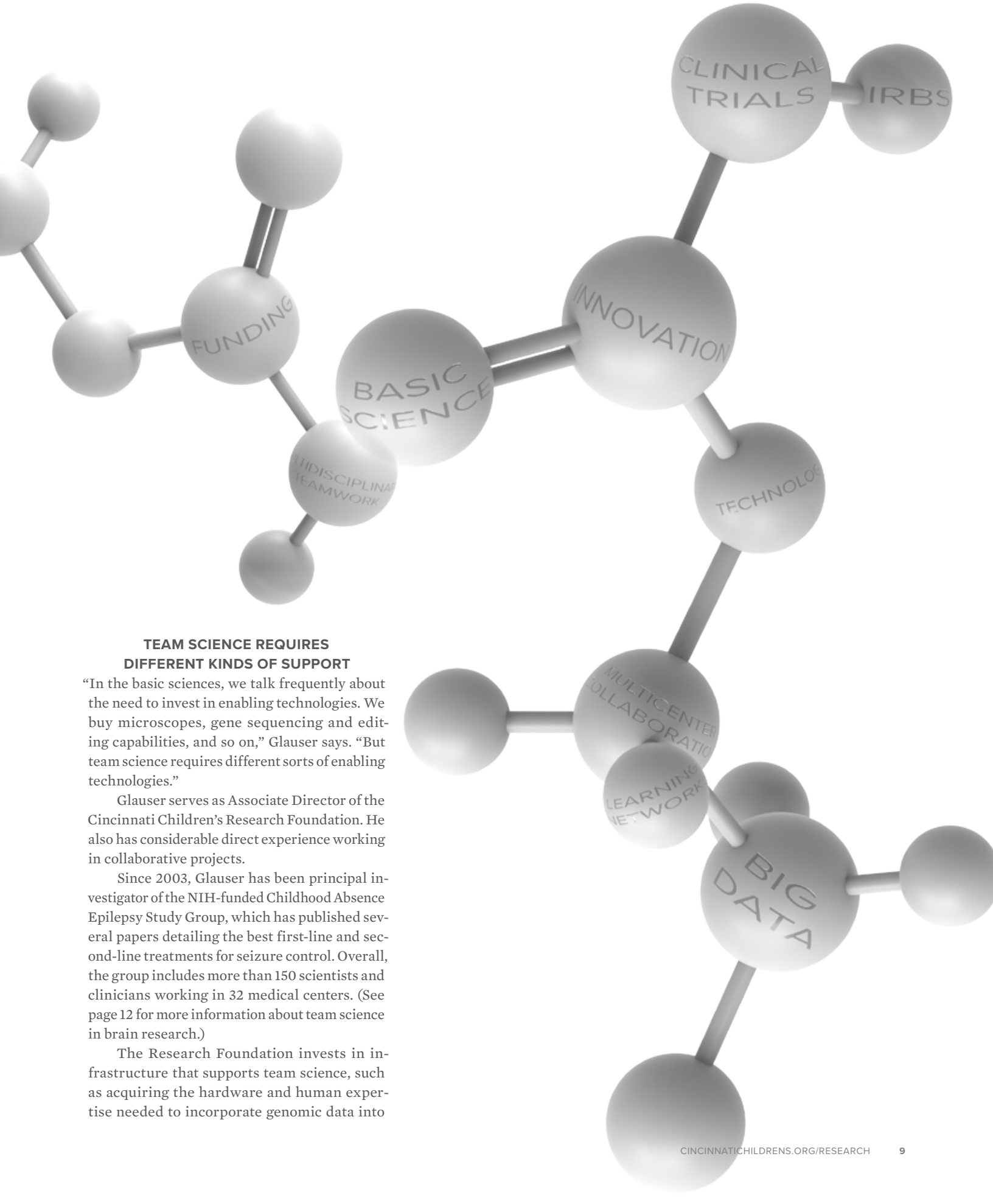
At the National Institutes of Health (NIH), the mostly individual R01 research grant remains the workhorse of federally funded discovery. Yet, despite an explosion of technology opening exciting new opportunities, the overall amount of R01 funding has been flat.

NIH data shows that annual funding for R01 grants has hovered between $9.8 billion and $10.6 billion since 2006.

However, the NIH has been increasing its support for team-oriented, multi-institutional collaborative agreements. The agency's U series of grants includes funding for various "high-impact" collaborations that seek to advance new technologies and build upon breakthroughs.

In 2006, the NIH devoted $1.9 billion to four types of research-focused U grants. By 2015, the NIH had increased that funding by 46 percent to commit $2.8 billion to 14 types of U grants.

The money involved remains a fraction of R01 spending, but the direction-setting influence is clear.




### TEAM SCIENCE REQUIRES DIFFERENT KINDS OF SUPPORT

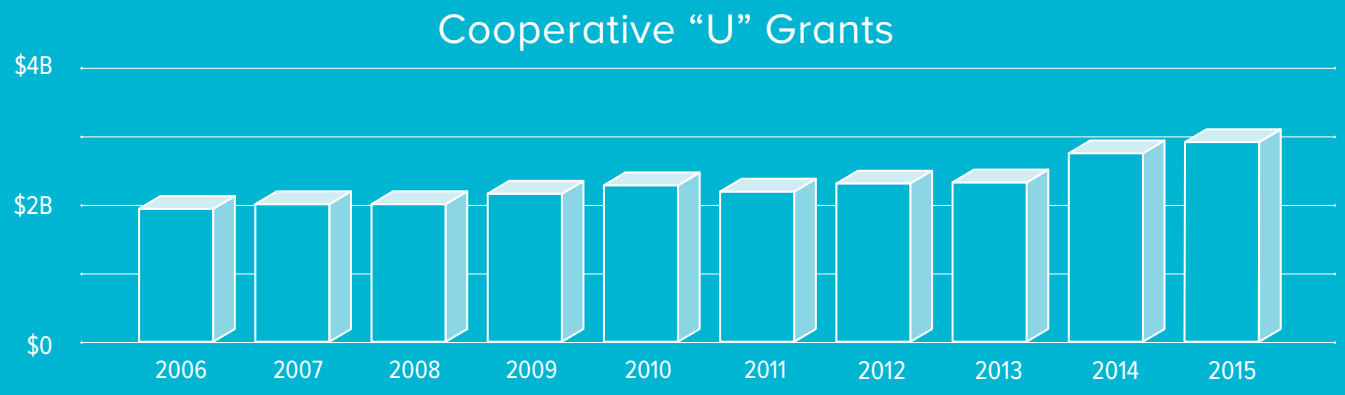
"In the basic sciences, we talk frequently about the need to invest in enabling technologies. We buy microscopes, gene sequencing and editing capabilities, and so on," Glauser says. "But team science requires different sorts of enabling technologies."

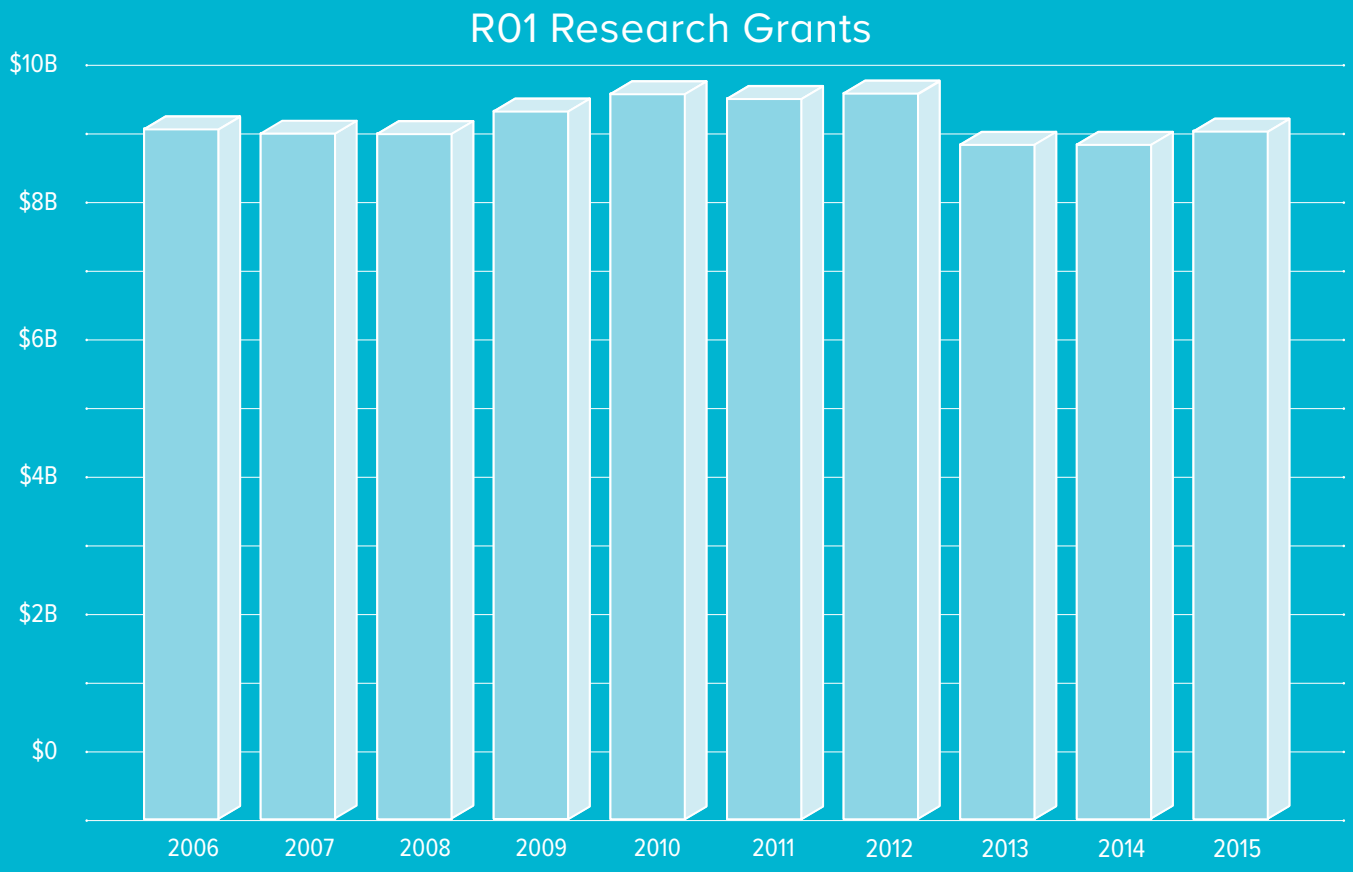
Glauser serves as Associate Director of the Cincinnati Children's Research Foundation. He also has considerable direct experience working in collaborative projects.

Since 2003, Glauser has been principal investigator of the NIH-funded Childhood Absence Epilepsy Study Group, which has published several papers detailing the best first-line and second-line treatments for seizure control. Overall, the group includes more than 150 scientists and clinicians working in 32 medical centers. (See page 12 for more information about team science in brain research.)

The Research Foundation invests in infrastructure that supports team science, such as acquiring the hardware and human expertise needed to incorporate genomic data into

# NIH Funding Shifts Toward Team Science



research across the institution. These growing capabilities helped the medical center recently win a $32.5 million Bench to Bassinet grant to accelerate progress against congenital heart defects. (See page 24 for more details).

Other investments occur even deeper behind the scenes: in the legal and regulatory aspects of science. Teaming up with other medical centers also means rewriting contracts to allow data sharing, hashing out intellectual property concerns, evolving institutional review board processes, and deciding how to share the credit as well as the work.

"How do we reward team science? In baseball, everybody on the team gets a World Series ring. But in academics, it can seem like there's only one ring to give out—to the principal investigator," Glauser says.

"How do we reward team science? In baseball, everybody on the team gets a World Series ring. But in academics, it can seem like there's only one ring to give out—to the principal investigator."

– Tracy Glauser, MD

Associate Director, Cincinnati Children's Research Foundation

## TEAMWORK TAKES MANY SHAPES

Cincinnati Children's plays leading roles in cooperative research at various levels and with a variety of funding sources.

For example, the national ImproveCareNow project brings together families, scientists and clinicians from more than 90 medical centers as a "learning network" dedicated to improving outcomes for young people living with Crohn's disease and ulcerative colitis. The network has been such a success that it recently earned the prestigious 2016 Drucker Prize.

Peter Margolis, MD, PhD, is a Co-Executive Director of ImproveCareNow. He and colleagues in the Anderson Center for Health Systems Excellence are working to expand the learning network concept to other forms of chronic illness, including cystic fibrosis. Support for their work comes from an NIH "Roadmap" grant for transformative research and other funds from the Agency for Healthcare Research and the Patient-Centered Outcomes Research Institute (PCORI).

Cooperative projects also occur outside the traditional NIH funding pipeline.

For example, federal, state, county and charitable funds support multiple initiatives to reduce infant mortality in Ohio. These programs include Cradle Cincinnati, the March of Dimes Prematurity Research Center Ohio Collaborative, and the Ohio Perinatal Quality Collaborative.

The Center for Prevention of Preterm Birth at Cincinnati Children's, directed by Louis Muglia, MD, PhD, is deeply involved in all these programs. The March of Dimes Ohio Collaborative includes more than 100 scientists, researchers, physicians and staff. More than two dozen public agencies and community organizations participate in Cradle Cincinnati. Meanwhile, hospitals across the state share best practices through the Perinatal Quality Initiative.

Sometimes, institutions choose to fund cooperative efforts without any public funding.

The new Genomics Research and Innovation Network (GRIN) brings together leaders from Cincinnati Children's, Boston Children's Hospital, and the Children's Hospital of Philadelphia to explore ways to accelerate research on the genetic causes of disease.

The work happening within GRIN establishes the crucial ground rules needed for long-lasting institutional cooperation, Glauser says. Three research projects involving pooled data already have begun. (See page 26 for more details.)

## CHALLENGES AHEAD FOR TEAM SCIENCE

In basic research, many important questions can still be tackled without involving dozens or hundreds of institutions, Glauser says. However, the demand for institutional collaboration at the clinical and translational level is clear and rising.

Today's big research projects can involve hundreds of people making important contributions. Expertise may come from dozens of institutions, sometimes spanning continents. That means research centers face constant challenges finding ways to work together across highly diverse cultures and forms of governance.

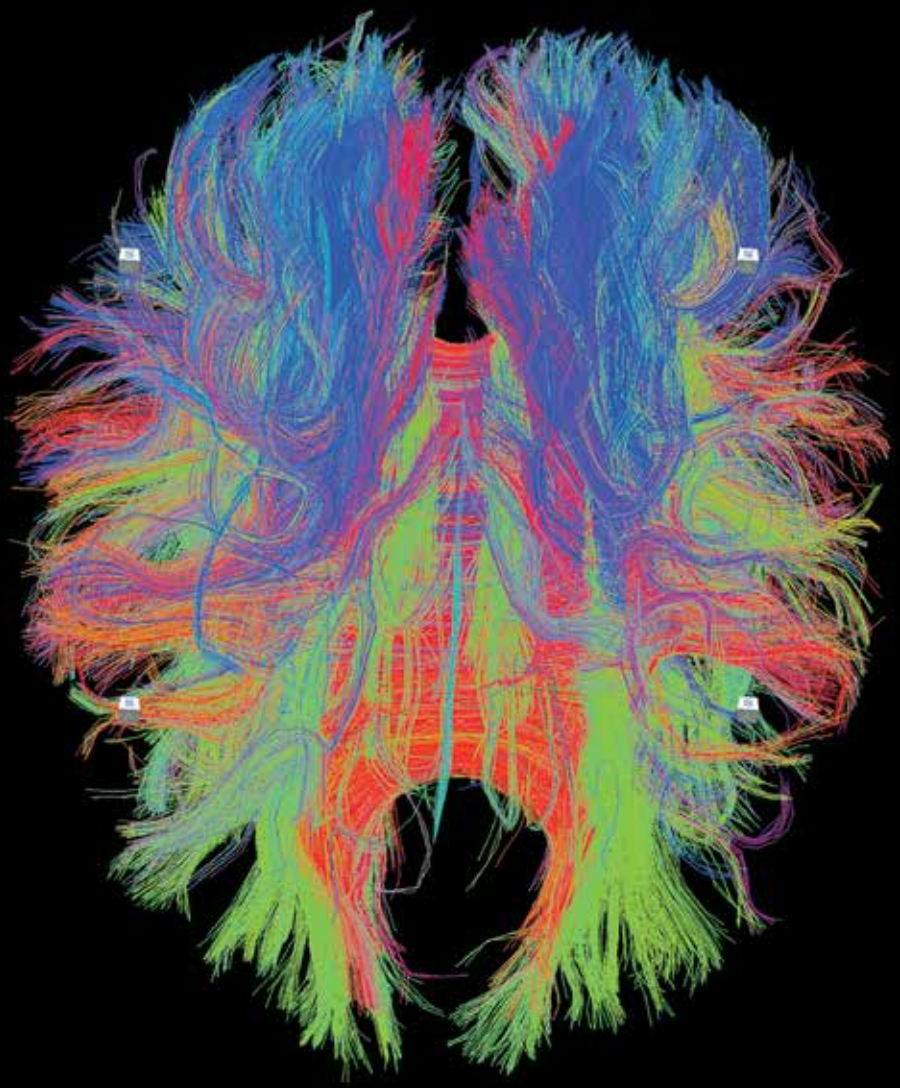
"If you cannot work out these issues, you'll never be able to do team science," Glauser says. "But the goal is worth the effort. The ultimate outcome of collaboration is great science that helps patients." ■

# BRAINSTORMING

## About the Brain, and the Storms Within

Strong collaboration has transformed research in neuroimaging, epilepsy and migraines

by Tom O'Neill



They came for the tea and cookies, but stayed for the main course: insights into reducing the neurological "noise" that complicates the science of brain imaging.

On a recent Tuesday afternoon, members of the Pediatric Neuroimaging Research Consortium (PNRC) and their guests gathered over sips of Twining's Earl Grey.

Inspired by a gathering format established at Princeton University, "team neuroscience" is equal parts informative and informal. The group's core includes 10 researchers from five divisions, but its work impacts research throughout Cincinnati Children's and institutions across the U.S.

This strong sense of collaboration is fueling major developments in many areas of neuroscience. From migraines and language processing to epilepsy and hydrocephalus. From the behavioral to the structural.

Simply put, the brain is a complicated place. Image is everything.

"To ask and answer all the questions of the 21st century, we need all the different specialties at the table," says Tracy Glauser, MD, Director of the Comprehensive Epilepsy Center.

"The questions of the brain and mind are so complex," he says, "so we rely on technology to look at the function and structure."

Glauser, who also serves as Associate Director of the Cincinnati Children's Research Foundation, says that multi-institutional research and the sharing of data are essential to the future of personalized medicine. He has considerable direct experience in collaboration as principal investigator of a major ongoing clinical trial to study treatments for absence epilepsy.

The double-blind, random trial is a monument to the power of multi-institutional cooperation. It involves 32 medical centers, 150 trial members and 446 patients.

The first two cycles of the trial established a baseline for medication strategies, and show promise that researchers can improve the genetic predictors of individual children's outcomes.

## COLLABORATION FITS CINCINNATI CHILDREN'S TO A TEA

The PNRC tea-hour might seem symbolic, but it works.

"It puts people more at ease, and that's the culture we want to have," says PNRC Director Jennifer Vannest, PhD, Division of Neurology. "Some might think we're a tough crowd, but really, it's about constructive feedback. We all benefit from that."

Meetings typically include scientists from all five core PNRC divisions (Radiology, Neurology, Neurosurgery, Anesthesia and Biostatistics). One recent gathering also included a neonatologist, a data analyst, and three first-year graduate students in neuroscience.

"We couldn't do what we do without being interdisciplinary," says Vannest, whose research focuses on neurological disorders and language impairments. "In order to develop better techniques for MRI, we need engineers and physicists."

Enter Gowtham Atluri, PhD, an assistant professor of electrical engineering and computer systems at University of Cincinnati. His presentation to the group focused on reducing the "noise" in data from functional magnetic resonance imaging (fMRI).

He says he only began to understand the nuances of neuroimaging once he realized "there was a good bit of noise" in the scans. fMRI captures brain activity in time segments.

The key, he says, is to understand how these images (say, one taken every two seconds for 10 minutes and then layered through various algorithms) can reveal patterns of connections between different brain regions.

Vannest is optimistic. "We're beginning to better understand how the brain is organized, that it's subdivided, and that its function happens with network interactions," she says. "That's the focus of new imaging techniques. It is changing how we look at learning and the acquisition of skills."

Not just where, but when, neurons fire off. A single image cannot capture that. But a tall stack of images, organized for maximum "noise reduction," might.

"This is, I think, exemplary about what's going in neuroimaging," says Scott Holland, PhD, a physicist who founded the consortium in 2005. He directs both Research in Patient Services and the Reading and Literacy Discovery Center at Cincinnati Children's.

"Neuroimaging has gotten so complicated that no one of us has all the pieces," he says. "I know how to make wonderful images of children's brains. But I'd say more than half the job now is the analysis of that data."

## fMRI DATA SHOWS THE IMPORTANCE OF READING TO CHILDREN

In a study published in September 2015 in *Pediatrics*, a team led by Holland and John S. Hutton, MD, MS, Division of General and Community Pediatrics, demonstrates that reading to preschool children at home is associated with the activation of brain areas that support mental imagery and narrative.

Furthermore, higher reading exposure showed up on scans as neural stimulation in the left-sided parietal-temporal-occipital

These artificial color images of white matter tracks in the brain were constructed with a 3-Tesla MRI scanner using a high angular resolution diffusion imaging method. Information from the C-MIND study at Cincinnati Children's—funded by the Eunice Kennedy Shriver Institute for Child Health and Human Development—is demonstrating the power of non-invasive imaging methods to reveal how the brain develops.


association cortex. This is the "hub" region for semantic language processing.

The following month, the journal *Brain Research* published a study by six PNRC members, including Holland and Vannest, showing that narrative comprehension at age 6 accurately predicted a child's performance on the ACT college-entrance test at age 18. The data came from fMRI in a longitudinal study that included measures of academic achievement 10 to 12 years later.

Still, for all the advancements in capturing the brain's activity, some things remain elusive. Holland recalled a dispiriting moment about 15 years ago, while giving a presentation to the American Association of Child and Adolescent Psychiatry.

One of the 300 doctors there stood up and expressed concern about a bipolar patient he feared might develop schizophrenia. Can you image him and tell if that's going to happen, he asked Holland.

"And I had to say, 'No. Our technology isn't there yet. Maybe one day.' "

A 2015 University of Minnesota study that Atluri was a part of, however, did reveal abnormalities in the connections of different brain regions in people with schizophrenia. So in terms of large cohorts, that day is here. In terms of individual patients, no.

You can't see schizophrenia on an fMRI scan, in much the same way neuroimaging can't capture psychological disorders or why children are compelled to certain behaviors.

Or why some children develop debilitating migraine headaches.

Andrew Hershey, MD, PhD, Director, Division of Neurology, and Scott Powers, PhD, Division of Behavioral Medicine and Clinical Psychology, are Co-Directors of the Headache Center at Cincinnati Children's.

## STUDY REVEALS THE POWER OF SUGGESTION & ANTICIPATION

In a study published Oct. 27, 2016, in *The New England Journal of Medicine*, a team led by Hershey and Powers set out to compare the effectiveness of the two leading migraine medications for children, amitriptyline and topiramate.

Both drugs have adverse side-effects, most commonly paresthesia (typically a pins and needles sensation), fatigue, dry mouth and weight loss.

Findings showed that a placebo, a mere sugar pill, proved just as effective at limiting the frequency and severity of children's migraines.

The Childhood and Adolescent Migraine Prevention (CHAMP) study was conducted at 31 sites in the U.S., with Cincinnati Children's responsible for all clinical oversight

Above: Scott Holland, PhD, and Jennifer Vannest, PhD, are leading efforts to capture brain activity with fMRI techniques while reducing data "noise." Next page: A team led by Andrew Hershey, MD, PhD, (left) and Scott Powers, PhD, published surprising findings about the effectiveness of migraine medications in the Oct. 27, 2016, issue of *The New England Journal of Medicine*.

activities. Researchers at the University of Iowa provided the statistical data management.

The 24-week clinical trial included 328 eligible patients. Sixty-one percent of those on a placebo saw the days they had a headache reduced by 50 percent or more. Topiramate hit that mark 55 percent of the time; amitriptyline 52 percent.

"We did find it surprising," says senior author Hershey.

"Not that we could get a placebo response rate that was equally as high," he explains, "but because we required that all the children receive acute therapy, healthy habit discussions and adherence management. That may be why they improved across the country."

Hershey and Powers believe the likely cause of the placebo's effectiveness is the expectation of relieving the migraine, and yet the impact on the brain was physiological—not imagined. In much the same way, children who anticipate getting a migraine are more likely to get one than they otherwise would. Stress is a factor.

This means that, for some children, the stress-reducing experience of taking medication—any medication—might be stronger than the actual biochemical effects of the medicine. It suggests a vital role for other forms of therapy.

"Our national team was hoping to develop evidence to drive the choice by medical providers of the first-line prevention medication for helping youth with migraine, but the data showed otherwise," says first-author Powers. "We see this as an important opportunity for health care providers, scientists, children, and families because our findings suggest a paradigm shift.

"First-line prevention treatment will involve a multidisciplinary team approach and focus on non-pharmacological aspects of care," he says. "The good news is we can help children with migraines get better."

## BALANCING BRAIN & MIND

The migraine medication findings underscore the potential value of cognitive behavioral therapy as a tool for controlling pain. They also show that the complexities of the brain and the mind are essentially inseparable.

No other organ of the body is like that.

Glauser says non-invasive imaging will continue to be crucial in unlocking the brain's mysteries. The big challenge is a simple function of anatomy. "The brain is not an easily accessible organ, like the heart or liver or kidney," he says. "You can't take someone's brain out."

So it takes a neuroimaging team focused on collaboration in all its tea-sipping forms.

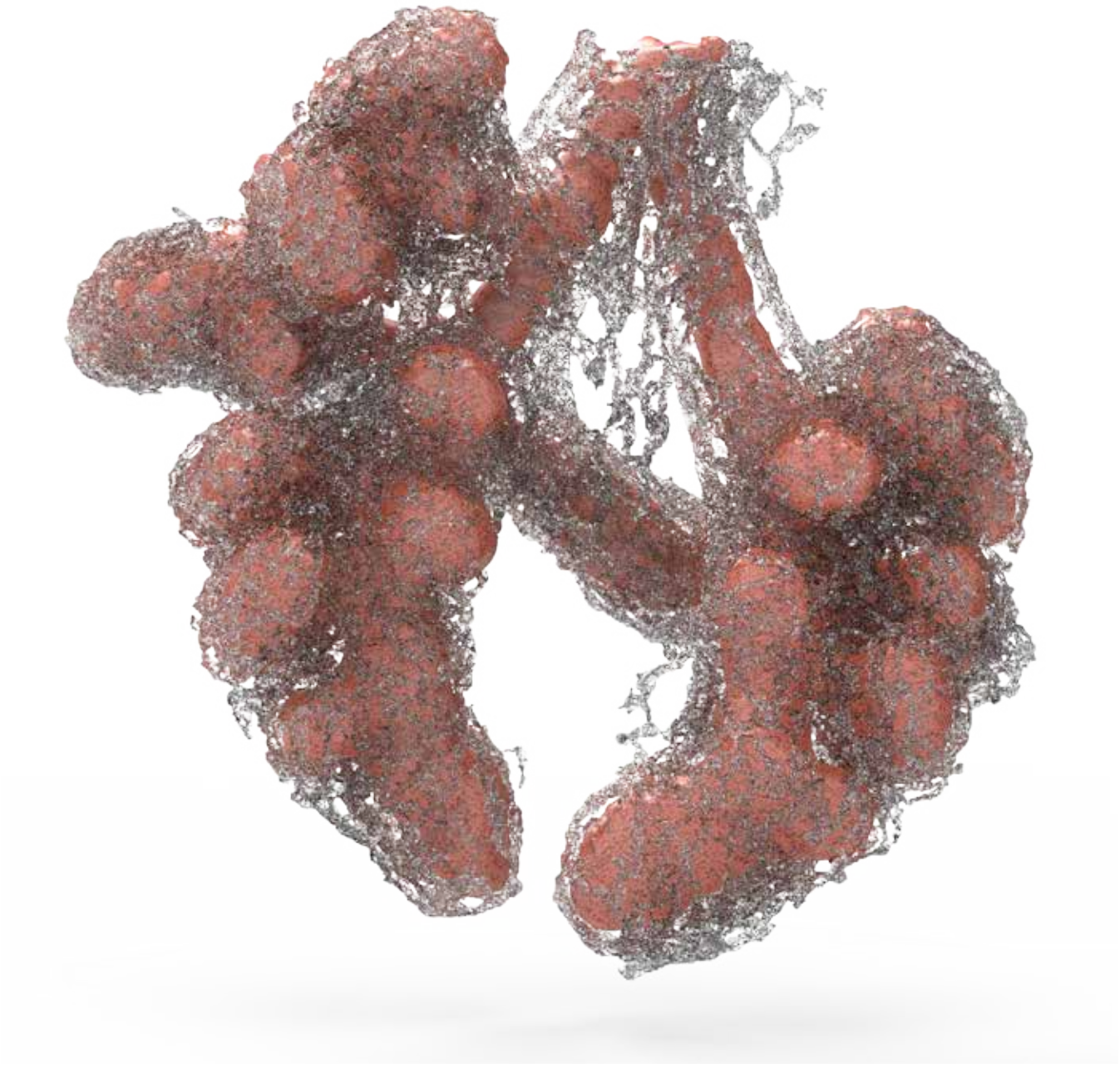
At the recent meeting of the PNRC, most of the 24 researchers in attendance thanked Atluri for his insights and filed away to the elevators. Left were just a few stragglers. A minute later, there was a sound of wheels rolling down the hallway.

For a guy with three degrees in Engineering and Applied Science from Yale, Holland might seem like an unlikely guy to be pushing the cart of tea supplies back to storage for another week. But there he was, yet another example of teamwork in action. ■

# Orchestrating the LungMAP Project

## Recording the score of lung development requires a symphony of teamwork

by Nick Miller



Learning how a lung is made, note by molecular note, may one day lead to life-saving new abilities to repair or regenerate lung tissue—but getting there requires nothing less than a symphony of scientific cooperation.

A full orchestra of research centers, scientists and physicians are playing important roles in the multi-million-dollar LungMAP project, sponsored by the National Heart Lung and Blood Institute. Jeffrey Whitsett, MD, Co-Director of the Perinatal Institute at Cincinnati Children's, serves as the head conductor.

LungMAP involves dozens of scientists and physicians at 10 research institutions who have divided the task into sections—such as different regions or developmental stages of the lung. Each is helping master the different parts of a molecular and cellular score that eventually will serve as a complete atlas of the developing lung.

Their instruments: various forms of advanced scientific technology. Single-cell genomics. Transcriptomics. Proteomics. Metabolomics. And so on. Rapid, recent advances in these technologies, plus the power of collaborative teamwork, make a project like LungMAP possible.

"We feel strongly that understanding the cellular and molecular basis of normal tissue development will inform us about the processes involved not only in abnormal lung structure but also in repair," says Whitsett. "This will help let us know if we can intervene, when we need to intervene, and what would be the processes that are good molecular targets for intervening."

Roughly two years in, LungMAP has already made significant progress. However, many more mysteries have yet to be unraveled before researchers can produce a definitive blueprint of how lungs develop in people.

"We are beginning to understand the cellular and molecular circuitry that form the tissue and tissue types that lead to lung development, but there is still a great mystery surrounding the later developmental stages when the alveolar septa are formed," explains Whitsett.

Alveolar septa are segmented compartments of air sacs that facilitate the transfer of oxygen and carbon dioxide between the lungs and bloodstream. If these do not develop normally, trouble ensues.

There is a stage for infants that Whitsett describes as the "perinatal transition to air breathing." This is an especially critical time for preterm babies—who he has spent much of his career caring for at Cincinnati Children's.

"Prematurity, infection and injury can forever change the structure of the lung," he says, "and contribute to a lifetime of chronic health problems."

Given that lung diseases are not confined to babies, discoveries revealed by LungMAP could one day help a wide range of people young and old.

## AT FIRST, A CACOPHONY

Reaching the crescendo—where doctors can regenerate or repair damaged lung tissue—remains a distant goal. Currently, the orchestra is warming up in a convoluted din of work to understand how the lung's 40 different cell types communicate across all stages of lung development.

Take for example Steve Potter, PhD, a developmental biologist and co-leader of Cincinnati Children's arm of LungMAP.

Potter is a champion of single-cell gene expression analysis. His work produces a quantitative readout of how each of roughly 23,000 genes functions within each and every cell.

"You learn a tremendous amount about what is going on," Potter explains. "Who is talking to who, who is making what, what their function is, how the whole process is working, how it's moving forward and how it's making a lung."

Going a step further, scientists can use known disease-specific gene mutations to trigger human lung disease in mouse models. They then use single-cell analysis to quantify detailed expression profiles for every gene in every cell of the diseased lungs—giving them an unprecedented view of these ailments.

This digital rendering of a developing lung is part of the terabytes of data being assembled as part of the LungMAP project. Teams at Cincinnati Children's needed to develop custom software to process the sheer volume of information.

Steve Potter, PhD, (left) and Jeffrey Whitsett, MD, are working with experts in bioinformatics, confocal imaging and other fields to make dramatic progress at developing a molecular-level map of lung development. Their tools include a 3D model of a mouse lung that is so data-rich it took days to print.

### FINDING MUSIC IN THE NOISE

Potter describes the collective accumulation of single-cell information as a "very powerful dataset" that's also a very challenging dataset. The sheer volume of data involved reaches into the terabytes. A single terabyte adds up to 1 trillion bytes, or 1,000 gigabytes.

This is where the bioinformatics experts join the concert, according to Potter.

Yan Xu, PhD, Divisions of Neonatology and Pulmonary Biology, and Bruce Aronow, PhD, Division of Biomedical Informatics, are significant players in LungMAP. Xu worked with Minzhe Guo, PhD, Pulmonary Biology, to create a computer program called SINCERA.

The program quickly processes and analyzes vast amounts of single-cell genomic data. It also helps identify distinct cell types, reads specific gene signatures and helps define the driving forces that cause specific cell types to form.

> "You learn a tremendous amount about what is going on..."
>
> – Steve Potter, PhD

Freely available to scientists, SINCERA is one of two internet-based analytical tools created here for the LungMAP project. Xu worked with Yina Du, a senior bioinformatics analyst, to also develop LungGENS. LungGENS allows researchers worldwide to analyze and visualize single-gene expression profiles. It also is linked to a diverse set of other analytical programs used to interpret data, many developed by Aronow and his team, says Whitsett.

However, this symphony goes well beyond single-cell and computer-based bioinformatics analysis.

### MANY PARTS TO PLAY

Other investigators in Developmental Biology and Pulmonary Biology are conducting immuno-staining of high resolution confocal microscope images to identify proteins in individual lung cells and performing other experiments to validate single-cell data.

Researchers working with the Confocal Imaging Core at Cincinnati Children's (led by Matt Kofron, PhD) are producing vivid color images that highlight the details of cells and microscopic structures within developing mouse lungs.

The teams also used a 3D printer to produce a plastic model that shows in exquisite detail a mouse's lungs, including a

surrounding lacework of vasculature. The data involved are so rich that printing the model took days.

Joe Kitzmiller, a senior research assistant in Neonatology and Pulmonary Biology, leads a project called LungImage, a web-based developmental library of mouse and human lung images available through LungGENS.

And to promote education, collaboration and idea generation, all data are shared openly on the project website at LungMAP.net.

> "We are beginning to understand the cellular and molecular circuitry..."
>
> – Jeffrey Whitsett, MD

Other institutions working on LungMAP include Children's Hospital Los Angeles, Pacific Northwest National Laboratory, the University of Texas at Austin, the University of Alabama at Birmingham, Yale University, the University of California, San Diego, Carnegie Mellon University and Duke University.

### THE NEXT MOVEMENT BEGINS

So far, investigators have formed an increasingly robust picture of the cellular and molecular crosstalk that goes into making a mouse lung. Now researchers are beginning to work on the next step—applying what they have learned about the mouse lung to the human lung.

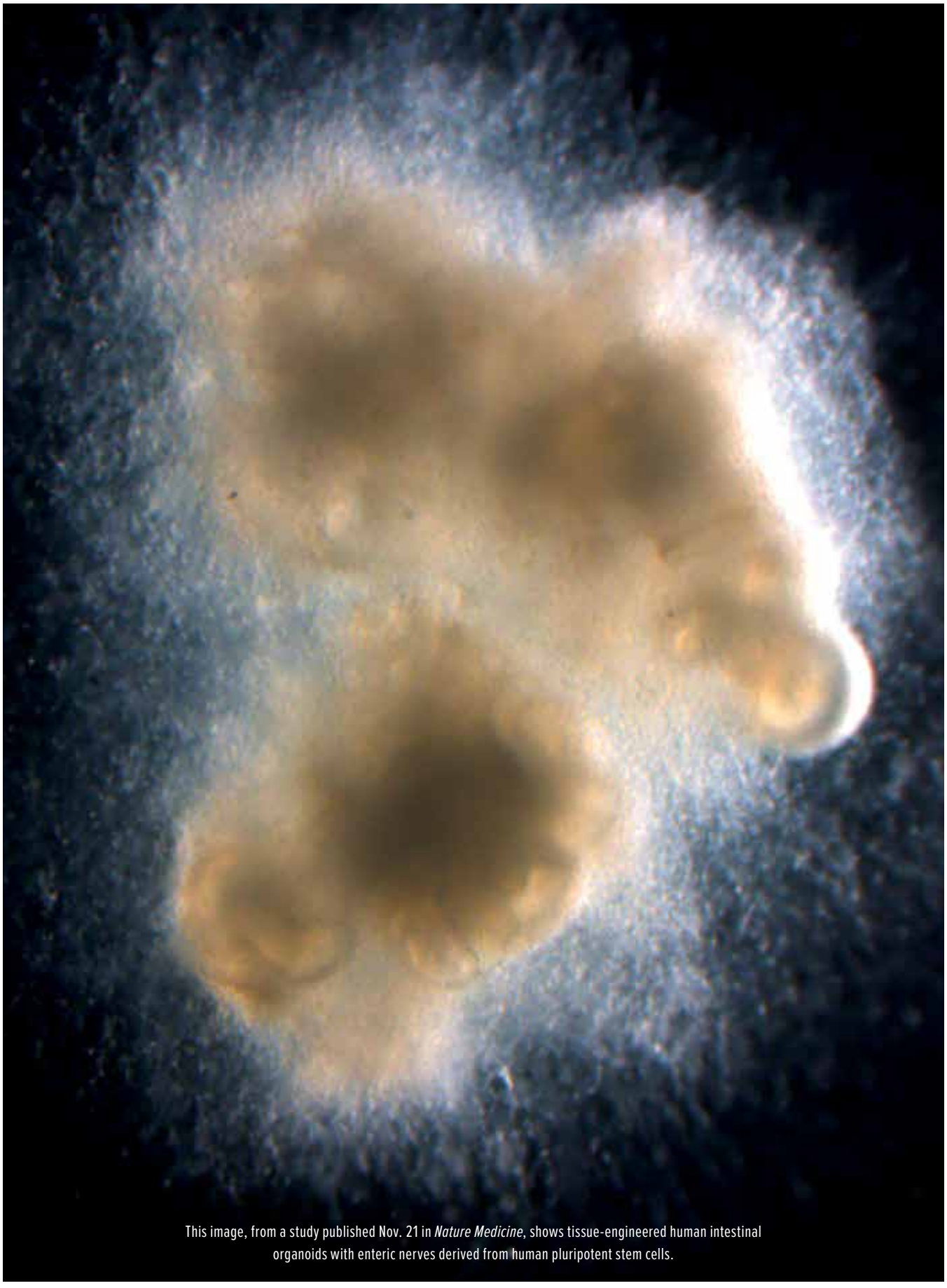
Obtaining human lung tissue samples requires a great deal of effort and care, as well as informed consent from families who have lost children. This critical task falls to the LungMAP Human Tissue Core at the University of Rochester Medical Center in New York.

Working with organizations such as the United Network for Organ Sharing, the tissue core is procuring, processing and distributing normal late fetal, neonatal and early childhood human lung tissue for the LungMAP project.

Whitsett says continued progress would not be possible without the help of many volunteers who make these tissue donations possible.

"The entire LungMAP team," he says, "is so very grateful for the donation of these precious materials, which will be used to understand the renewable functions of the human lung on which every breath depends." ■

This confocal microscope image shows a developing mouse lung. Images like these are revealing new understandings of the molecular processes at work in lung formation.



This image, from a study published Nov. 21 in *Nature Medicine*, shows tissue-engineered human intestinal organoids with enteric nerves derived from human pluripotent stem cells.

# Engineering Tissue by Getting out of Nature's Way

Years of collaboration leads to important breakthroughs in growing functional organ tissue

by Nick Miller

A long-shot idea that started on a lab drawing board has become an innovative and broadly applicable research technology—one that nudges ever closer to tissue-engineered personalized medicine for people with intestinal disorders.

Sketched out a few years ago in the Developmental Biology and Endocrinology lab of Jim Wells, PhD, the Cincinnati Children's scientists were brainstorming over a daunting task: generating complex, functioning human intestine with an enteric (intestinal) nervous system in a laboratory petri dish.

The concept dovetailed into a multidisciplinary collaboration mixing clinical insight and basic science know-how. The clinical insight (and additional emphasis on translational aspects of the research) comes from the laboratory of thoracic surgeon Michael Helmrath, MD.

On Nov. 21, 2016, the research team published findings in *Nature Medicine*. They report using human pluripotent stem cells and embryonic neural crest cells to grow complex, functioning human intestinal tissues with nerves in a petri dish.

Wells recalls savoring the eureka moment when his graduate student at the time, Michael Workman, told him the developing intestines were actually growing nerves.

"The hypothesis was that if we put the right cells together at the right time and in the right place, they'll know what to do," says Wells. "It was a complete long shot, but it worked."

## RE-CREATING HIRSCHSPRUNG'S DEMONSTRATES POTENTIAL

Investigators then tested the developing innervated intestines in laboratory mice, transplanting the sphere-shaped organoids onto the animal's kidneys. This served as a living bio-incubator with a rich blood supply. The intestines grew, matured and went through waves of peristalsis, the nerve-initiated muscle contractions that move food through the digestive tract.

Then, in a convincing demonstration of translational potential, the researchers used the innervated intestines to recreate and study Hirschsprung's disease, where a lack of nerves prevents sections of the intestine and colon from passing stool.

The net result: a close-knit team developed an unprecedented, lab-based human research tool for studying diseases of the intestine.

> "The gut is our interface to the world. It's where we develop our immune system, where allergies and autoimmune diseases come from."
>
> – Michael Helmrath, MD
> Thoracic Surgery

The potential impact of this tool is significant. All food, drink, oral medications, and many other external substances interact with our bodies through the intestines.

"The gut is our interface to the world," ex-plains Helmrath, Surgical Director of the Intestinal Rehabilitation Program at the Cincinnati Children's Colorectal Center. "It's where we develop our immune system, where allergies and autoimmune diseases come from. We, and others, can use this tool to answer so many different questions. It will eventually give us a piece of intestine we can put into a human, but before we get there we are going to learn so much more about human disease than we've ever been able to before."

Beyond studying diseases that specifically affect the intestine, these new nerve-equipped organoids could be used to test the toxicity of virtually any new drug heading toward human clinical trials. The technology could support nutritional health studies, food allergy investigations, and the fast-growing field of microbiome research.

The latest achievement also puts biomedical research a critical step closer to generating healthy, patient-specific intestine for transplant.

Wells expects the modeling system to be especially helpful in studying diabetes—one of his primary focus areas. For example, after morbidly obese children with diabetes undergo gastric bypass surgery, some see their diabetes resolve even before losing much weight. No one is sure why this happens, says Wells, Director of the Pluripotent Stem Cell Facility at Cincinnati Children's.

Questions like this are why Helmrath and Wells see vast potential in the new technology.

## NECESSITY OF NERVES

Wells and his lab originally tissue-engineered human intestinal organoids in a petri dish (albeit without a nervous system) in work reported by a landmark 2010 paper in *Nature*. Barely taking time to celebrate that success, the scientists immediately began working to grow an enteric nervous system, with Wells recruiting collaborators from other disciplines to round out the team.

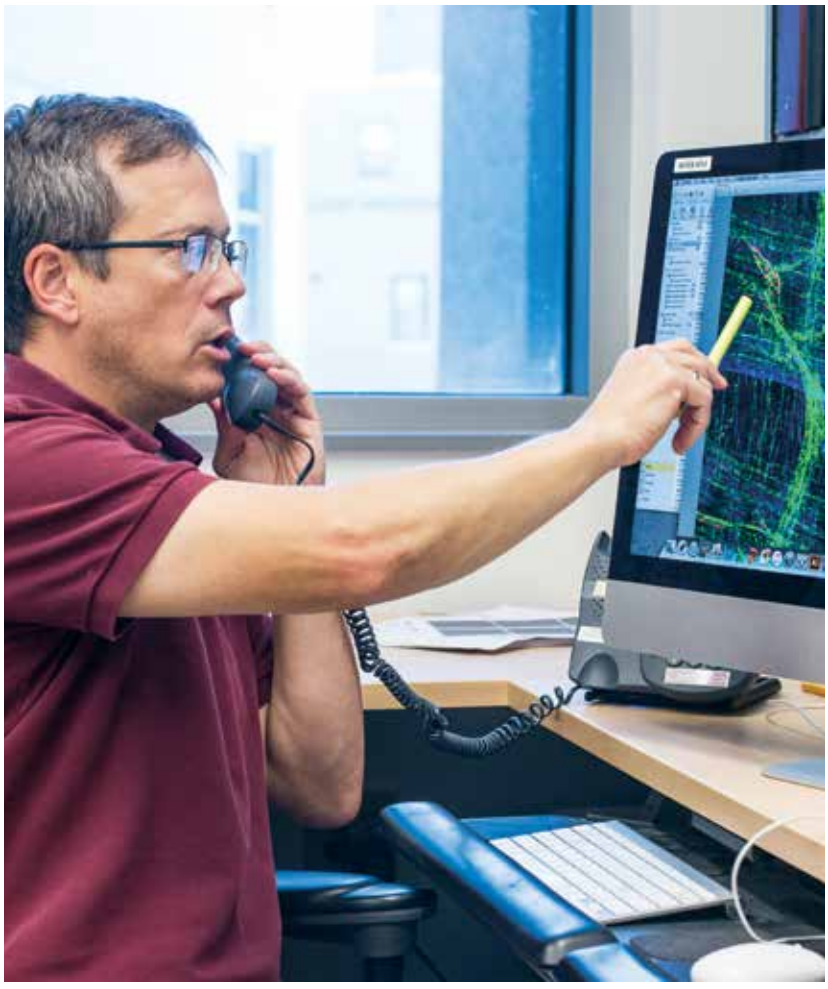
That push forward revealed critical new information. Although long understood that nerves are important to intestinal function, the latest *Nature Medicine* paper underscores that enteric nerves may have a far more central role in normal intestinal development and human health than previously known.

For Helmrath, who operates on babies and young children with a variety of intestinal disorders, the profound negative impact of a hindered enteric nervous system was a striking aspect of the new research.

"I underestimated the dynamics of the enteric nervous system and I think it holds a lot of answers to questions for problems we see in the hospital every day," Helmrath says. "This is why the ability to use this technology to ask and test all of these new questions is the contribution that will help human health to the greatest extent."

## NATURE'S WAY

For insights on tissue-engineering nerves, Wells reached out to fellow developmental biologist



Jim Wells, PhD

Samantha Brugmann, PhD, who studies cranial-facial development for the Division of Plastic Surgery. Wells credits Brugmann's input with "helping us find our footing in this area."

The cells that give rise to the nerves of the intestine are called neural crest cells. Brugmann is an expert in these cell types. The goal was to generate the neural crest precursor cells in one petri dish, and then incorporate them into intestinal tissues growing in a separate petri dish using the method developed by the Wells team back in 2010.

Although it took a few tries to get the timing right, once they identified the best way to put the two types of tissues together, the researchers stepped back and let nature and biology take over.

### STEP-BY-STEP PROGRESS

The latest nerve breakthrough in organoid development builds upon a series of related advances.

In an October 2014 *Nature Medicine* study, the Helmrath and Wells labs demonstrated that intestinal organoids grafted to a mouse kidney can grow into fully mature human tissue. This tissue included muscle layers and a self-renewing mucosal lining. The success suggests that stem cell-derived organoids might be able to grow on their own once transplanted into the human body.

The very same month, the Wells lab published a paper in *Nature* announcing success at forming a mini-stomach. This "gastric organoid" specifically resembled the antrum, the portion of the stomach that connects to the intestine. They also showed the organoids can harbor gut bacteria, which makes them immediately useful in research related to *H. pylori*, the bacterium that causes stomach ulcers.

### TRIUMPH OF TEAMWORK

The Wells and Helmrath labs have worked closely together for several years. They reflect a model stressed emphatically at Cincinnati Children's: that forging multidisciplinary bench-to-clinic (and back to bench) collaborations can foster innovations that lead to better health.

Their success suggests that team science is about much more than a mission statement.

"This study has been possible because of that teamwork," says Maxime Mahe, PhD, an instructor in the Helmrath lab and co-first author on the November 2016 *Nature Medicine* paper. "We combined our different skills together to make a strong and meaningful story." ■

"The hypothesis was that if we put the right cells together at the right time and in the right place, they'll know what to do. It was a complete long shot but it worked."

– Jim Wells, MD
Developmental Biology and Endocrinology

Michael Helmrath, MD

# Bench to Bassinet Data Hub Manages 250 Terabytes of 'Big Data'

$32.5 million grant gives Cincinnati Children's a pivotal role in national cardiac genomic research

by Jill Schlabig Williams

Team science arrived here in a big way in March 2016 when Cincinnati Children's became the administrative coordinating center and data hub for the Bench to Bassinet (B2B) Program for cardiac research.

The $32.5 million, five-year grant from the National Institutes of Health is believed to be the largest single award ever received by the medical center.

Launched in 2010 and renewed in 2015, the B2B Program aims to accelerate research on the molecular basis of congenital heart disease, from discovery and translational research to clinical testing. The consortium encompasses three separate but intersecting initiatives that involve 17 research institutions and 26 auxiliary sites.

Eileen King, PhD, Peter White, PhD, and James Cnota, MD, MS, are spearheading work on the new project, which offers the medical center a central role in determining new directions for pediatric heart research.

## TEAM SCIENCE ON A NATIONAL SCALE

Congenital heart defects are the most common birth defect in the U.S., with about 40,000 children diagnosed each year. These complex conditions involve the interplay of multiple genetic and environmental factors, which makes them ideally suited to a team science approach.

Determining causes and developing new treatments will require extensive coordination between neuro-developmental biologists, cardiologists, geneticists, imaging specialists, and data scientists. The work requires support from regulatory experts, contracts and finance personnel.

In securing the grant, Cincinnati Children's brought to the table its unique strengths in cardiac research, data management, a top-tier informatics infrastructure, and a strong advisory group comprised of senior leadership. In return, Cincinnati Children's gains the opportunity to become closer working partners with the NIH and other national cardiac research leaders.

The award also offers the medical center an avenue to translate discoveries from the bench to the bedside—or in this case, the bassinet.

## COORDINATING RESEARCH, AIMING FOR NEW DISCOVERIES

To date, the B2B Program has enrolled more than 10,000 children with congenital heart disease, along with nearly 14,000 parents and relatives.

Cincinnati Children's will coordinate activities for two components of the project. The Cardiovascular Development Consortium conducts basic research with laboratory models to discover which genes are turned on and off during heart development. The Pediatric Cardiac Genomics Consortium uses genomic data from thousands of individuals to uncover genes that may cause congenital heart disease, and then studies how those genes influence clinical presentation.

The two groups are complementary. Genes implicated in human studies can be tested for contribution in laboratory models, and vice-versa.

Eileen King, PhD, Division of Biostatistics and Epidemiology, will lead the coordinating center's efforts to provide infrastructure to enhance collaborations

among program members. Her team, including Rachel Akers, MPH, and Nicholas Ollberding, PhD, will be responsible for operations, protocol development, core oversight and support, and data management.

"Team science has long been the norm at Cincinnati Children's," says King. "Now, being able to do team science not only within this institution but across the United States is a great opportunity."

"Our goal is to support efforts across the project's many sites and partners to create reliable data and reproducible results," she says. "We want to be strategic partners, not just a pair of hands. We want to help set the strategic direction of the research team to assist with determining the priorities that are the most important to the clinicians, patients and their caregivers."

King says the NIH funders chose Cincinnati Children's in part because they were looking for a strong academic partner. They found one. Since July, Cincinnati Children's has:

- Led development of a new protocol that will investigate the causes of neurodevelopmental disorders in heart patients
- Created new informatics dashboards
- Worked with the grant's leadership team to make processes more efficient and ensure scientific rigor across the project.

"In research, as you reach the end of a study, the question is always, 'Where do I go next?' " says King. "Our goal is to make sure those next steps are clear, by facilitating information sharing, joint meetings, and always keeping an eye on the big picture."

## DATA HUB DEALS WITH VERY BIG DATA

As the program's new genomic data hub, Cincinnati Children's is collecting, integrating, and providing over 250 terabytes of molecular data to the cardiac research community. A team led by Peter White, PhD, Director, Division of Biomedical Informatics, will manage the hub.

"This is truly big data," White says. "We will be pushing the limits on effectively managing, integrating, and analyzing this data. The goal is to design technologies and computational methods that will allow researchers to understand a very complex combination of molecular and patient observational data."

Team members Michael Wagner, PhD and Michal Kouril, PhD, are already working on new methods for storing and computing on large and complex data sets through cloud technologies. Wagner's group also is further developing HeartsMart, a data application for querying and reporting cardiac data that will be adapted to the cloud and expanded with a user-friendly public interface.

"The vision is, with this data, we will eventually be able to perform a genetic profile on a new patient with heart disease and use those results to better predict the course of their illness, as well as to target surgical and postsurgical interventions," says White.

## THE PROMISE OF PRECISION MEDICINE

The Bench to Bassinet Program ultimately aims to blend genomic and clinical research. In addition to the two basic science projects, the B2B Program includes the Pediatric Heart Network. Established in 2001, this network represents a group of pediatric cardiovascular centers conducting clinical research. Cincinnati Children's has been a research site for this project since 2006.

James Cnota, MD, MS, Heart Institute, leads our involvement in the Pediatric Heart Network project. Now he also serves as Medical Director for the administrative coordinating center. In that role, he aims to bring the perspective of clinicians, patients and caregivers to inform research programs and study designs.

"Developmental biologists who study animal models, geneticists, and clinicians all complement each other, as each looks at problems differently," Cnota says. "When our abilities are combined, we can achieve novel insights. We need to learn each other's languages and work together to make progress and take advantage of all those strengths."

The payoff from the team science approach will be better outcomes for patients.

"We need a better understanding of the causes of heart defects," he says, "but we also need to understand the role of the genome in predicting medical and surgical outcomes and the long-term course of disease."

"Even between patients with the same anatomic diagnosis, we see a lot of variation in the response to standard treatments. With a better understanding of these differences, we can tailor treatments in more personalized and precise ways."

In the latest funding round, experts in the heart network are especially interested in investigating the high incidence of neurodevelopmental disabilities in children with severe heart defects. The researchers plan to study the genomes of congenital heart disease patients who develop poor neurological outcomes to uncover genetic mutations that affect both heart and brain development.

"With clinically-oriented questions like this," Cnota says, "we should see research outcomes that inform and guide the care of our patients.". ■

## Bench to Bassinet: by the Numbers

**24,770**
subjects enrolled

**9,703**
genomes studied

**212,858**
biosamples stored

**250 TB**
of data available

# Top Pediatric Centers Team Up to Boost Progress

## GRIN collaboration supports data and resource sharing in genomics

by Heide Aungst

Collaboration between principal investigators at different institutions is common on grant-funded research projects. However, finding major research centers working together outside of specific grants does not happen often.

Or, at least it was before the creation of the Genomics Research and Innovation Network (GRIN)—a groundbreaking project involving the top three pediatric hospitals in the U.S.

Cincinnati Children's, Boston Children's and Children's Hospital of Philadelphia (CHOP) have joined forces through GRIN to share data and resources. Their mission: to better understand the underlying genomic causes of disease and to accelerate efforts to develop potential therapies and, ultimately improve children's health.

## COMPETITORS FIND VALUE IN COLLABORATION

It was a rare event when the leadership of the three hospitals first began discussing the collaboration and common mission in September 2014.

The CEOs of all three institutions—Michael Fisher of Cincinnati Children's; Madeline Bell of CHOP; and Sandra Fenwick of Boston Children's—have committed ongoing resources to sustain this new project, which they consider critically important to the field of pediatrics.

"Our mission began as a way to accelerate discovery of rare genetic disorders through collaboration with other leading pediatric institutions," explains Arnold Strauss, MD, Associate Director of External Relations and Strategic Projects and former Chair of the Cincinnati Children's Research Foundation. Strauss helped create GRIN, along with his counterparts at CHOP and Boston Children's.

The power of such an alliance can impact rare disease research in two key ways. First, by pooling the brainpower of some of the world's best pediatric clinicians and researchers. And second, by magnifying the statistical significance of their work.

For example, a single hospital may have only a handful of children with a particular disease. Multiply that by three or more hospitals and researchers can make progress more quickly. As GRIN has developed, the planning team has recognized that the new network will empower research.

"There are more than 7,000 different pediatric diseases," explains Tracy Glauser, MD, Associate Director of Cincinnati Children's Research Foundation, who also serves on the executive team of GRIN's Joint Steering Committee. "Each is rare, but in aggregate, they add up to a big public health issue."

In fact, more than half of Cincinnati Children's admissions each year are the result of genomic diseases, adds Peter White, PhD, Director, Biomedical Informatics, and Co-Director of the Center for Pediatric Genomics at Cincinnati Children's. White also serves on GRIN's Joint Steering Committee.

"Many adult diseases have their genesis in pediatrics," adds Glauser. "So pediatric study is important for adult medicine."

That means that a powerful collaboration that works to understand, treat, and maybe eventually prevent, genomic-based diseases could greatly benefit the health of many people, not just children.

## THREE PROJECTS BEGIN

To get started, GRIN is focusing on three disease areas: early childhood obesity, growth disorders/short stature, and epilepsy.

"Each of the sites is leading on one of those projects and has identified collaborators at the other two sites. Together they are recruiting patients, collecting materials, generating data and sharing data—both genomic data and associated descriptive data," White says.

## LAYING A FOUNDATION FOR LONG-TERM COLLABORATION

Much of GRIN's inaugural year has been devoted to building the regulatory and legal infrastructure to allow the three hospitals to work together and share information. This has included establishing material transfer and IRB agreements, says Glauser.

"We're working on aligning consent processes for participants, so that all data that's collected can be shared consistently across GRIN sites," says Kristen Sund, PhD, MS, the point person of institutional genomics at Cincinnati Children's and GRIN program manager, who has worked on the project since its inception.

GRIN seeks to expand a shared library of genomic data that currently flows primarily from whole-genome and whole-exome sequencing. Other types of data to collect and share could include RNA, proteomics and metabolomics. The network also wants to connect the genomic data with imaging results and other electronic health records, Sund says.

Eventually, the GRIN team hopes that more pediatric hospitals—of all sizes—will join the network.

"There might be sites out there that don't have a huge research program, but we can still learn a lot from their patients," says Sund. "And we can give their patients an opportunity to participate in research that otherwise wouldn't be available to them. So we can really make a difference in pediatric genomics." ■


Collaboration comes in many forms and can cross many miles. On the screen, Casey Gorman, GRIN project manager for Children's Hospital of Philadelphia, consults with Cincinnati Children's researchers (from left) Peter White, PhD, Kristen Sund, PhD, MS, and Tracy Glauser, MD.

# GRANTS

From June 1 through Sept. 30, researchers at Cincinnati Children's were awarded 193 grants totaling $130.2 million. Here are the recipients of grants of $1 million or more:

## Stephen Becker, PhD,

**Behavioral Medicine & Clinical Psychology**, received a four-year, $1.4 million grant from the U.S. Department of Education to examine sluggish cognitive tempo and its impact on education.

## Burns Blaxall, PhD,

**Molecular Cardiovascular Biology**, received a four-year, $2 million grant from the National Heart, Lung, and Blood Institute to study targeting pathologic G-protein signaling.

## Samantha Brugmann, PhD,

**Plastic Surgery**, will study the role of primary cilia in murine craniofacial development, using a three-year, $2 million grant from the National Institute of Dental and Craniofacial Research.

## Kristen Copeland, MD,

**General and Community Pediatrics**, was awarded a five-year, $1.9 million grant from the Health Resources and Services Administration for her work with its fellowship program.

## Tony De Falco, PhD,

**Reproductive Sciences**, received a five-year, $2 million grant from the National Institute of General Medicine Sciences, to study macrophage regulation of the spermatogonial stem cell niche.

## Sudhansu. K. Dey, PhD,

**Director, Reproductive Sciences**, received a five-year, $2.1 million grant from the National Institute of Child Health and Human Development, to study the molecular signaling in uterine receptivity to implantation.

## Jeffery Epstein, PhD,

**Behavioral Medicine and Clinical Psychology**, will use a four-year, $1.6 million grant from the Agency for Healthcare Research and Quality to explore ways to improve ADHD behavioral treatment.

## Craig Erickson, MD,

**Child and Adolescent Psychology**, received a three-year, $1.5 million grant from the National Institute of Child Health and Human Development, to study the mechanisms of neocortical and sensory hyperexcitability.

## Donald Gilbert, MD, MS,

**Neurology**, will study GABAergic sensorimotor dysfunction in Tourette syndrome, using a five-year, $1.2 million grant from the Kennedy Krieger Institute, which focuses on disorders of the brain, spinal cord and musculoskeletal system.

## H. Leighton Grimes, PhD,

**Immunobiology**, received a three-year, $1.8 million grant from the National Cancer Institute, to study a rapid spontaneous murine model of cytogenetically normal acute myeloid leukemia.

## John Harley, MD, PhD,

**Director, Center for Autoimmune Genomics and Etiology (CAGE)**, will study the genetic linkage of lupus, using a five-year, $2 million grant from the National Institute of Allergy and Infectious Diseases.

## Gurjit Khurana Hershey, MD, PhD,

**Director, Asthma Research**, received a five-year, $7 million grant from the National Institute of Allergy and Infection Diseases, to study the epithelial genes in allergic inflammation.

## Tzipi Horowitz-Kraus, PhD,

**Program Director, Reading and Literacy Discovery Center**, will study the role of executive functions in reading, with a five-year, $2.6 million grant from the National Institute of Child Health and Human Development.

## Stacey Huppert, PhD,

**Gastroenterology, Hepatology and Nutrition**, will study the building of a functional biliary system from hepatocytes, using a five-year, $2.7 million grant from the National Institute of Diabetes and Digestive and Kidney Diseases.

## Thomas Inge, MD, PhD,

**Director, Center for Bariatric Research and Innovation**, received a five-year, $7.9 million grant from the National Institute of Diabetes and Digestive and Kidney Diseases, to examine the limited competition for the continuation of TeenLABS clinical centers. TeenLABS stands for Longitudinal Assessment of Bariatric Surgery, a multi-center collaboration focused on the safety and health effects of weight-loss surgery.

## Tatiana Kalin, MD, PhD,

**Neonatology and Pulmonary Biology**, will study targeting of the Foxm1 gene in pulmonary fibrosis, using a four-year, $1.5 million grant from the National Heart, Lung, and Blood Institute.

## Leah Kottyan, PhD,

**Center for Autoimmune Genomics and Etiology (CAGE)**, will study the mechanisms of genetic risk at chromosome 2p23 in the chronic immune disease eosinophilic esophagitis, using a five-year, $1.8 million grant from the National Institute of Diabetes and Digestive and Kidney Diseases.

## Brad Kurowski, MD, MS,

**Physical Medicine and Rehabilitation**, will study the genetic and environmental influences on recovery from severe brain injury, using a five-year, $3.3 million grant from the National Institute of Neurological Disorders and Stroke.

# GRANTS

## Sonata Jodele, MD,

**Bone Marrow Transplant and Immune Deficiency**, received a one-year, $1.1 million award from Novartis Pharmaceuticals for a randomized study to evaluate the antibody LFG316 in patients who develop transplant-associated microangiopathy after hematopoietic precursor cell transplantation.

## Qing Richard Lu, PhD,

**Scientific Director, Brain Tumor Center**, received a four-year, $1.1 million grant from the National Institute of Neurological Disorders and Stroke, to study the molecular and signaling mechanisms of peripheral nerve sheath tumorigenesis.

## Peter Margolis, MD, PhD,

**Director of Research, James M. Anderson Center for Health System Excellence**, was awarded a two-year, $1.5 million grant from the Patient-Centered Outcome Research Institute for his work with ImproveCareNow. Margolis also received a five-year, $4.7 million award from the Patient-Centered Outcome Research Institute to study the impact of anti-TNF monotherapy and combination therapy.

## Jeffery Molkentin, PhD,

**Molecular Cardiovascular Biology**, will study the molecular examination of mitochondrial calcium control, using a four-year, $3.1 million grant from the National Heart, Lung, and Blood Institute.

## Greg Myer, PhD,

**Director of Research, Sports Medicine**, will study the real-time sensorimotor feedback for injury prevention, using a five-year, $3.2 million grant from the National Institute of Arthritis and Musculoskeletal and Skin Diseases.

## Marsha Polk, HPT, OCPS,

**Drug and Poison Information Center**, was awarded a five-year, $2 million grant from the Department of Health and Human Services for her work with its Communities Addressing Childhood Trauma program.

## Joseph Qualls, PhD,

**Division of Infectious Diseases**, will study L-citrulline and anti-tuberculosis host defense, using a five-year, $2 million grant from the National Institute of Allergy and Infectious Diseases.

## Richard Ruddy, MD,

**Emergency Medicine**, will study pediatric emergency care using a four-year, $2.6 million grant from the Health Resources and Services Administration.

## Senthilkumar Sadhasivam, MD, MPH,

**Anesthesia**, will study the pharmacogenetics of oxycodone, with a five-year, $2.7 million grant from the National Institute of Child Health and Human Development.

## Mary Allen Staat, MD, MPH,

**Infectious Diseases**, received a five-year, $6.6 million grant from the national Centers for Disease Control and Prevention, to study enhanced surveillance for new vaccine-preventable disease. The grant is funded through the Prevention and Public Health Fund of the Affordable Care Act.

## Susan Thompson, PhD,

**Center for Autoimmune Genomics and Etiology (CAGE)**, received a five-year, $3.9 million grant from the National Institute of Arthritis and Musculoskeletal and Skin Diseases, for her work with the Cincinnati Rheumatic Diseases Resource Center.

## Bruce Trapnell, MD, MS,

**Pulmonary Medicine**, received a four-year, $1.6 million grant from the National Heart, Lung, and Blood Institute to study pathogenesis-based diagnostics and pharmacotherapeutics.

## Alexander Vinks, PhD, PharmD,

**Director, Clinical Pharmacology**, received a five-year, $1 million grant from the National Institute of Child Health and Human Development for his work with the Cincinnati Pediatric Clinical Pharmacology Postdoctoral Training Program.

## Timothy Weaver, PhD, MS,

**Co-Director, Pulmonary Biology**, will study the deficiency of phospholipid transfer protein, using a four-year, $2 million grant from the National Heart, Lung, and Blood Institute.

## Jeffrey Whitsett, MD,

**Co-Director, Perinatal Institute**, received a seven-year, $8.3 million grant from the National Heart, Lung, and Blood Institute, to study the editing of alveolar progenitor cells for correction of monogenic disease.

## Jianqiang Wu, MD, MS,

**Experimental Hematology and Cancer Biology**, received a five-year, $1.7 million grant from the National Institute of Neurological Disorders and Stroke, to study the miR-155 and RUNX function in neurofibroma tumorigenesis.

## Yi Zheng, PhD,

**Director, Experimental Hematology and Cancer Biology**, received a four-year, $1.6 million grant from the National Heart, Lung, and Blood Institute to study blood stem-cell aging and biomarkers.

# HONORS

## Katherine Auger, MD, MSc,

**Hospital Medicine**, received the 2016 Nemours Child Health Services Research Award., which recognizes emerging scholars in the field. Auger studies pediatric readmission issues, and is the only pediatrician serving on the National Quality Forum's expert readmissions committee.

## Andrew Beck, MD, MPH,

**Hospital Medicine**, was listed in the *Cincinnati Business Courier*'s 40 Under 40 Class of 2016. The honor recognizes young professionals who have reached major career milestones and have made significant contributions to the community.

## Daniel Choo, MD,

**Director, Otolaryngology**, was elected to the Board of Directors for the American Cochlear Implant Alliance, a not-for-profit organization that sponsors research, raises awareness and advocates for improved access to cochlear implants.

## Theresa Frey, MD,

**Fellow, Pediatric Emergency Medicine**, received the 2016 Ken Graff Young Investigator Award from the Section on Emergency Medicine of the American Academy of Pediatrics.

## Michael Gittelman, MD,

**Emergency Medicine**, received a special achievement award from the Ohio Chapter of the American Academy of Pediatrics (Ohio AAP) for his outstanding work on the chapter's Operations Pillar. Gittelman is president-elect of the chapter.

## Maurizio Macaluso, MD, DPH,

**Director, Biostatistics and Epidemiology**, was elected in September 2016 to the Board of Directors for the American College of Epidemiology.

## Kimberly Risma, MD, PHD,

**Allergy and Immunology**, received the 2017 Distinguished Service Award from the American Academy of Asthma, Allergy and Immunology. Risma was honored for her leadership with the Chrysalis Project, a program for medical students and residents that helps them explore careers in allergy and immunology.

## Erin Shaughnessy, MD,

**Hospital Medicine**, was recently appointed to the editorial board of *Hospital Pediatrics*.

## Keith Strauss, MSc,

**Radiology**, received the Marvin M.D. Williams Award from the American Association of Physicists in Medicine (AAPM). Strauss, a clinical imaging physicist, was recognized for his eminent career in applying the principles of medical physics to improving patient care. Strauss is only the 29th physicist to receive the award in the AAPM's 59-year history.

## Cincinnati Children's, was listed among the nation's 100 "Most Wired" hospitals of 2016 in the July 2016 issue of Hospitals & Health Networks. This is the fifth straight year Cincinnati Children's has received this honor.

## The ImproveCareNow Network, a collaborative group co-founded by Cincinnati Children's to improve outcomes in Crohn's disease and ulcerative colitis, was selected from 495 applicants to receive the 2016 Drucker Prize from Claremont Graduate University. The prize honors non-profit organizations that show leadership in innovation. Peter Margolis, MD, PhD, Co-Director, Anderson Center, serves as the network's Executive Scientific Director.

## Way Named an HHMI Faculty Scholar, receives NIH Pioneer Award

Groundbreaking research into how the immune system works in early newborn development has led to Sing Sing Way, MD, PhD, being named a Faculty Scholar by The Howard Hughes Medical Institute, the Simons Foundation and the Bill & Melinda Gates Foundation.

Way, an investigator in the Division of Infectious Diseases, studies how genetically foreign maternal and fetal tissues coexist during pregnancy. Understanding how the immune system works in unique developmental contexts could lead to new therapies for improving pregnancy. Way is one of 84 Faculty Scholars selected from 43 institutions.

Way also is one of 12 recipients of the 2016 NIH Director's Pioneer Award, which supports scientists of exceptional creativity who propose transforming research approaches to major biomedical challenges.

As part of this honor, Way will use a five-year, $5.5 million grant from the National Institute of Allergy and Infection Diseases, to study how immunological identity is redefined by genetically foreign microchimeric cells.

Sing Sing Way, PhD

# HONORS

## Faculty Honored with Research & Endowed Chairs

Several leading faculty members at Cincinnati Children's were recently honored with new research and endowed chairs to support their ongoing work.

### Research Foundation Chairs

Margaret Hostetter, MD, Physician-in-Chief, Chair of Pediatrics and Director, Cincinnati Children's Research Foundation, announced the recipients of three new CCRF chairs:

Evaline Alessandrini, MD, MSCE
Javier Gonzalez del Rey, MD, MEd
Thomas Kimball, MD

### Endowed Scholars

Three emerging leaders in their fields became the first to be selected for the Research Foundation's new Endowed Scholars Program. Each recipient will receive three years of flexible research support. The honorees are:

Samantha Brugmann, PhD
Yutaka Yoshida, PhD
Avani Modi, PhD

### Endowed Chairs

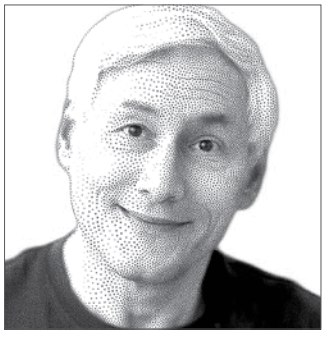
**Stuart Goldstein, MD,** is the first recipient of the Clark West Endowed Chair. Goldstein is Director of the Center for Acute Care Nephrology; Medical Director of Pheresis Service; Medical Director, Dialysis; and Co-Medical Director of the Heart Institute Research Core.

The new chair is named for the physician and researcher who founded the specialty of pediatric nephrology at Cincinnati Children's in 1953. West went on to head the division for 40 years.

Stuart Goldstein, MD

**Jeff Robbins, PhD,** Executive Co-Director, Heart Institute, received the inaugural Berenfield Family Endowed Chair of Molecular Cardiovascular Biology.

Len Berenfield, a long-time supporter of Cincinnati Children's, established the chair in honor of his mother and of family members born with heart complications. Robbins studies the cause-and-effect relationships between mutations in proteins and their connection to heart disease.



Jeff Robbins, PhD

**Marc Rothenberg, MD, PhD,** Director, Division of Allergy and Immunology, became the first recipient of the Denise and Dave Bunning Chair for Allergy and Immunology.

The Bunning family has supported Rothenberg's work and the Division of Allergy and Immunology for nearly 10 years. The family's generosity has helped Rothenberg and colleagues make important strides in diagnosing, understanding and treating eosinophilic gastrointestinal diseases (EGIDs).

Marc Rothenberg, MD, PhD

SAVE THE DATE

2017 Bioethics Conference:

# Ethics of Integrating Research & Clinical Care

## MARCH 23–24, 2017

**at Cincinnati Children's Sabin Education Center**

Featured presentations will include:

ARE RANDOMIZED CLINICAL TRIALS COMPARING STANDARD OF CARE TREATMENTS TRULY MINIMAL RISK?

**Scott Kim, MD, PhD,**

*Department of Bioethics, National Institutes of Health*

FIRST IN HUMAN TRIALS AND SAFETY ASSESSMENT FOR RARE AND ORPHAN DISEASES

**Andrew Mulberg, MD,**

*Amicus Therapeutics (former Deputy Director of FDA)*

NOTIFICATION AND AUTHORIZATION OF ALTERNATIVE APPROACHES IN PRAGMATIC CLINICAL TRIALS OF COMMONLY USED MEDICAL PRACTICES

**Kevin Weinfurt, PhD,**

*Department of Psychiatry and Behavioral Sciences, Duke University School of Medicine*

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Event co-sponsored by the Cincinnati Children's Ethics Center and the Center for Clinical and Translational Science and Training at the University of Cincinnati.

To learn more: visit: https://cctst.uc.edu/bioethics2017


## Research Horizons

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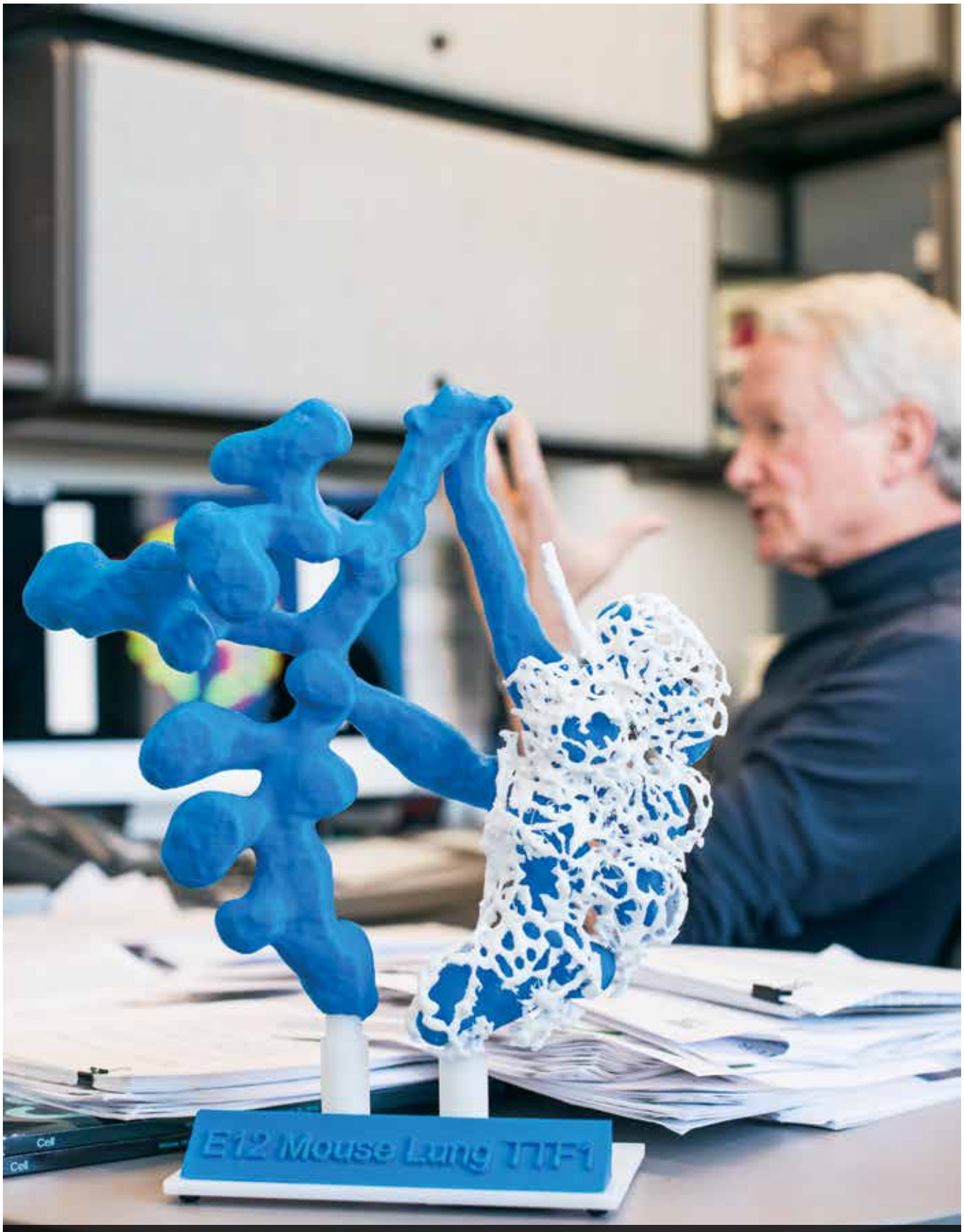


This 3D model of a developing mouse lung was so data-rich it took days to print. Go to https://www.youtube.com/watch?v=8EHLONVrcOo to watch a video interview about the LungMAP project with Jeffrey Whitsett, MD.

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