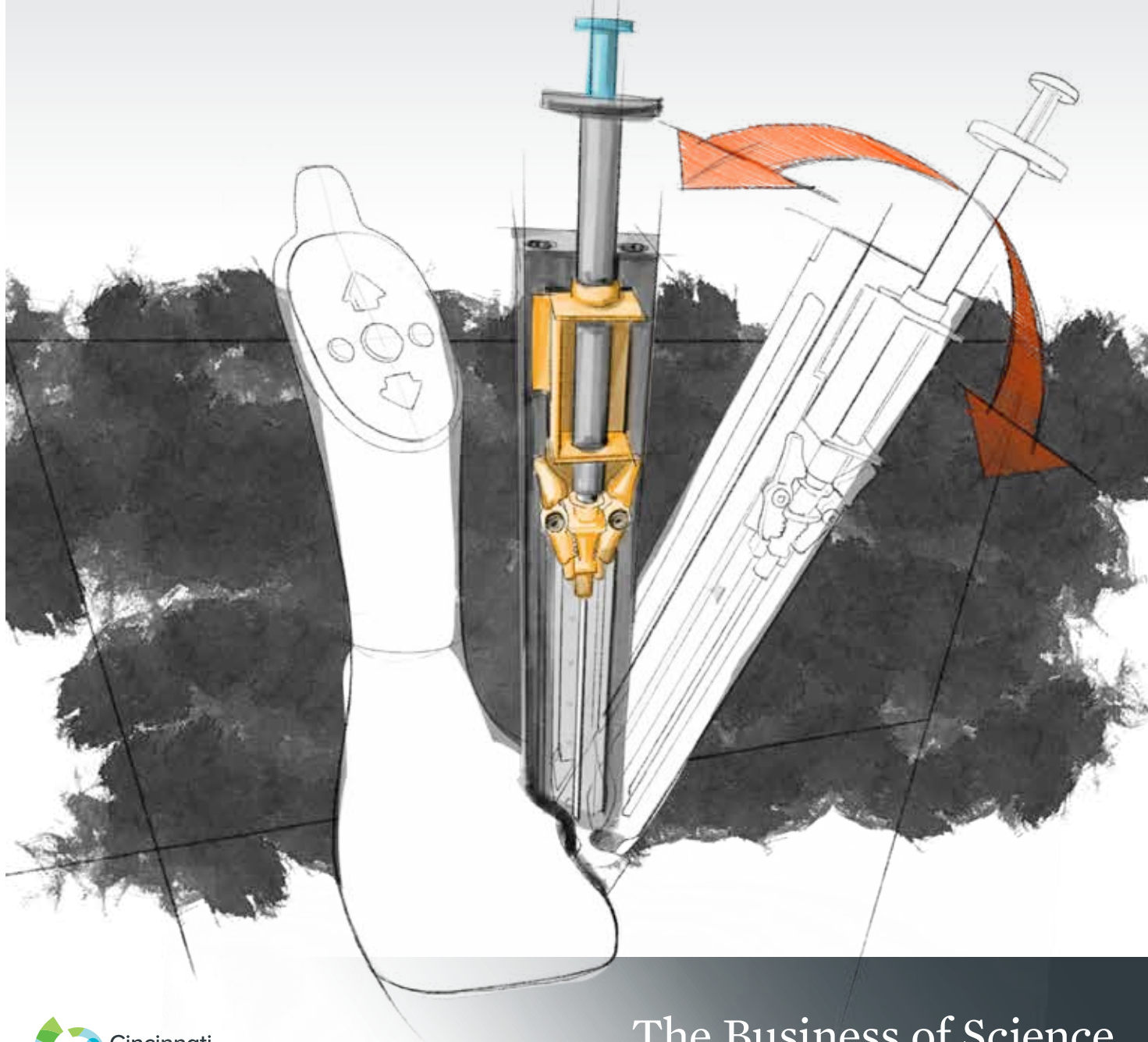
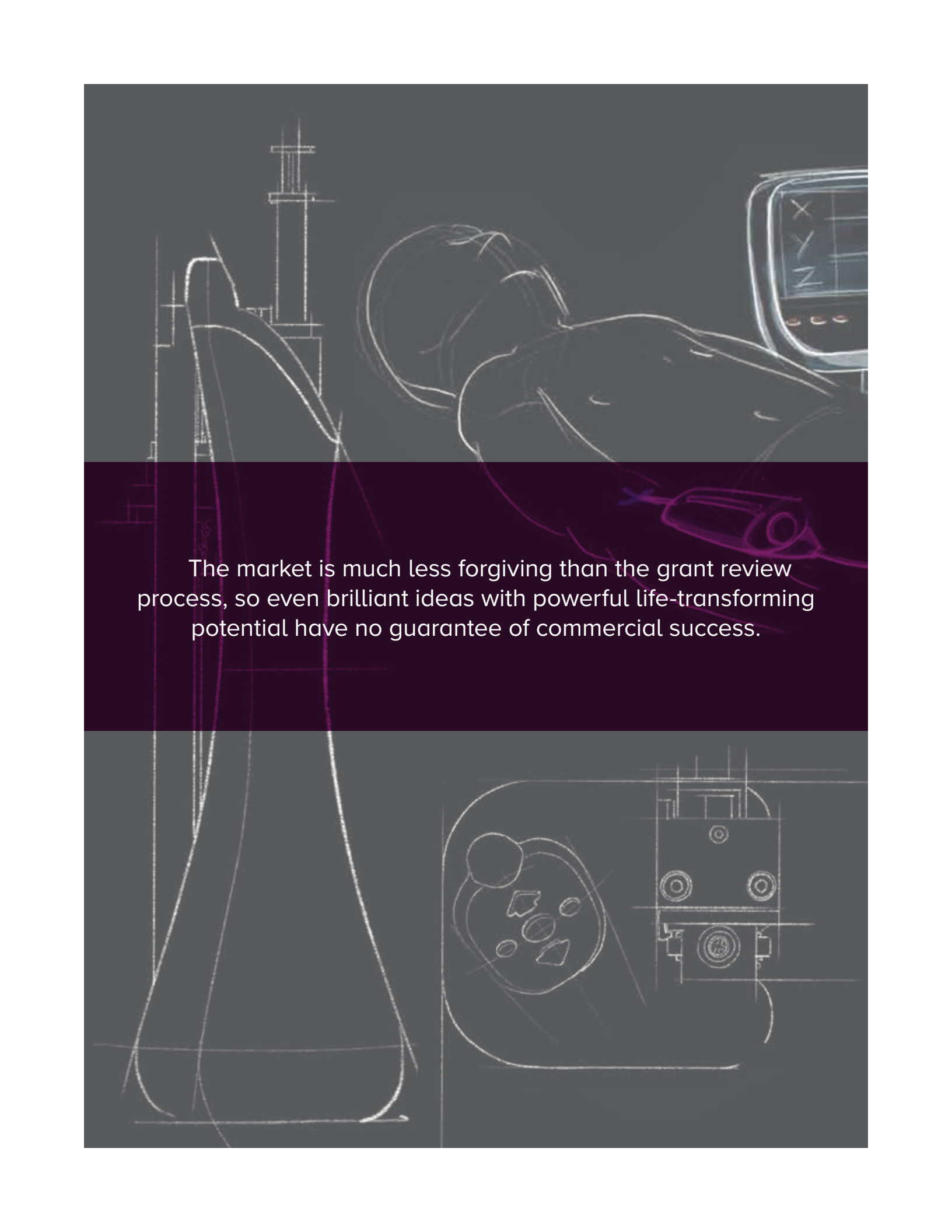


RESEARCH HORIZONS

A Publication of the Cincinnati Children's Research Foundation

SUMMER 2018





The market is much less forgiving than the grant review process, so even brilliant ideas with powerful life-transforming potential have no guarantee of commercial success.

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'Mono' Virus Linked to Seven Serious Diseases



John Harley, MD, PhD



Leah Kottyan, PhD



Matthew Weirauch, PhD

A far-reaching study conducted by scientists at Cincinnati Children's reports that the Epstein-Barr virus (EBV)—best known for causing mononucleosis—also increases the risks for some people of developing seven other major diseases.

Those diseases are: systemic lupus erythematosus (SLE), multiple sclerosis (MS), rheumatoid arthritis (RA), juvenile idiopathic arthritis (JIA), inflammatory bowel disease (IBD), celiac disease, and type 1 diabetes. Combined, these diseases affect nearly 8 million Americans.

Results were published in April 2018 in *Nature Genetics*. The project was led by John Harley, MD, PhD, Director of the Center for Autoimmune Genomics and Etiology (CAGE); Leah Kottyan, PhD, an immunobiology expert with CAGE; and Matthew Weirauch, PhD, a computational biologist with the center. Critical contributions were provided by Xiaoting Chen, PhD, and Mario Pujato, PhD, both also in CAGE.

The study shows that a protein produced by the Epstein-Barr virus, called EBNA2, binds to multiple locations along the human genome that are associated with these seven diseases. Overall, the study sheds new light on how environmental factors can interact with the human genetic blueprint to trigger disease.

"Now, using genomic methods that were not available 10 years ago, it appears that components made by the virus interact with human DNA in the places where the genetic risk of disease is increased," Harley says. "And not just for lupus, but all these other diseases, too."

The study breaks ground by focusing on a constellation of transcription factors connected to EBV infections.

"Normally, we think of the transcription factors that regulate human gene expression as being human," Kottyan says. "But in this case, when this virus infects cells, the virus makes its own transcription factors, and those sit on the human genome at lupus risk variants (and at the variants for other diseases)."

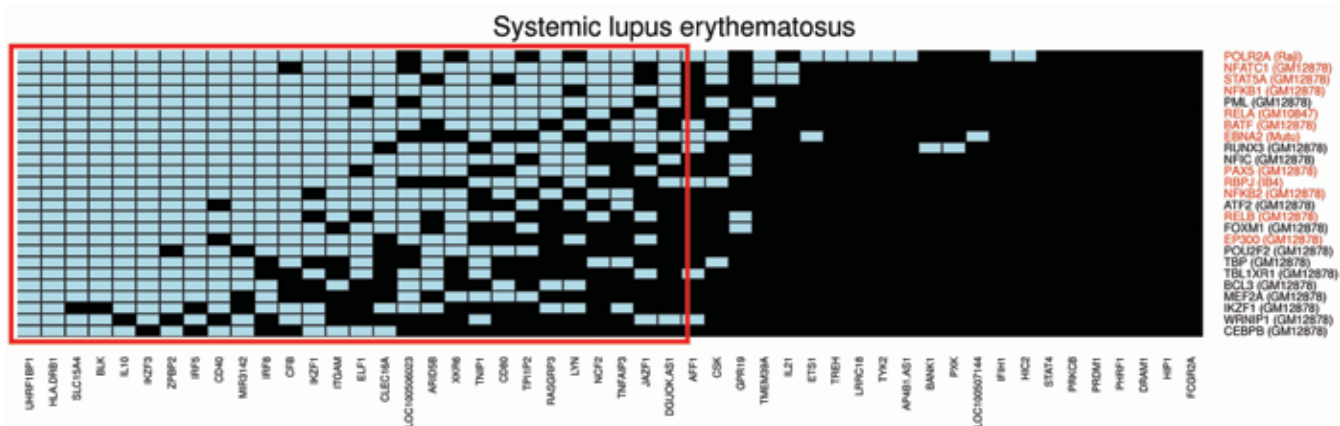
Completing the massive genomic analysis involved creating two new algorithms, called RELI and MARIO, both of which will be made available to the science world. The paper also reports the outcomes of applying the same analytic techniques to 94 other diseases, a finding that could take years to explore.

"This same cast of characters is a villain in multiple immune-related diseases," Weirauch says. "They're playing that role through different ways, and doing it at different places in your genome, but it's the same sinister characters. So if we could develop therapies to stop them from doing this, then it would help multiple diseases."

So far, no vaccine exists that will prevent EBV infection.

"I think we've come up with a really strong rationale for encouraging people to come up with more of an effort," Kottyan says.

This figure depicts the intersection of known gene risk variants for lupus (horizontal axis) in European-Americans with a list of transcription factors (vertical axis). Colored rectangles depict potential associations. The red box outlines risk genes and transcription factor binding sites that cluster together.



How Liver Cells Switch Identities to Build Missing Plumbing

By studying a rare liver disease called Alagille syndrome, scientists from Cincinnati Children's and the University of California San Francisco (UCSF) have discovered the mechanism behind an unusual form of tissue regeneration that may someday reduce the need for expensive and difficult-to-obtain organ transplants.

The team's findings, published May 2, 2018, in *Nature*, show that when disease or injury causes a shortage of cholangiocytes, the type of liver cell that forms bile ducts, the organ can instruct hepatocytes, the cell type that provides most of the liver's functions, to change identities to provide replacement supplies.

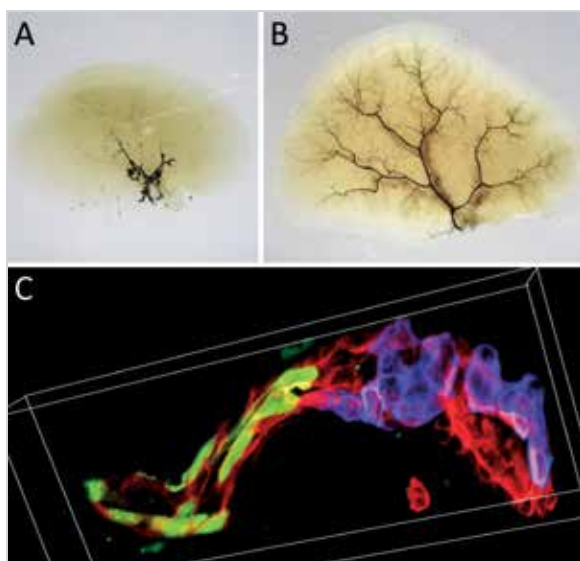
This discovery was made in mice but in years to come may lead to a viable treatment for human disease. If ongoing follow-up studies succeed, the medical world may gain an alternative method for repairing tissue damage that does not require manipulating stem cells to grow organs from scratch in a lab dish.

"We have known for a long time that the liver has more ability to regenerate than other organs. Only recently have we had the tools to study this ability in depth. Now we have a high-level understanding," says Stacey Huppert, PhD, a developmental biologist in the Division of Gastroenterology, Hepatology and Nutrition at Cincinnati Children's, and one of two leading co-authors of the paper.

Mice that mimic Alagille syndrome are born without the branches of the biliary tree (A) but show a near-normal appearing biliary system at adult age (B). To build the missing branches, liver cells switch identity and form tubes, shown in green, that connect to the trunk of the biliary tree, shown in blue. (C), according to findings published May 2 in *Nature*. Shown right, a model of the biliary tree.



Stacey Huppert, PhD





Brain Trauma Linked to ADHD Risk

Traumatic brain injury (TBI) sends more than 1 million children, adolescents and young adults to emergency departments every year in the United States. A study published March 19, 2018, in *JAMA Pediatrics* found that moderate to severe injuries can increase the risk for onset of attention-deficit/hyperactivity (ADHD) for up to seven years after injury.

“The findings from this study have important clinical implications and support the need for post-injury monitoring for attention problems and planning clinical follow-up children with traumatic brain injury,” says Brad Kurowski, MD, Division of Rehabilitation Medicine, who co-authored the study with Megan Narad, PhD, Rehabilitation Medicine.

The team studied parent-provided assessments of children ages 3 to 7 who were hospitalized overnight for TBI or orthopaedic injury at four Ohio hospitals from 2003 to 2008. One-fourth of the children (48 out of 187) met the definition of having secondary ADHD.

The four Ohio hospitals involved were Cincinnati Children’s, Nationwide Children’s Hospital (Columbus), Rainbow Babies and Children’s Hospital (Cleveland) and MetroHealth Medical Center (Cleveland).

Kids like Ricky Solis, who was in a car accident that resulted in brain injury, could benefit from follow-up care, according to a recent study in *JAMA Pediatrics*.

New Method Mass Produces Organoid Cells

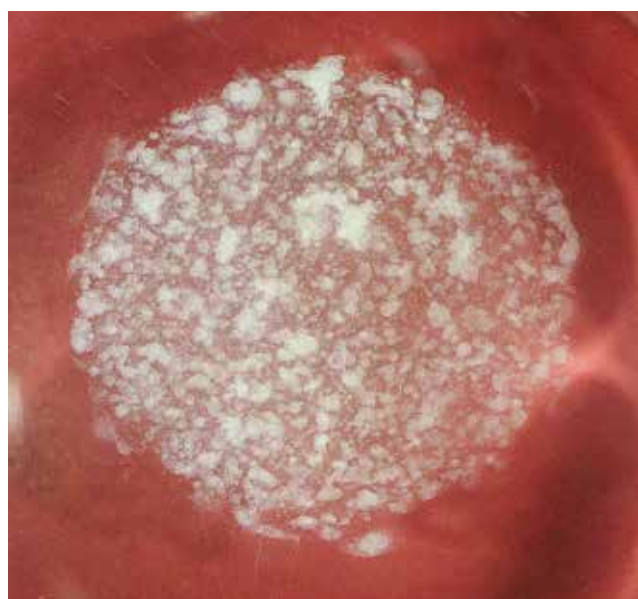
Scientists from our Center for Stem Cell and Organoid Medicine and Yokohama City University (YCU) in Japan have developed a way to safely bioengineer human gut and liver tissues.

The researchers reported in *Stem Cell Reports* that they eliminated the two remaining hurdles in bioengineering the human organs: ensuring genetic stability and producing enough tissue for transplant into humans.

The process transformed human induced pluripotent stem cells (iPS) into posterior gut endodermal progenitor cells (PGEs), says Takanori Takebe, MD, lead investigator and physician at Cincinnati Children’s and YCU.

Scientists manipulated the PGEs to form human hindgut and liver organoids. The result was “... robust, genetically stable formation of different tissue GI types, without causing benign tumors called teratomas,” says research fellow Ran-Ran Zhang, PhD. The liver organoids, transplanted into immunodeficient mice with liver disease, grew, functioned well and prevented liver failure.

Researchers will continue refining the bioengineering process, with emphasis on liver organoids. With Japan’s National Centers for Child Health and Development, they plan a clinical trial to transplant a bioengineered liver into a patient.



These 2D cultures of human posterior gut endoderm cells (PGE) were genetically queued to drive generation of 3D hindgut spheroids and intestinal tissues.

A Way to Repair Nerve Damage

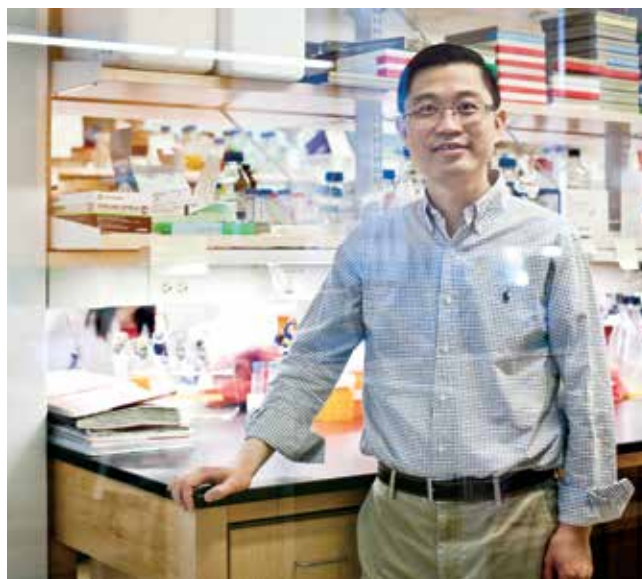
Scientists here have developed an experimental molecular therapy that appears to relieve pain and restore the damage done to nerves by autoimmune disease.

Published Feb. 12, 2018, in *Nature Medicine*, the study reports a method that restores insulation on peripheral nerves in mice, improves limb function, and appears to alleviate pain.

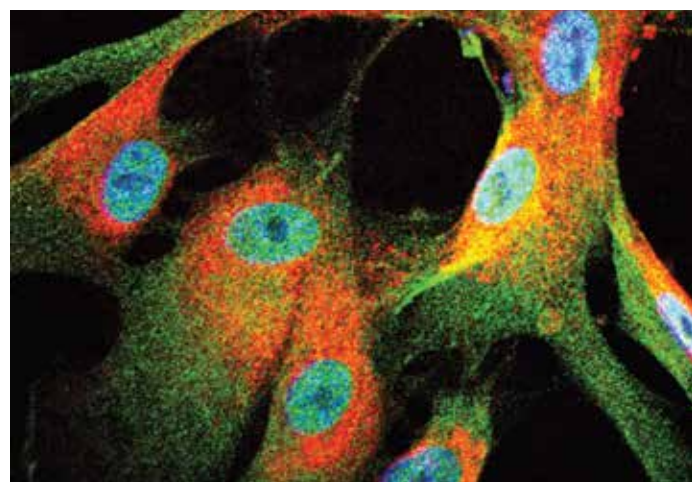
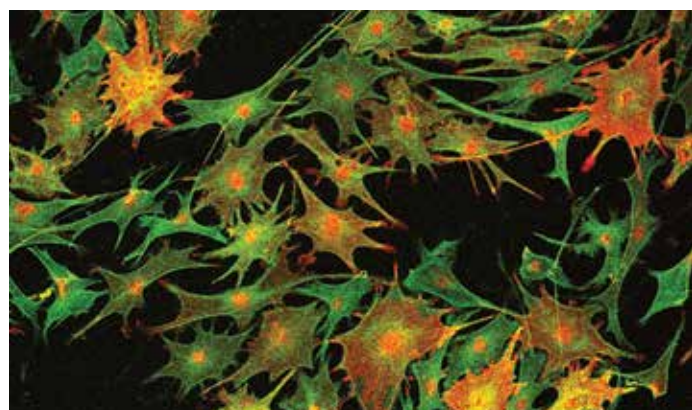
Until now, there was no way to treat the peripheral nerve damage caused when the body attacks its own tissues. But investigators led by Q. Richard Lu, PhD, Director of our Brain Tumor Center, tested small molecule inhibitors—normally used for cancer—on mice with injured sciatic nerves.

They found that temporarily inhibiting the enzyme histone deacetylase 3 (HDAC3) sped myelin formation in the animals after peripheral nerve injury. Carefully timing treatment to inhibit HDAC3 only during a critical phase of nerve regeneration resulted in sufficient re-myelination to restore normal function in the mice. Blocking HDAC3 for too long caused myelin to overgrow.

Translating the findings to clinical application in patients will require extensive additional research, Lu says.



Q. Richard Lu, PhD, Director of our Brain Tumor Center



(Top) Image from *Nature Medicine* study showing effects of inhibiting an enzyme called HDAC3. (Bottom) Image from *Cancer Cell* shows the presence of TAZ/YAP (green) in peripheral nerve sheath tumors.

A Potential Treatment for Deadly Nerve Tumors

Genomic profiling of untreatable nerve sheath tumors has uncovered secrets about them—and a potential treatment, researchers reported Feb. 12 in *Cancer Cell*.

“We uncovered therapeutic targets we did not expect for these untreatable tumors,” says Q. Richard Lu, PhD, the study’s lead author and Scientific Director of our Brain Tumor Center.

After a thorough genetic screening of malignant peripheral nerve sheath tumors (MPNSTs), researchers showed that the gene *Lats 1/2* suppresses cancer. Loss of *Lats 1/2* causes genes and cells to become hyperactive and cancerous. The genes and their associated proteins (in this case, TAZ and YAP) activate molecular programs that form MPNSTs.

By disrupting the TAZ and YAP proteins in mice, scientists reduced the size and number of MPNSTs. They also inhibited the growth of human MPNST cells in laboratory cultures.

MPNSTs are aggressive, treatment-resistant tumors that develop in Schwann cells. Lu and colleagues next want to identify small molecule inhibitors and locations on MPNST cells where the drugs could attach to and attack the tumor cells.

New Hybrid OR a First in Pediatrics

A collaboration between our Radiology and Surgical Services departments has led to a first-of-its-kind operating room (OR) in a pediatric hospital—and more precise, safer, less invasive procedures for our patients.

The Philips Azurion Hybrid OR allows interventional radiologists and surgeons to work together to plan and perform surgeries, all from one location and using real-time navigation. Patients no longer need to be transported while under anesthesia, a significant step in improving surgical safety and efficiency.

“With advanced technology embedded in the room, patients stay in the same room and are positioned for the entire procedure,” says Surgeon-in-Chief Daniel von Allmen, MD.

The teams also use a research laboratory with equipment identical to that in the OR to plan new procedures and translate them directly to the operating room, and to test the latest technologies.

“By combining the skills and expertise of surgeons and interventional radiologists, we maximize the imaging and navigational capabilities of these technologies,” says John Racadio, MD, Director, Interventional Radiology Research and Innovation.



The new Philips Azurion Hybrid OR at Cincinnati Children's allows for integrating advanced surgical techniques with high-tech navigation imagery.

Congenital Heart Disease Raises Risk of Dementia

A new study may be the first to show a higher risk of dementia in adults born with heart disease.

The study, published online Feb. 12, 2018, in *Circulation*, looked at more than 10,000 Danish adults with congenital heart disease (CHD), and discovered an increased risk for early dementia by middle age.

“Research shows that children born with heart problems are at greater risk for neurodevelopmental issues,” says Nicolas Madsen, MD, pediatric cardiologist and study senior author. “We can now say the risk for these types of problems continues well into adulthood.”

Using medical registries and records from Danish hospitals, researchers identified 10,632 adults born between 1890 and 1982 who had CHD diagnosed between 1963 and 2012. They found a 60 percent increased risk of dementia compared to the general population.

Although many of these adults were born when medical and surgical interventions were more limited, Madsen says, “We need to understand the healthcare needs and risk factors affecting the larger number of middle-age and older adults currently living with CHD.”



Nicolas Madsen, MD

Follow-up Crucial After Fetal Opioid Exposure

Infants exposed to opioids *in utero* show a greater incidence of torticollis, an abnormal twisting of the neck, and plagiocephaly, a flattening of the head often seen with torticollis.

In a study published online Jan. 22, 2018, in *The Journal of Pediatrics*, researchers followed 783 children over five years. Eighty-seven (11.1 percent) of those born with Neonatal Abstinence Syndrome from opioid exposure *in utero* were diagnosed with torticollis. The rate in the general population is under 2 percent.

“Awareness of these issues is essential, as torticollis may not develop for several months after the infant is discharged from the hospital,” says study author Jenny McAllister, MD. Occupational and physical therapy can prevent the problems, and their associated developmental delays.

McAllister, who co-directs our Neonatal Abstinence Syndrome Long-Term Follow-Up Clinic, says it is not known whether opioid exposure caused the torticollis. The infants might have had muscle tightness that predisposed them to torticollis, or it could have resulted from swaddling to keep them calm after birth.



Jenny McAllister, MD

Inhibiting Deadly Enzyme Could Heal Immune Disorders



Kasper Hoebe, PhD

Scientists here discovered how a gene mutation causes immune disorders, and used their discovery to test a treatment that repaired immune cells donated by a 16-year-old boy with lymphopenia.

Researchers reported their findings Jan. 30, 2018, in *Nature Communications*. The discovery centered on a mutation in the gene *Gimap5*, important to healthy formation and function of infection-fighting T-cells. The mutation renders *Gimap5* unable to hamper the troublesome enzyme *GSK3 β* , which causes T-cells to malfunction and die.

The researchers tested drugs to inhibit *GSK3 β* in mice and human blood cells. They boosted immune system function in mice and restored normal T-cell function in the human cells. *GSK3* inhibitors already are used to treat Alzheimer's, mood disorders and diabetes mellitus.

Experiments are underway to translate the findings into the clinic, says Kasper Hoebe, PhD, Division of Immunobiology, who led the study. “We believe the use of *GSK3* inhibitors to prevent or correct these type of immune-related diseases holds great potential.”



Paul Spearman, MD

Cincinnati Children's Joins National Effort to Battle Avian Flu

With China experiencing at least six human outbreaks of H7N9 avian flu since 2013, vaccine experts here are working to help prevent a wider pandemic.

Cincinnati Children's is one of nine Vaccine and Treatment Evaluation Units (VTEU) under contract with the National Institute of Allergy and Infectious Diseases. The unit here is collaborating on one of two Phase 2 clinical trials to evaluate a new vaccine for H7N9.

In China, six outbreaks have infected a total of 1,567 people, according to the World Health Organization. H7N9 has a 39 percent mortality rate. As of early April, 2018, the strain had not been found in the U.S.

"An outbreak earlier this year is the largest to date in China, and potentially it could spread outside of Asia," says Paul Spearman, MD, Director of Infectious Diseases here and lead investigator of the study's Cincinnati arm. "If the H7N9 strain mutates and develops the capacity to spread easily from person-to-person it could cause a widespread epidemic, or pandemic."

Lab-grown Human Pancreas Cells Treat Diabetic Mice

Researchers tissue-engineered human pancreatic islets that develop a circulatory system, secrete hormones like insulin and successfully treat sudden-onset type 1 diabetes in mice.

In a study published by *Cell Reports* in May 2018, researchers used a new bioengineering process they developed called a self-condensation cell culture. This helps nudge medical science closer to one day growing human organ tissues from a person's own cells for regenerative therapy.

"This method may serve as a principal curative strategy for treating type 1 diabetes, of which there are 79,000 new diagnoses per year," said co-lead investigator Takanori Takebe, MD, of the Center for Stem Cell and Organoid Medicine.

Scientists tested their processing system with donated human organ cells (pancreas, heart, brain, etc.), and with mouse organ cells. Reprogrammed from a person's adult cells (like skin cells), induced pluripotent stem cells act like embryonic cells and can form any tissue type in the body.

Vascularized pancreatic islets (areas in green) are shown seven days after transplant.



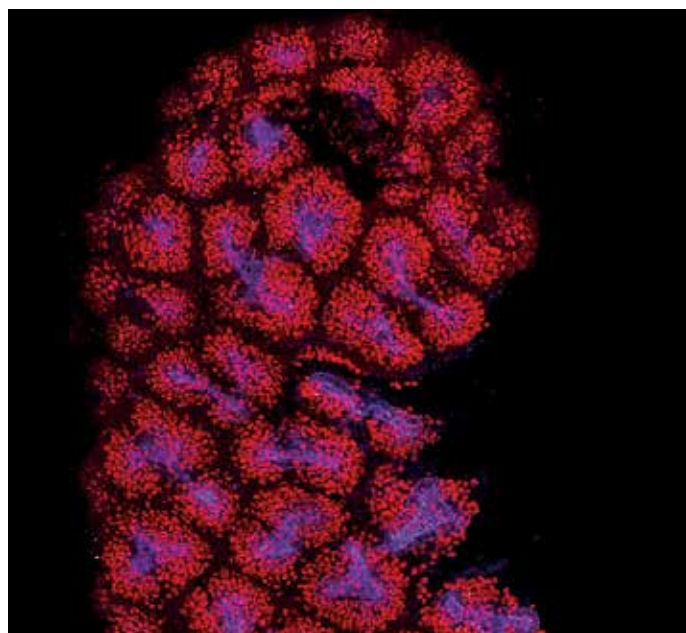
Can the Kidney Development Window be Propped Open for Preterm Infants?

A study from scientists at Cincinnati Children's reveals a potential mechanism that eventually might help preterm babies extend a crucial nephron development window and reduce their risk of kidney disease later in life.

Nephron formation occurs between weeks 25 to 36 of gestation, a process that can be interrupted by preterm birth. Now, in findings posted online, May 21, 2018, in *PNAS*, a research team led by Raphael Kopan, PhD, Director, Developmental Biology, reports that a protein called hamartin plays a central role in shutting down the nephron formation process.

Until now, this protein was known primarily as a factor involved in tuberous sclerosis complex. When mice were bred to produce reduced hamartin levels, their kidneys developed 25 percent more nephrons than a control group. However, when bred to produce no hamartin, the mice developed fatal kidney defects.

At first glance, the findings suggest targeting hamartin to protect kidney development. However, in people, that could increase tuberous sclerosis risk. "We are hoping that the mechanism hamartin acts through to regulate nephron numbers will contain druggable targets," Kopan says.



In this developing mouse kidney, individual progenitor cells appear in red; future collecting ducts appear as purple.



Drew Barzman, MD

Pilot Study Validates AI to Help Predict School Violence

A pilot study indicates that artificial intelligence may be useful in predicting which students are at higher risk of perpetrating school violence.

The researchers found that machine learning—the science of getting computers to learn over time without human intervention—is as accurate as a team of child and adolescent psychiatrists, including a forensic psychiatrist, in determining this risk. The study was published online in June 2018 in *Psychiatric Quarterly*.

"Previous violent behavior, impulsivity, school problems and negative attitudes were correlated with risk to others," says lead author Drew Barzman, MD, Director of the Child and Adolescent Forensic Psychiatry Service.

The team evaluated 103 at-risk teens in 74 traditional schools throughout the U.S. Their machine learning algorithm achieved 91.02 percent accuracy, considered excellent, when using interview content to predict risks. The next step: gathering outcome data to assess whether machine learning could actually help prevent school violence.

Accelerating Innovation

Cincinnati Children's dives deeper into product development with reorganized business unit

by Tim Bonfield

Our former Center for Technology Commercialization has new leadership, a bigger team, and a new name: Cincinnati Children's Innovation Ventures.

The rebranding reflects an expanded mission: to go beyond traditional technology transfer to support more start-up ventures, secure a wider variety of funding sources, and pursue other steps to bring promising health innovations to market.

"Under our new Co-Innovation Accelerator model, we will work with our partners to jointly accelerate innovations that impact our triple-bottom-line mission of improving child health, providing benefits to our institution, and providing benefits to our community," says Andrew Wooten, Vice President, Cincinnati Children's Innovation Ventures.

INNOVATION POWERHOUSE

The Cincinnati Children's Research Foundation ranks among the nation's largest engines of pediatric science. More than \$200 million a year in extramural funding (primarily from the National Institutes



Andrew Wooten joined Cincinnati Children's in 2017 to lead an expansion and reorganization of commercialization services now called Innovation Ventures.

of Health) flows into approximately 1.5 million square feet of research space. From there, experts in more than 50 specialty divisions produce more than 2,000 peer-reviewed scientific papers a year.

The science ranges from exploring the most fundamental aspects of human development to creating new medications, better ways to diagnose disease, improved medical software, and entirely new technologies such as growing miniature human organs in a dish. Every year, Cincinnati Children's discloses more than 150 new inventions.

The perennial challenge is to move more of these bold discoveries beyond the world of academia and into the marketplace, where they can make a difference in the lives of children—and adults.

Cincinnati Children's has a decades-long history of breakthroughs. These include the Sabin oral polio vaccine that helped nearly eradicate the disease worldwide, artificial surfactant that has saved a generation of premature infants, the Rotarix rotavirus vaccine used in more than 100 countries, and the GeneSight

drug metabolism test that has helped more than 650,000 people receive the best dose of psychiatric medications.

Now the medical center is making a bigger commitment to do even more.

FORDING THE 'VALLEY OF DEATH'

"Traditional technology commercialization offices are seen primarily as brokers of intellectual property," Wooten says. "They

In too many cases, promising ideas run out of initial research grant funding long before the concepts have matured into prototype products that the commercial sector might consider worth an investment. Many call this gap the "valley of death."

"This is more than a funding gap. It's also a gap in the kinds of product development expertise and infrastructure that's

The perennial challenge is to move more of these bold discoveries beyond the world of academia

help inventors obtain patents, then they market their portfolios to potential investors. Typically, the end of that process is a licensing agreement with a pharmaceutical company or other commercial partners. We intend to continue fulfilling that role, but we also are going beyond."

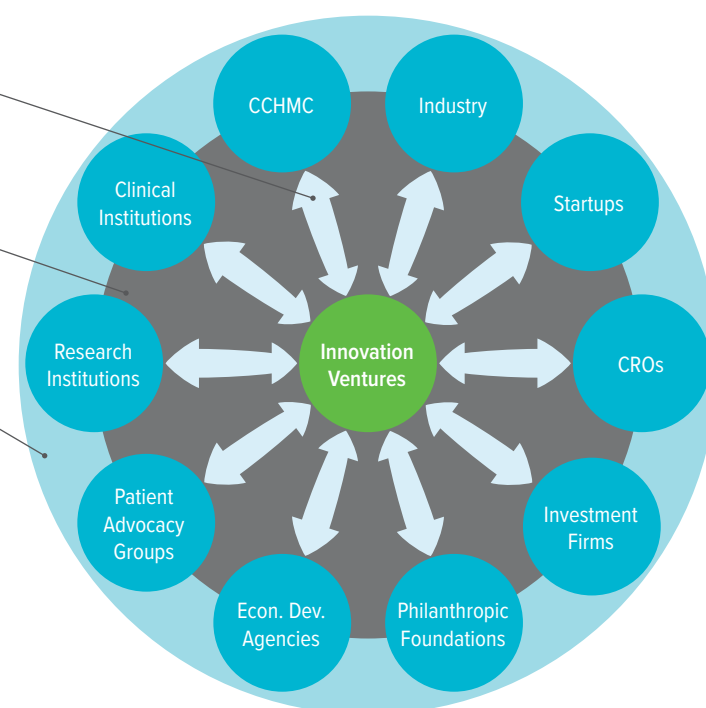
needed to advance an idea," Wooten says. "Without investment and support, many promising innovations never have a chance to prove their value to society."

In recent years, private industry has demanded that the non-profit sector take on more of the burden and risk of moving

Partner Value Proposition

Domestic Partners

International Partners



Traditional models of commercialization focus heavily on licensing deals to secure outside corporate funding. The team at Innovation Ventures was organized to pursue funding partners and collaborations across numerous potential sources.

innovations through early-stage development. However, many pediatric medical centers have not been structured to do such work.

Cincinnati Children's began building its capacity with the Center for Technology Commercialization. The organization helped establish internal funds to provide seed money to promising innovations. It negotiated agreements with two pharmaceutical firms to support early-stage product development. It even built a collaboration with a university in Israel to design pediatric surgical devices.

The new Innovation Ventures unit seeks to accelerate this work.

WHAT IS 'CO-INNOVATION'?

Beyond the traditional for-profit licensing agreement, Wooten describes a "co-innovation" model that nurtures funding support from at least 10 kinds of potential partners. The next "home run" from Cincinnati Children's, Wooten says, is more likely to flow from a consortium of diverse backers versus a pure for-profit deal involving a single underwriter.

"Industry is primarily motivated by profit, but the non-profit sector often has reasons to care about an innovation before it is clear that it will be profitable," Wooten says.

Patient advocacy groups care about specific patient groups. Economic

development organizations care about building business in specific geographies or industry sectors. Other charitable foundations often have missions to improve society in some measurable way.

"Tapping into those resources during the early high-risk phase of development can make all the difference in successful commercialization," Wooten says.

Now, part of the re-structured Innovation Ventures group focuses exclusively on building deeper relationships with non-traditional funding partners.

"One reason we chose a new name is to send the message that we do much more in the areas of commercial planning, product development and new venture creation than many realize," Wooten says.

ORGANIZED BY ASSET CLASS

After examining the growing portfolio of discoveries at Cincinnati Children's, Wooten's team organized them into four groups:

- Small molecule therapies
- Biologic, cell and tissue therapies
- Diagnostics and medical devices
- Digital health and care delivery

Each of these categories has unique regulatory requirements and industry networks to understand. Innovation Ventures expanded its team to 21 people

in large part to provide specific expertise in product development in each of these areas. (This issue of *Research Horizons* describes work in each of the four categories).

This "Innovation Acceleration Group," led by Mike Pistone, Director of Innovation Acceleration, has selected several projects in each category that are most-ready for a concentrated push. For these projects, the group devises commercialization plans, works with co-innovation partners to acquire resources, and manages projects to achieve higher value and impact.

In some cases, but only some, this can mean launching a spin-off company. In the past two years, Cincinnati Children's has launched three new ones. In the past decade, start-ups launched here have created more than 500 jobs. (see page 32 for more detail)

"One of the key differentiators for the Innovation Ventures team is our ability to invest in projects and new ventures," Pistone says. "We have two mechanisms to do this, the Cincinnati Children's Innovation Fund and the Cincinnati Children's Investment Fund. The former primarily exists to support early-stage projects with commercial potential and the latter primarily exists to seed early investments in new companies."

ABOUT ANDREW WOOTEN



Title: Vice President, Cincinnati Children's Innovation Ventures

Start date: January 2017

Experience

- Holds a bachelor's degree in chemistry and master's degrees in biotechnology and business administration.
- Started as an embryologist for Reproductive Biology Associates.
- Moved into business development with ThermoFisher Scientific and Applied Biosystems.
- Helped launch AviGenics, which was renamed Synageva Biopharma, and eventually acquired by Alexion.
- Moved into the non-profit sector, most recently with Baylor College of Medicine.

Mission

I started out thinking that I wanted to be a scientist, and I still think of myself as a scientist. For me, business and law are tools to facilitate the groundbreaking advances produced by scientific research. This is my calling.

I came to Cincinnati Children's because the institution represents a great sandbox for someone like me to play in. The base of high-quality research is here. The combination of a top research engine and a top clinical care operation under the same roof is a very powerful combination for someone in my role. Finally, the role that I was offered afforded me the opportunity to pull a lot of the levers necessary for success.

A "home run" would be great. But this business is more about increasing the number of shots on goal. Increase our odds of achieving a big deal. Mature assets have better odds of success. The further we can take something, the more value we can ask for it.

Getting Real with Organoids

How to Turn 3D Mini-Organs into Practical Medicine

by Nick Miller

A critically ill baby waits too long for a liver transplant as a life slips away. A doctor needs to learn why a promising teen athlete develops a complex and debilitating intestinal disease. A drug company wants to know if its new wonder pill is safe and effective before testing it on people.

Ten years ago, solutions to these problems seemed unreachable. Now, scientists at the Center for Stem Cell and Organoid Medicine at Cincinnati Children's are making a concerted effort to offer the world a new technology—one on the verge of helping the baby live, showing the doctor how the young athlete got sick, and telling pharmaceutical researchers whether a new drug is safe or toxic to living human tissues grown in lab.

Human organoid technology boils down to the ability to bioengineer genetically matched, three-dimensional organ tissues from a person's own cells. It's a technology that pundits would call "transformative" or "disruptive."

Organoids are helping push medical science into a new era of personalized regenerative medicine, according to Aaron Zorn, PhD, a developmental biologist and Executive Director of the new organoid center. But to realize that potential, the technology must make the often-unsuccessful transition from the laboratory bench to the real world of patient care.

"I think the biggest advances and opportunities in the short term are going to come from understanding the basic biological



Aaron Zorn, PhD, (left) directs the new Center for Stem Cell and Organoid Medicine at Cincinnati Children's. The center is expanding upon research breakthroughs led by developmental biologist James Wells, PhD, (right) and a growing team of experts.

mechanisms of how a disease progresses so we can find novel therapies and use organoids for drug screening. A decade ago the idea of growing working human tissues in a lab was still a fantasy. Now it's a reality, so things move quickly," Zorn says.

At Cincinnati Children's Innovation Ventures—the medical center's renamed and expanded technology commercialization arm—organoids reside in a category called Biologic, Cell and Tissue Therapies. The category includes tissue engineering projects such as organoid development, but also gene correction therapies for conditions such as sickle cell anemia, and vaccine innovation.

BRIDGING THE ACADEMIC BIOTECH GAP

As challenging as the science behind human organoids and gene therapy can be, overcoming financial and infrastructure limitations inherent to non-profit academic research are equally daunting. This gap between moving a promising new technology from the lab to patients is known among researchers as the "valley of death."

To cross the gap, the non-profit academic world depends on private-sector expertise in many ways, from the medicinal chemistry to design and make deliverable clinical compounds to venture

capital to the infrastructure for large-scale production, distribution, and marketing. This is where the team at Innovation Ventures steps in. Their job is to help busy scientists work through the business end of finding real markets for their innovations.

Innovation Ventures helps identify investors and potential industry partners, assists with forming start-up companies, and helps manage the pre-clinical red tape. So far, Cincinnati Children's has formed more than a dozen start-ups in recent years.

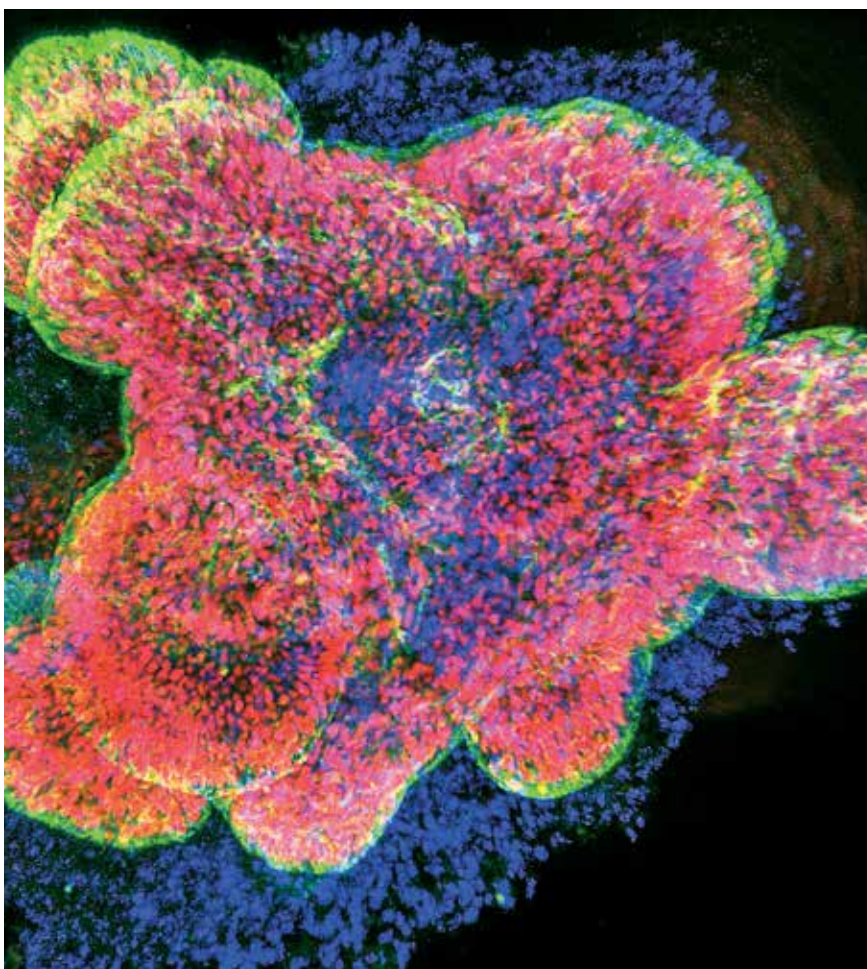
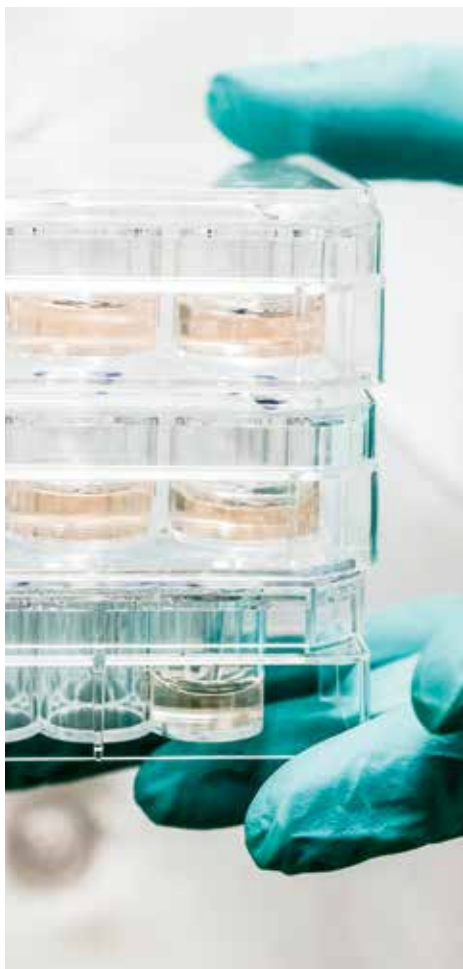
Take organoids as an example, where many decisions regarding licensing to outside partners vs. launching startup companies are still being assessed. Finding the right strategy for each innovation is critical to success.

"It is very important for our team to help get these assets to a place—whether through intellectual property protection or identifying experiments—that will help make technologies attractive to industry," says Justin Levy,

Director of Portfolio Management at Innovation Ventures. "From there, for-profit companies can take it on, bring their unique capabilities, and invest dollars needed to get that technology to patients who need it."

Biologic, Cell and Tissue Therapies is such a promising category that three people are helping oversee commercialization—Levy,

THE PROBLEM
to understand
the nature
of the
human body



Portfolio Manager David Wang, and Senior Acceleration Manager Leandro Christmann. All have biotech industry backgrounds and expertise.

“Organoids are a very revolutionary technology that could fundamentally alter healthcare,” Wang explains. “It has potential for multiple applications—drug discovery, a research tool for modeling human disease, or helping replace damaged organs.”

But even a potentially game-changing technology must be developed and managed.

NON-PROFIT MISSION VS. PROFIT

There is an adage in non-profit academic research and medicine: “no money, no mission.” It reflects the sometimes-delicate balancing act of commercial collaborations that advance the medical center’s non-profit mission.

Zorn and the team of collaborators that make organoid technology real—in Cincinnati and around the world—started out as basic scientists. This includes James Wells, PhD, the developmental biologist who pioneered stem cell and organoid science at Cincinnati Children’s.

A decade ago when they were studying frogs and mice to unravel how bodies grow and organs form, the scientists didn’t know how their work might lead to a potentially transformative technology. But they are not necessarily surprised, either.

“I think the motivation for the basic scientist in this instance is to understand the nature of the human body, how cells work, how organs form and the basic causes of disease,” Zorn explains. “We always had the long-term vision that research in animals could be translatable to human therapy. But even as we try to commercialize and translate these discoveries, the need for basic research continues.”

Commercialization—applied the right way—can strengthen Cincinnati Children’s mission, according to Zorn.

TANGIBLE PRODUCT ON DECK

In 2016, the medical center granted a commercial license agreement to STEMCELL Technologies to make laboratory stem cell-organoid lab kits. The product may be available within two years.

The kits will provide the protocols and technology needed to allow other scientists to reprogram a person’s adult cells (like skin cells) into induced pluripotent stem cells (iPSCs), a process Cincinnati Children’s has been refining over the years.

This kind of product advances the medical center’s mission by sharing new knowledge that can improve child health, Zorn and colleagues at Innovation Ventures say. ■

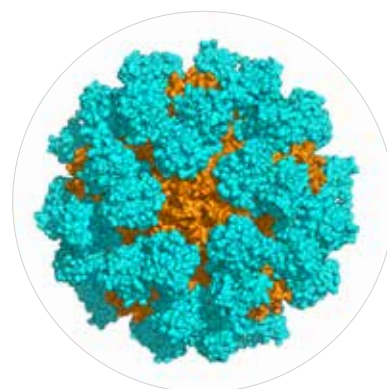
Tiny organoids growing in the lab (above) have enormous potential to study disease and new medicines in fully functional human tissues without putting patients at risk.

BIOLOGIC, CELL & TISSUE THERAPY: MEDICINE MEETS ITS FUTURE

Inserting the correct copy of a gene into a person's cells may help scientists grow mini-organs to determine how to treat a disease or eventually provide healthy replacement tissues. These three examples illustrate how this bold new class of therapeutic technology is making its way along the commercialization pipeline:

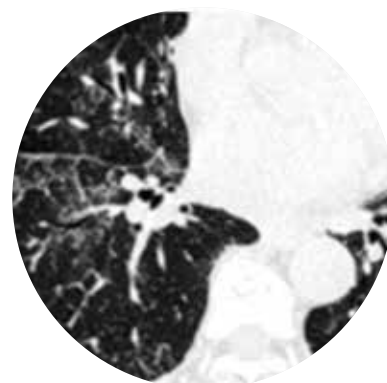
Nanoparticle Vaccine Development

Traditional vaccines use attenuated viruses but have limitations including adverse side effects, failure to induce durable immunity, and high production costs. Ming Tan, PhD, and Jason Jiang, PhD, in the Division of Infectious Diseases, created a norovirus nanoparticle vaccine technology that uses recombinant antigens, which trigger an immune response and antigens against a disease. This versatile platform can be used for multiple types of vaccines, including against rotavirus (RV), which kills thousands of children each year worldwide, especially in developing regions. Beyond RV, the team is working on nanoparticle vaccines for influenza and other diseases.



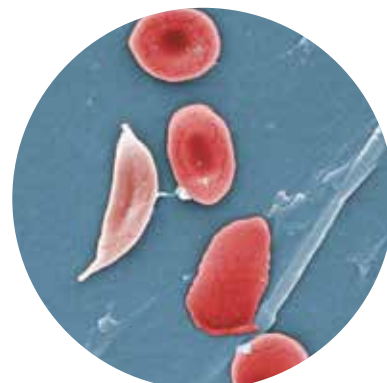
Gene Therapy for Pulmonary Alveolar Proteinosis (hPAP)

This genetic disease hinders lung function by allowing insoluble surfactant sediment to accumulate. The only treatment is a periodic whole-lung lavage—a highly invasive lung wash procedure. Pulmonologist Bruce Trapnell, MD, and colleagues have developed a gene and cell therapy called pulmonary macrophage transplantation (PMT). This treatment delivers a functional copy of the disrupted gene (CSF2RA) to the lungs after insertion into bone marrow-derived macrophages. Preclinical research shows that a single, targeted PMT delivery cures the disease in mice. Now Innovation Ventures is helping the team pursue investigational new drug status from the U.S. Food and Drug Administration and scale-up funding from a private industry partner.



Gene Therapy for Sickle Cell Disease

This blood-cell deforming illness affects millions of people worldwide and can be challenging to manage. Hematologist/oncologist Punam Malik, MD, developed a patented gene therapy that uses a modified cold virus to transfer a healthy fetal hemoglobin gene to people with sickle cell disease. Research shows the therapy will allow their bodies to produce normal red blood cells.



A Vision of Precision

Surgeon-in-Chief's creation of a needle delivery system FINDs its target, thanks to an inspired idea, an ordinary napkin, an Israeli engineer, and Innovation Ventures

by Tom O'Neill

Legend has it, Daniel von Allmen took his seat at a 2012 luncheon at Ben Gurion University in Israel, and the guy next to him turned out to be a professor of electrical and computer engineering named Hugo Guterman.

They chatted, and before plates were cleared, von Allmen had shown him some images on his laptop and explained his idea for a robotic needle delivery system guided by ultrasound imaging. He then sketched it out the best way available. On the back of a napkin.

Von Allmen, MD, Surgeon-in-Chief and the Lester W. Martin Chair of Pediatric Surgery at Cincinnati Children's, lacked two important things that day: a consistent funding pipeline and anything remotely resembling an engineering degree.

He did not, however, lack vision that such a system could transform how children receive needle sticks, a potentially significant breakthrough given that a third of initial central placement attempts by care providers are unsuccessful. Children, after all, have far smaller veins than adults and are at times moving targets.

"Being seated there was pure happenstance," von Allmen recalls. "Hugo was big in engineering expertise. This was very educational for me in terms of what it takes to bring a conception to reality."

Fast forward a half-decade to last year's launch of Xact Medical LLC, a new company that Cincinnati Children's and Ben Gurion (BGU) co-founded to commercialize the Fast Intelligent Needle Delivery (FIND). Guterman, PhD, was a driving force on the technical side.

"It was," von Allmen says modestly, leaning forward in his chair, "an incredibly big learning curve." The best legends are always the true ones.

THE JOURNEY TO CLINICAL TRIAL, AND BEYOND
FIND uses ultrasound imaging to precisely, quickly, and conveniently place a needle tip at a point on the body that significantly improves the odds of successful vascular access. Then, robotics does the rest.

The device is now in pre-clinical development with a second prototype expected by this summer that will have different



Andrew Cothrel, (left) is CEO of Xact Medical LLC, a spin-off company formed to develop prototypes of a guided needle delivery device envisioned by Daniel von Allmen, MD, Surgeon-in-Chief at Cincinnati Children's (right) and engineered by experts at Ben Gurion University in Israel.

mechanics and be easier to sterilize. The hope after that is FDA approval.

In all, \$1.5 million has been invested so far, including from Innovations Ventures, external grants, and CincyTech, which funds companies in life science and digital fields. Von Allmen serves as Chief Medical Adviser in Xact Medical, Guterman as Technical Adviser, and Andrew Cothrel, a veteran of medical technology development and commercialization, is CEO.

Even the device's name had an evolution to it. Initially, it was called Image Guided Autonomous Needle Insertion Device, or IGANID. Then came Human Assisted Needle Delivery System, or HANDS. And finally, FIND.

One of the team's challenges throughout FIND's journey to clinical trial is an age-old one: investors simply view the financial ceiling for devices as lower, compared to pharmaceuticals and biologics. And for pediatric-centric devices, the market is even smaller.

For instance, when Innovation Ventures first began to market FIND's technology, it drew interest from a range of potential investors, but their answers were

decisions about intellectual property filings, and that costs money. Having a group like Innovation Ventures allows Cincinnati Children's to take that kind of risk."

THE PROBLEM

it sometimes takes a ½ hour
to 2½ hours to place an IV

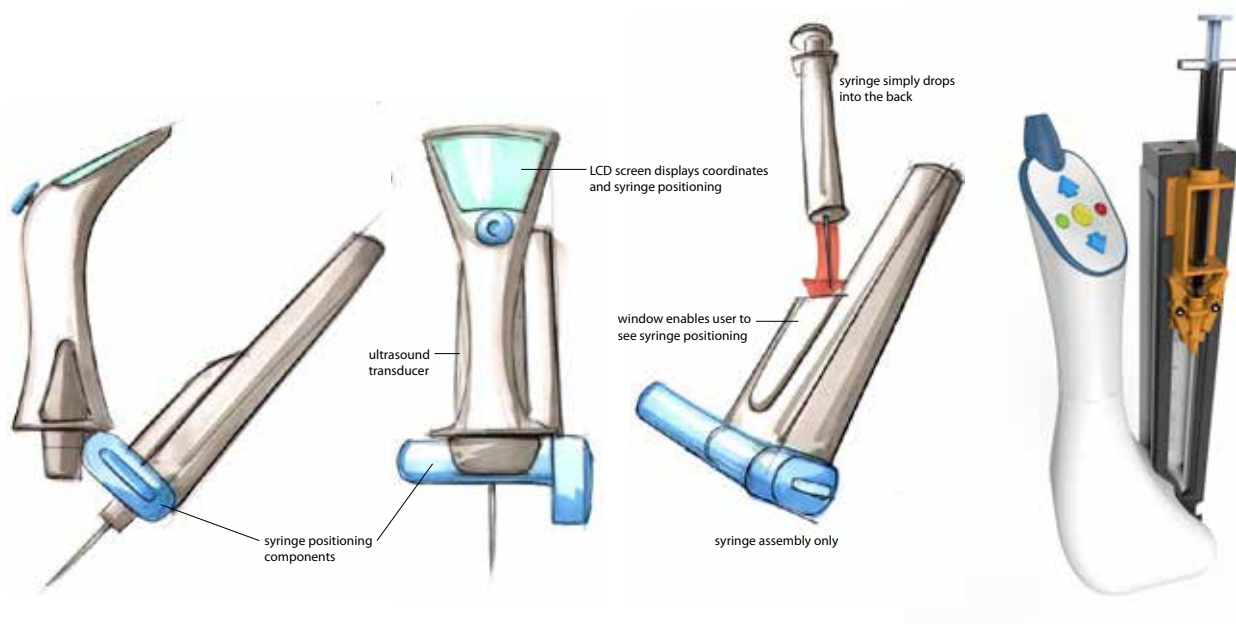
the same: This is fantastic. Keep going a little further. Call us back.

THE POWER OF WISHFUL THINKING

"So we're looking at making a patent finding that may never be valuable to the commercial world for, say, 10 years. No business does that," explains Jon Brophy, a portfolio manager at Innovation Ventures who oversees its "devices" asset class. "Because of that, we take on a little more risk on

Ultimately, the FIND technology could be expanded to include adult vascular access, aspirations, biopsies, injections and regional anesthesiology. Von Allmen, who also serves as Surgical Director of Cincinnati Children's Neuroblastoma Program, points out that during chemotherapy, it sometimes takes a half hour to two and a half hours to place an IV.

Sketching the basic design on a napkin took far less time. Guterman, the



The FIND device has evolved across multiple design improvements from the idea that started as a napkin sketch and the not-quite-inspiring name IGANID.

BGU engineer, was intrigued from the beginning.

“I thought that it was an interesting problem that I wasn’t aware existed,” he recalls. “He presented it as a special issue in children’s treatment. Only later, I discovered that the problem exists for adults as well. The real challenge was to take Dan’s description, which was just wishful thinking, and transform it into reality.”

That wishful thinking is a big part of FIND’s story, but the backstory of von Allmen’s idea is even more layered, reaching back more than a decade to the Research Triangle of North Carolina.

WANTED: MORE BABY STEPS, FEWER OBSTACLES

As Surgeon-in-Chief at North Carolina Children’s Hospital in the mid-2000s, von Allmen worked on the idea of needle guidance with a biomedical engineering group at Duke University and a team of aerospace engineers at North Carolina State University. They arrived at a proof-of-concept, building the robotic aspect on what they’d learned about the application of ultrasound.

In a paper published in November 2006 in *IEEE Transactions on Ultrasonics, Ferroelectrics, and Frequency Control*, von Allmen and the engineers demonstrated the potential of the concept by using

images acquired with a 3-D laparoscopic ultrasound device. Scanned coordinates directed a robotically controlled needle toward *in vitro* targets in a canine model.

The error rate for measurements using ultrasound guidance was 0.76 mm. In optical alignment—the longstanding eyeball test—it was 1.34 mm.

That success was a relative baby step. For one, von Allmen recalls, “We didn’t have patent lawyers.”

When he arrived at Cincinnati Children’s in 2009, one of his first stops was the Center for Technology Commercialization, now Innovation Ventures. The following year, von Allmen co-authored a second feasibility study, published in *Ultrasound in Medicine and Biology*, using of all things, turkey breast tissue.

Moving beyond simple thresholding algorithms, the team showed that the robot autonomously processed 3D ultrasound images to locate a metal rod embedded in tissue. The rod represented calcification. They then simulated a cyst by filling a void in the tissue with water.

‘IT WAS INCREDIBLY ACCURATE’

With no user input, the robot directed the needle to the desired target. Separate needle-touch experiments performed in a water tank yielded an error rate of 1.15 mm.

“By simulating simple procedures common in typical breast biopsies,” the authors wrote, “this study has demonstrated that autonomous guidance might eventually be extended to many relatively straightforward surgical tasks performed in large volume at hospitals and clinics.”

Three months after that study, the same team published a follow-up study in *Ultrasonic Imaging* that demonstrated the robot’s ability to deliver a needle stick in each of eight sectors in the phantom in a single session, with a success rate of 93 percent. A phantom is used to replicate the target area.

“What we found was, it was incredibly accurate,” von Allmen recalls. “But there’s a big difference between an idea versus a viable product. That’s where Innovation Ventures comes in. But I’m the one who takes care of the patient.”

On a recent morning, he and Cothrel met briefly at Cincinnati Children’s with the FIND device, discussing the second prototype that is now months away.

Then the two men went their separate ways: Cothrel to catch a flight to Washington, D.C., to make a presentation to potential investors; Von Allmen, still in scrubs, back to the O.R. ■

DEVICES ON TRACK TOWARD MAKING A DIFFERENCE

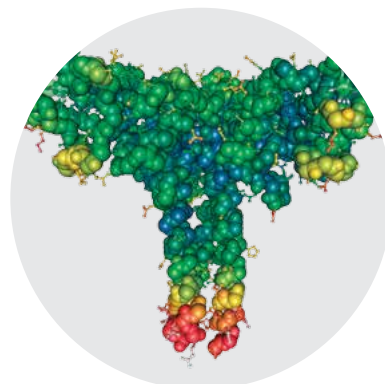
NICU MRI

While scientists develop a second prototype of a magnetic resonance (MR) scanner specifically designed for babies in the neonatal intensive care unit (NICU), the first one has provided scans of more than 600 newborns. The scanner, designed by Charles Dumoulin, PhD, Director of the Imaging Research Center, and colleagues, is the only infant-sized MR scanner in the world housed within a NICU. The device supports moving infants to the MR unit in their own isolette and allows easy transfer to the imaging table. The project has received more than \$3 million in early-stage funding. Now, the team is collecting clinical data while the device's lead investor awaits additional improvements.



Surfactant Nanoparticle Project

A fruitful collaboration between Cincinnati Children's and Ben Gurion University in Israel has produced a unique product that wraps a nanoparticle around surfactant protein D, and can be administered via a biodegradable polymer. The product eventually could improve surfactant treatment for premature infants. The collaboration includes Paul Kingma, MD, PhD, Neonatal Director, Cincinnati Fetal Center; Jeff Whitsett, MD, Co-Director, Perinatal Institute; and Yossi Kost's lab at BGU in Israel.



Shape Memory Patch for Fetal Spina Bifida Procedures

The ingenuity of the shape memory patch for fetal spina bifida procedures is that it does its job very well—and then goes away. The patch closes the neural tube defect and creates a water tight seal, eventually degrading over 16 to 20 weeks. The patch allows procedures to be conducted as early as 20 to 26 weeks gestation. The patch is the brainchild of Jose Peiro, MD, PhD, Endoscopic Fetal Surgery Director at Cincinnati Children's, and Chia-Ying Lin, Biomedical engineer, Research Director of Orthopaedic Surgery at the University of Cincinnati. However, commercializing a product likely to be used only 200 to 400 times a year can be a challenge. "It can be hard for a traditional company to take these early development risks, but the fact that we're a children's hospital thinking creatively and comprehensively about impact puts us in a unique position," says Jon Brophy, Portfolio Manager at Innovation Ventures.



A Cold-Blooded Concept

Acceleration efforts begin for safer, long-lasting platelet storage

By Tim Bonfield

Every year, trauma patients, cancer patients and other people who need blood products in the United States receive more than 2 million units of platelets at an estimated cost of \$1.5 billion.

Every year, however, as many as 20 percent of those platelets expire before they can be transfused. The problem: when stored at room temperature, as required by federal regulation, platelets last only five days. Unlike other blood products, platelets cannot be refrigerated without losing efficacy.

At least not yet.

Experts at Cincinnati Children's are further developing a method they invented of treating platelets that appears to allow refrigerating them for up to 14 days, potentially tripling shelf life. Such an improvement could transform blood banking, be it to serve children with leukemia or soldiers wounded on distant battlefields.

THE GERM OF AN IDEA

Yi Zheng, PhD, is a blood expert who directs the Division of Experimental Hematology and Cancer Biology at Cincinnati Children's. He has been hunting for small molecule compounds that can improve treatment for blood-borne cancers and other disorders for more than 25 years.

For many of those years, he has collaborated with Jose Cancelas, MD, PhD, who directs the Hoxworth Blood Center, the primary blood supplier to more than 30 Cincinnati-area hospitals. Their long-term collaboration led to the realization



Basic scientific exploration led by Yi Zheng, PhD, (right) revealed how platelets could be placed into a statis-like state. Jose Cancelas, MD, PhD (left), Director of the Hoxworth Blood Center, realized the discovery's potential for improved blood banking.

that some of the small molecule compounds offered potential that could extend well beyond pediatrics.

“This is one of the biggest problems in blood banking. Just like meat, the longer you leave platelets at room temperature, the higher the risk of bacterial contamination,” Cancelas says. “Right now, even though we take great care to prevent contamination, approximately one in every 70,000 platelet products in the U.S. carries detectable levels of bacteria. One in 200,000 people who receive transfusions develop a clinically significant infection, and one in 500,000 develop sepsis.”

Minimizing this risk requires constant testing and juggling of platelet supplies.

“Unfortunately, platelets remain the only blood product that cannot withstand refrigeration. As a result, we experience shortages on some days when we have high patient volumes, and wasteful oversupplies on other days,” Cancelas says.

HOW TO STOP COLD-INDUCED CELL DAMAGE

The platelet-protecting discovery flows from Zheng’s basic science work to understand cellular signaling mechanisms, specifically the structure-function relationship that regulates Rho family GTP-binding proteins.

Rho GTPases are a class of signal senders that play several important roles in regulating cellular activities, including actin cytoskeleton reorganization, transcription activation, and DNA synthesis.

THE PROBLEM

platelets last
only five days

During this exploratory work, the Zheng and Cancelas labs developed a mouse model that lacks a specific Rho protein. Once deleted, the team discovered that mouse platelets entered a hibernation-like state. Then they developed a small molecule that also can trigger a similar effect, but reversibly.

Further testing revealed that the small molecule can be applied to a bag of platelets as an *ex-vivo* treatment, allowing the platelets to withstand damage triggered by cellular reactions to cold temperatures.

In a critical final step, the team learned that diluting the compound effectively washes it away, allowing platelets to emerge from hibernation and resume normal function. This can be achieved either by mixing platelets with plasma in the lab, or by allowing the platelets to mix with other blood components during transfusion.

“The binding of this compound to its target is reversible and relatively weak,” Zheng says. “As soon as these platelets join a larger blood supply, the drug is diluted and the platelets ‘wake up.’”

So far, in mice, no toxic side effects have been detected from exposure to the compound.

ENTERING THE BUSINESS DEVELOPMENT STAGE

Now the journey begins for moving this potential breakthrough technology into human clinical trials—and that is where the work of the recently expanded Cincinnati Children’s Innovation Ventures group kicks in.

The platelet storage project is part of the “small molecules” portfolio at Innovation Ventures, which represents about one fourth of the discoveries at Cincinnati Children’s earmarked for accelerated commercialization efforts, says Karen Lammers, a portfolio manager for the group.

“Who better to come up with therapies to treat our patients than us?” Lammers says. “We have extensive genetic understanding. We are experts at developing mouse models. And we can manipulate those mouse models for drug development.”

Another reason why small molecules became an asset class was to continue working on a library of more than 250,000 chemical compounds that Procter & Gamble donated to the University of Cincinnati and Cincinnati Children’s in 2007. “We’ve been using that library to identify target molecules that we are developing further. I know of only a few other academic institutions that have that type of in-house resource,” Lammers says.

On the platelet project, the Innovation Ventures group is working with the inventors to perform several critical tasks.

So far, patent filings have occurred in the U.S., Canada, Europe, China, and Australia. The acceleration team, with support from Cincinnati Children’s investment committee, intends to advance this product towards the filing of an Investigational New Drug (IND), which is anticipated to cost approximately \$2 million, says David Wang, portfolio manager for biologics and cell therapies. Applications for other federal and state funds have begun.

Ultimately, obtaining U.S. Food and Drug Administration approval also will require human-cell toxicology testing in a GMP-certified lab, plus planning and performing phase I and II clinical trials.

“Our goal is to help move the product development process along, find strategic partners for investment, and ultimately provide clinical impact,” Wang says.

WHAT’S NEXT:

An encouraging sign: in January 2018, the FDA and the Department of Defense announced a collaboration to “expedite availability of medical products essential to the health of our military service members, particularly those products used to treat injuries in battlefield settings.”

Platelet cold storage is one of the top needs joining that priority list. ■

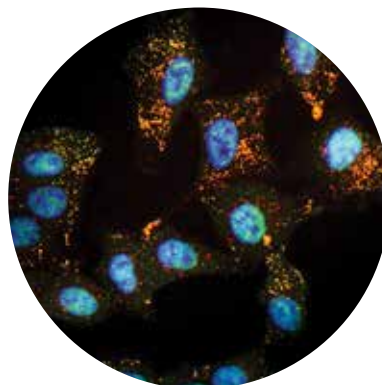


Today, the shelf life is only five days for platelets like these under preparation at Hoxworth Blood Center—two of which often get used to test the blood products for signs of bacterial contamination.

OTHER SMALL MOLECULE PROJECTS

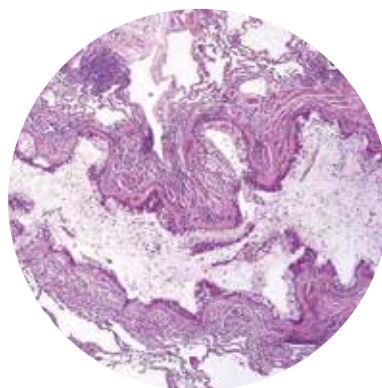
Promising Compound for Lung Disease

Several years ago, Vladimir Kalinichenko, MD, PhD, screened the compound library donated by P&G and found a molecule dubbed RCM-1. This molecule inhibits the transcription factor FOXM1, which plays an important role in excessive mucous production in the lungs. Now Kalinichenko and colleagues are working with Innovation Ventures to further fund and develop the compound as a potential treatment against diseases including cystic fibrosis and asthma. Unlike some other compounds in its portfolio, Cincinnati Children's has a "composition of matter" patent on RCM-1 that provides more control than process or formulation patents.



A New Weapon Against Asthma

Cincinnati Children's has an ongoing agreement with Adare Pharmaceuticals to explore promising potential drugs. One of those projects involves work led by Gurjit Khurana Hershey, MD, PhD, Director of Asthma Research. She is leading studies that could repurpose a drug, cysteamine, which is already approved to treat the rare disorder cystinosis for asthma care. Khurana Hershey and Adare are designing new formulations for an asthma indication and plan to launch a Phase 1 trial soon.



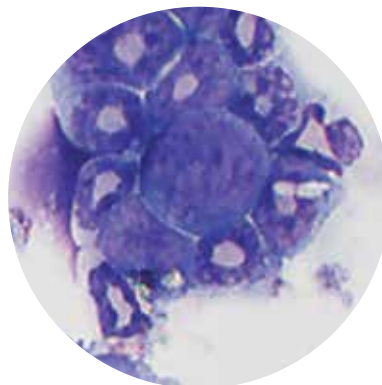
Teaming up against Fragile X

Craig Erickson, MD, is leading research into a possible treatment for Fragile X Syndrome (FXS), the most common inherited cause of intellectual disability and autism. The project involves a shelved small molecule owned by a large pharmaceutical company. The Innovation Ventures team is supporting work that includes a Phase I clinical trial already underway.



Targeting bone marrow disorders

Cancer biologist Daniel Starczynowski, PhD, is working with Innovation Ventures to further develop small molecules that can block hyperactive IRAK1 and IRAK4 signaling, a kinase complex that can drive the onset of myelodysplastic syndrome (MDS). This group of bone marrow disorders can lead to deadly cancers such as acute myeloid leukemia (AML).



When Saving Lives is Tough to Sell

A breakthrough in machine language learning provides early identification of suicidal behavior. But moving such a product beyond the lab is no simple task.

by Tom O'Neill

John Pestian, PhD, MBA, Tracy Glauser, MD, and Michael Sorter, MD, have thousands of reasons to feel a profound sense of urgency in getting their latest innovation into the hands of as many caregivers as possible.

In 2016 alone, nearly 45,000 Americans took their own lives, according to the U.S. Centers for Disease Control and Prevention. Of those, more than 6,000 were young people aged 10 to 25—and the rate of adolescent suicide has been rising steadily since 2007.

The suicide rate for girls ages 15 to 19 has doubled, reaching its highest point in 40 years in 2015. The suicide rate for boys ages 15 to 19 increased 30 percent across the same period. Now, suicide is the second-leading cause of death for those aged 15 to 24 and the third-leading cause of death among children aged 10 to 14.

As nationally known experts in artificial intelligence, computational medicine, psychiatry and brain science, the coinventors know these statistics better than most. But one number is especially powerful: 1,319.

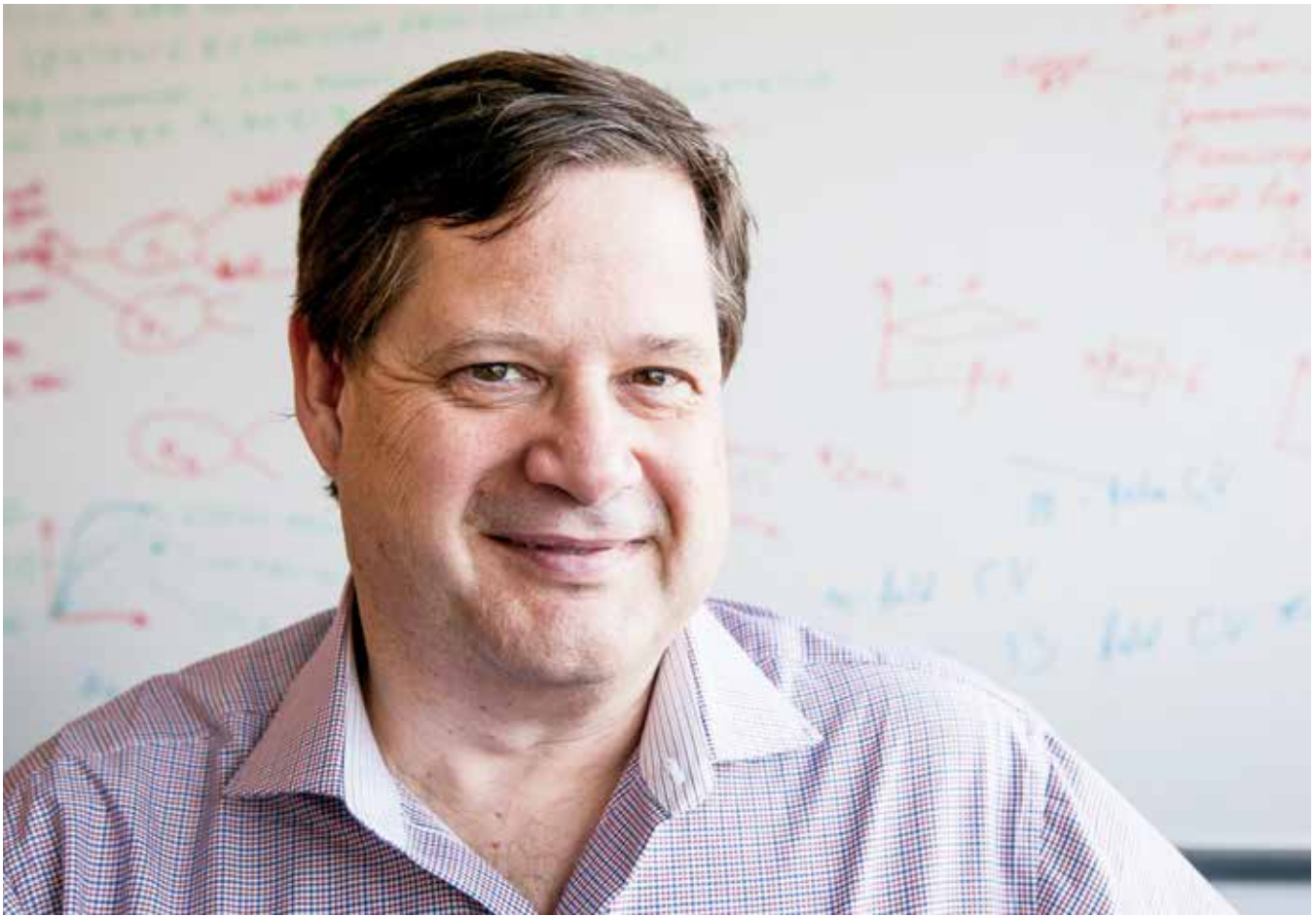
That is the number of suicide notes used in this project to teach computers how to understand the language of suicide. It's the world's largest known collection of its kind. Pestian and 30 colleagues from around the world devoted years to collecting and analyzing these notes.

From this exhaustive research, Pestian and colleagues reported a breakthrough in 2012 that to this day seems mind-boggling: it is possible to teach a computer to do a better job than a trained human mental-health professional at determining how serious a person actually is about taking their own life.

The potential benefit of such a tool is hard to overstate. Imagine having the chance to step in before things go too far. Imagine avoiding the anguish, the overwhelming guilt, the crushed hopes that flow from so many premature funerals. Imagine instead the many contributions to our world that could come from budding young lives getting their chance to blossom.

REAL PROGRESS, REAL POTENTIAL

In 2010, Pestian and colleagues recruited 163 volunteers who had personal experiences with suicidal thoughts to help annotate the collection of suicide notes. They mapped words and sentences to emotions and related categories, such as abuse, anger, blame, fear, guilt, hopelessness, sorrow, forgiveness,



John Pestian, PhD, MBA, led a team that converted the world's largest known collection of suicide notes into a data set to begin teaching a machine learning program how to recognize signs of suicidal thought in a person's speech, voice and expression.

happiness, peacefulness, hopefulness, love, pride, thankfulness, instructions, and information.

The result was a database of suicide information that the researchers agreed could become the basis of a computerized scoring system.

In 2012, Pestian was the lead author on a paper describing the potential of the machine learning approach, published in *Biomedical Informatics Insights* as "Sentiment Analysis of Suicide Notes: A Shared Task." That paper described the work of 106 scientists from 24 teams from North America, Europe and Asia who volunteered to explore the best ways to digitally capture the emotions conveyed through suicide notes.

They concluded that "human-like performance on this task is within the reach of currently available technologies."

Pestian then set out to redefine "currently available." His lab developed algorithms—complex sequences of instructions

for a computer—to identify individuals at risk of suicide, depression, and bipolar and anxiety disorders.

The wording of suicide notes was just the beginning. Since 2012, the research team has added data from visual cues ex-

of suicide that human ears may not always hear.

"When some people talk about suicide, they might express sadness, or being upset. They might say, 'My girlfriend left me, so I'm going to stand in front of a train.'

THE PROBLEM

in 2016 nearly 45,000
Americans took their own lives

hibited during counseling sessions that also capture differences in how people at high risk of self-harm smile and speak. From this combined pool of data, the team developed a highly advanced "app" that uses natural language processing to determine, in real time, how closely a person's communication reflects a language

But these are predominantly impulsive factors that may not reflect underlying chronic issues that also can lead to suicide," Pestian explains.

"When we talk about machine learning, we're talking about measurable features of the language used, the characteristics in the data that can predict outcomes.

We learned, for example, that one of the most important factors to the machine was the ratio of nouns to pronouns. Also, through video and acoustic recordings, we found differences in cadence in the suicidal person.”

While a person might be able to mask their emotional state from a human counselor for a few minutes, it is harder to hide from the machine across the entirety of an interview session. Patients seriously considering suicide not only tend to use specific words and phrases, they tend to talk slower. When they smile, they don’t show as much of their teeth.

“We can measure that with machines,” Pestian says.

The latest version of the product is called Spreading Activation Mobile (SAM). With consent from therapists and patients, SAM records sessions and interprets words and inflections in real-time. These “thought markers” include voice cadence, language, hand motion, body language and facial expression.

Pestian’s algorithms received its first patent in 2015. Then the results of a pilot study were published in 2015 and 2016 in *Suicide and Life-Threatening Behavior*.

More than 370 patients, including some known to be suicidal, others who were diagnosed as mentally ill but not suicidal, and some who were neither, completed standardized behavioral rating scales and participated in semi-structured interviews. After extracting and analyzing verbal and non-verbal language, the machine learning algorithms discerned the differences between the groups with up to 93 percent accuracy.

Nearly two years later, Pestian asks a simple question: With mounting evidence that the algorithm works, why is it taking so long to convert this breakthrough into a product that can start saving lives?

RE-DOUBLING THE EFFORT

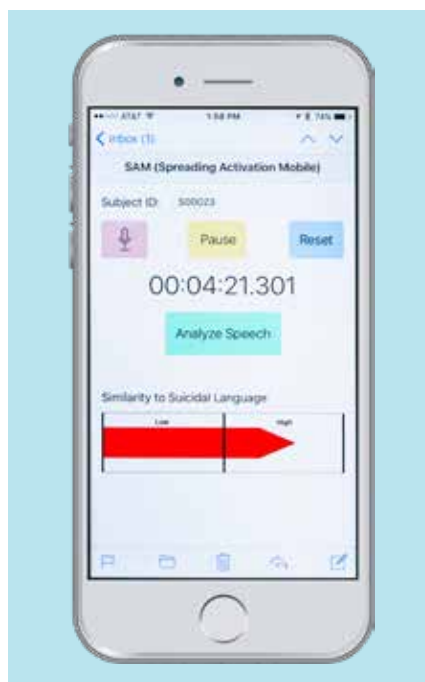
Scientists like Pestian have three choices for disseminating their discoveries: release to the public domain, publish in academic journals, or use the market to disseminate their findings.

Pestian is no stranger to using the market. He, along with three co-inventors, developed a genetic testing tool, now called GeneSight, that has helped caregivers determine ideal medication doses for more

than 750,000 patients with psychiatric conditions. Assurex Health, the company formed to market the tests, was acquired in 2016 by Myriad Genetics.

Pestian and colleagues see similar potential in the suicide risk identification app. The machine learning approach that led to the first app may also serve as a platform for apps addressing other conditions. So, the team opted to pursue a commercial approach.

Early collaboration included work with CincyTech, a regional business incubator, and commercialization staff at



Cincinnati Children’s. Now Pestian is working with the re-organized and renamed Innovation Ventures group at Cincinnati Children’s to continue advancing the product.

The science behind the innovation has been described in 10 peer-reviewed publications. The work also has attracted news coverage from *The Wall Street Journal*, the *Washington Post*, NPR, *USA Today*, and others.

So far, Pestian and colleagues have secured two patents, and have formed a spinoff company. The product also has received two Innovation Fund grants from Cincinnati Children’s.

Innovation Ventures and CincyTech have selected Pestian’s machine language algorithm as one of a handful of discoveries slated to receive accelerated development

support. That means devoting more expertise and resources to developing business plans, supporting the start-up company, pursuing investors and more.

The market is much less forgiving than the grant review process, so even brilliant ideas with powerful life-transforming potential have no guarantee of commercial success.

Andrew Wooten, MST, MTM, Vice President of Innovation Ventures, says the research world and the commercial world spin on different axes. Lining up those worlds is part art, part science, and takes time.

“This is like trying to build a car while driving it,” Wooten says. “The old approach was to just put a discovery out there and find someone to do the product development. That can be a good model if you get people to take it. But this project is an early-stage innovation. Many investors will say ‘I’m not taking the risk.’”

Unlike the difficult but well-understood pathway for developing a new medication, digital healthcare products remain a tough sell. Especially when the subject matter carries the societal taboos of suicide and the technology involved is emerging.

“With software and algorithms, you can patent some of the software involved, but there are other protections too, like a copyright, or the kind of patents that protect a business process,” says Matthew Wortman, a portfolio manager who oversees the digital health and care delivery asset class for Innovation Ventures. “Then it becomes a question of, who is going to buy it? And who is going to pay? The insurance company? The hospital? Parents?”

MILES TO GO

It remains too early to predict how, or even if, SAM will emerge as a fully commercialized product. One hopeful sign: The start-up company’s CEO is Don Wright, who helped launch the Assurex start-up. Wright has a particular passion for this project because his own son, 29, died from suicide last year.

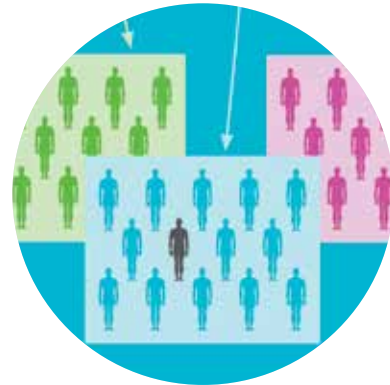
Regardless of commercial success, supporting the effort is core to Cincinnati Children’s non-profit mission, Wooten says.

“Our loyalty is to children,” Wooten says. “Getting things to market that help children.” ■

A GROWING PIPELINE OF DIGITAL ASSETS

AERSMine

This two-year-old, web-based data tool has connected more than 9.2 million de-identified patient reports to a massive database of FDA-approved drugs. The system helps track and identify unexpected clinical harm, benefits and alternative treatment choices. Developed by scientists in the Division of Biomedical Informatics and the Center for Clinical and Translational Science Training, the database helps reduce negative side effects from prescription drugs by enabling analysis of millions of clinical records containing details on drug exposures, disease indications, and clinical outcomes. It has yet to be commercialized, but “That’s one of the things, when researchers write for their scientific needs, we have access to databases that a commercial business might not have,” says Matthew Wortman, Innovation Ventures’ portfolio manager for digital health and care delivery.



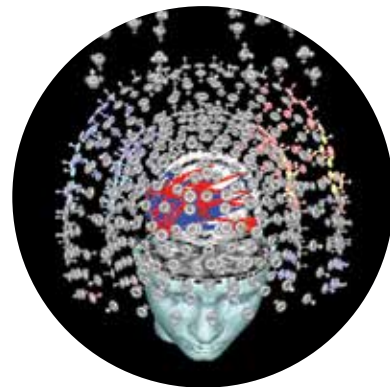
Virtual Reality Simulated Heart Surgery

The brainchild of David Morales, MD, Director of Congenital Heart Surgery, and Ryan Moore, MD, a pediatric cardiologist, both of the Heart Institute, VR surgery helps surgeons map out operation strategies in what amounts to a computerized trial-run. Traditionally, many of those decisions were made after the patient was opened. “The goal is to routinely do these simulations based on scans,” Wortman says. The key is to direct the blood flow to the right place, in real-time. The team is using grants from the National Conference on Artificial Intelligence and other sources to continue development.



Magnetoencephalography (MEG)

Magnetoencephalography (MEG) involves the recording and assessment of brain activity from recordings of magnetic field fluctuations that occur just outside the skull. The core program is run by Jing Xiang, MD, PhD, Director of MEG Research in the Division of Neurology. It is a big advancement from EEG, which confirms a seizure but doesn’t show the precise location. By mapping the signals from the brain, the magnetic field fluctuations directly reflect changes in neuronal activity. To facilitate the capture of tiny field changes, Xiang’s team uses a dense array of extremely sensitive superconducting quantum interference devices (SQUIDS). Today, the device looks a bit like a spacecraft. One day, it might be the size of a helmet. Xiang wants to find a partner to build the head part, but once he gains FDA approval, Wortman says, “then the world is your oyster. There is a huge market.” One challenge: the current cost to build a prototype is around \$100,000.



GRANTS

From Oct. 1 through Feb. 28, researchers at Cincinnati Children's were awarded 215 grants valued at \$69.6 million in total costs. Here are the recipients of grants of \$1 million or more.

Mohammad Azam, PhD,

Cancer Pathology, received a five-year, \$1.8 million grant from the National Cancer Institute to study mechanisms of non-oncogene addiction.

Maria Britto, MD, MPH,

Anderson Center, received a two-year, \$2.5 million grant from the Ohio Department of Medicaid, for her work with the project Quality Improvement Capacity Building.

Claire Chougnet, PhD,

Molecular Immunology, will study prenatal inflammatory exposures and neonatal immune development, with a five-year, \$1.7 million grant from the National Institute of Environmental Health Sciences.

Lee Denson, MD,

Gastroenterology, Hepatology and Nutrition, received a three-year, \$2.8 million from the Bill and Melinda Gates Foundation, to study malnutrition and environmental enteropathy, a disease of the intestine.

Maryam Fouladi, MD, MSc,

Medical Director, Brain Tumor Center, received a three-year, \$3.6 million grant from The Cure Starts Now Foundation, for her leadership role with the Collaborative Network of Neuro-Oncology Clinical Trials, or CONNECT, a network of trials conducted at international sites dedicated to pediatric brain cancer research.

Michael Helmrath, MD, MS,

General and Thoracic Surgery, will study the investigation of regional identity in human intestinal stem cells, using a five-year, \$1.9 million grant from the National Institute of Diabetes and Digestive and Kidney Diseases.

Gurjit Khurana Hershey, MD, PhD,

Director, Asthma Research, received a five-year \$3.8 million grant from the National Institute of Allergy and Infectious Diseases, to study role and regulation of TSLP in childhood allergic disease.

Alan Jobe, MD, PhD,

Neonatology and Pulmonary Biology, received a three-year \$985,000 grant from the Bill and Melinda Gates Foundation to study antenatal steroid treatment strategies for low resource nations.

Jennifer Kaplan, MD, MS,

Critical Care Medicine, will study the role of STAT3 in sepsis-induced adipose tissue browning and the impact on obesity, using a five-year, \$1.9 million grant from the National Institute of General Medicine Sciences.

Carole Lannon, MD, MPH,

Anderson Center, received a two-year, \$2 million grant from the Center for Medicare/Medicaid Services, for her role in a project by The Ohio Perinatal Quality Collaborative evaluating progesterone supplementation during pregnancy.

Peter Margolis, MD, PhD,

Anderson Center, received a one-year contract renewal valued at \$1.6 million from ImproveCareNow, Inc.

Anjaparavanda Naren, PhD,

Pulmonary Medicine, received a five-year, \$1.7 million grant from the National Institute of Diabetes and Digestive and Kidney Diseases, to examine the role of using human enteroids, colonoids, and induced pluripotent stem cell-derived human intestinal organoids in study disorders related to cystic fibrosis.

Qishen Pang, PhD,

Experimental Hematology and Cancer Biology, received a four-year, \$1.6 million grant from the National Heart, Lung, and Blood Institute, to study the role of Fanconi anemia (FA) proteins in regulating cellular response to oxidative stress in the context of hematopoiesis.

Michael Seid, PhD,

Pulmonary Medicine, received a two-year, \$3.9 million grant from Cystic Fibrosis Foundation Therapeutics Inc., for his work with the program "A CF C3N Care Model of the Future: Proposal for Piloting a Learning Health System."

Lisa Privette Vinnedge, PhD,

Oncology, received a five-year, \$1.8 million grant from the National Cancer Institute to study mechanisms coupling DEK to oncogenesis.

HONORS

Kotagal Receives Procter Medallion

Uma Kotagal, MBBS, MSc, whose career in quality improvement science has influenced medical care across the U.S. and in many other nations, has become the first woman to receive the William Cooper Procter Medallion—the highest honor bestowed by Cincinnati Children’s.

Kotagal, currently Senior Executive Leader of Population and Community Health, has been with Cincinnati Children’s since 1975. She began as a postdoc in neonatal physiology. Over the years, she rose to Director of Health Policy and Clinical Effectiveness, and in 2010 became the first Executive Director of the James M. Anderson Center for Health Systems Excellence.

Kotagal has earned several prestigious awards during her career, including being elected to the Institute of Medicine—one of the highest honors in healthcare. She received the Daniel Drake Award from the University of Cincinnati College of Medicine, has been recognized as one of Ohio’s Most Powerful and Influential Women, and was named a YWCA Career Woman of Achievement.



Uma Kotagal, MBBS, MSc

Congratulations to our faculty members recently elected to the Society for Pediatric Research:

Hitesh Deshmukh, MD, PhD, **Neonatology**; Tanya Mullins, MD, MS, **Adolescent Medicine**; Jennifer O’Toole, MD, MEd, **Hospital Medicine**; Daniel Schumacher, MD, MEd, **General and Community Pediatrics**; and Eric Kirkendall, MD, **Hospital Medicine**.

Congratulations to our faculty members recently elected to the American Pediatric Society:

Hermine Brunner, MD, MSc, **Rheumatology** and Stephen Porter, MD, MPH, **Emergency Medicine**.

Faculty Awards Honor Research Achievement

In February, leaders at Cincinnati Children’s honored outstanding faculty achievements in the categories of advocacy, clinical care, education, mentorship, research and service during the 6th Annual Faculty Awards. Research Achievement Award honorees were:

- Tesfaye Mersha, PhD, **Asthma Research**
- Sing Sing Way, MD, PhD, **Infectious Diseases**
- Center for Pulmonary Imaging Research: Jason Woods, PhD, **Pulmonary Medicine and Radiology**; Zackary Cleveland, PhD, **Pulmonary Medicine and Radiology**; Robert Fleck, MD, **Radiology**; Jean Tkach, PhD, **Radiology**.

Donald Gilbert, MD, **Neurology**, was selected as a 2017 Doctor of the Year by the Aubrey Rose Foundation, which supports families with life-threatening illnesses.

Erin Hickey, MD, **a second-year resident**, has received the Academic Pediatric Association’s Resident Investigator Award for her project “Food as medicine: Evaluating the impact of a pediatric primary care clinic-based food pantry on food insecure families.” Her project began at the Hopple Street Clinic, then spread to the Pediatric Primary Care Center.

Tesfaye Mersha, PhD, **Asthma Research**, received a 2017 Business and Professional Achievement Award from the African Professionals Network.

Marc Schecter, MD, **Medical Director, Pediatric Lung Transplant Program**, was selected the inaugural leader of the Lung Transplantation Taskforce for the Pediatric Council of the International Society of Heart and Lung Transplantation.

Andrew Spooner, MD, MS, **Hospital Medicine**, was named one of the Top 50 chief medical informatics officers to know in 2017 by Becker’s Hospital Reports.

Paul Steele, MD, **Medical Director, Pathology and Laboratory Medicine**, was named one of the 20 most influential people in the 20-year history of the University of Cincinnati’s College of Allied Health Sciences. Steele has directed the clinical labs at Cincinnati Children’s since 1999.

Cincinnati Children's Start-Ups

Cincinnati Children's is one of the world's leading pediatric research centers. Here, investigators use more than \$200 million a year in grant funding to produce more than 2,000 peer-reviewed publications that advance biomedical science. From that flow of knowledge, Cincinnati Children's generates more than 150 innovation disclosures a year and has spun off more than a dozen start-up companies, including those shown here. Its commercial license payments and related income generate approximately \$6.5 million in revenue, all of which goes back into its non-profit mission of improving child health.

Spreading Activation
Technologies



Persepsys



NEOVUE



Ausio Pharmaceuticals, LLC



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Editorial Advisors:

Margaret Hostetter, MD
Louis Muglia, MD, PhD
Kristine Justus, PhD

Editorial Staff:

Tim Bonfield/Managing Editor
Tom O'Neill, Nick Miller

Contributor:

Mary Silva

Design and Illustration: The Fairview Agency

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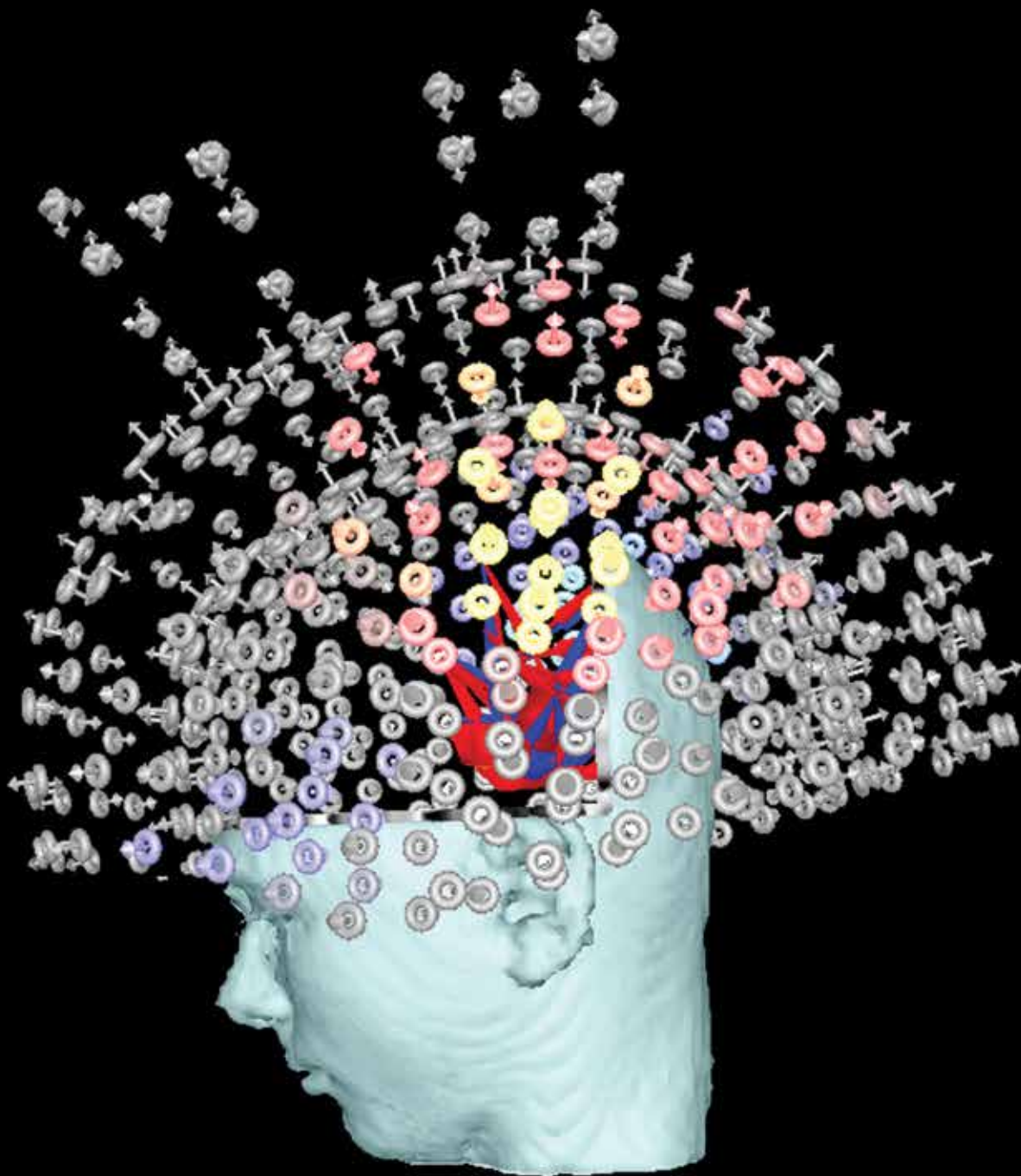
Department of Marketing and Communications
Cincinnati Children's
3333 Burnet Avenue, MLC 9012
Cincinnati, OH 45229-3026
513-636-4420

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Magnetoencephalography (MEG) involves the recording and assessment of brain activity from recordings of magnetic field fluctuations that occur just outside the skull. The core program is run by Jing Xiang, MD, PhD, Director of MEG Research in the Division of Neurology. More digital innovations on page 26.



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New Devices Make a Difference
Small Molecules in the Pipeline
Practical Uses for Organoids

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