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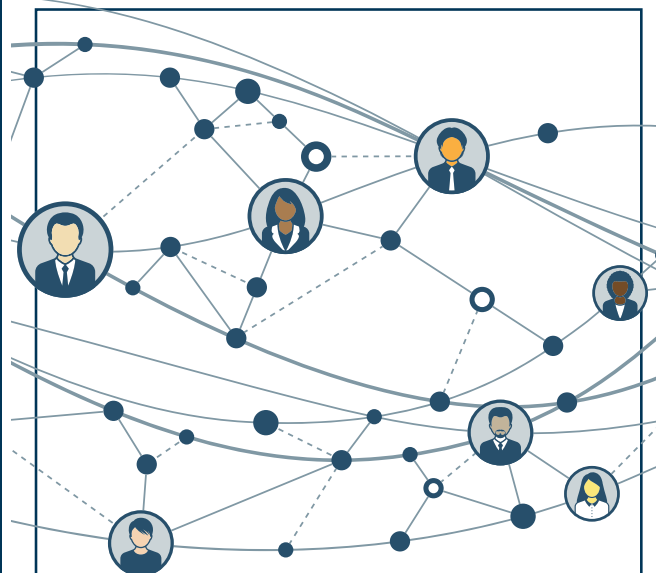
Cleveland
Emerges as
Biotech Hub

Origins of
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About Medicus

Medicus is the biannual magazine of Case Western Reserve University School of Medicine. This magazine and the stories within are selected to honor and showcase the school's threefold mission: excellence in medical education, advancing discoveries from laboratories to patients, and improving the health of the community.

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contents



02

Dean's dialogue

Wagering on Cleveland's bid to become a biotech hub



06

Searching for solutions

A roundup of recent research with a business bent

10

Origins of a budding biotech

Research duo develops stem cell insights to launch a new company

20

From bench to boardroom

Alumni entrepreneurs taking a business approach to curing disease

30

Inside initiatives

School-based programs assist student entrepreneurs

32

Education in action

Innovation and entrepreneurship come together in new curricular program

34

Honors and accolades

Recognizing our faculty

36

Left brain | Right brain

Visualizing research







Dean's dialogue



Developing Cleveland as a biotech hub

Cleveland is at the crossroads and the path it chooses could spell a future that places it on the map as a biotech hub. The city has the innovative minds, the academic research infrastructure, and the know-how to create a launching pad for biotech that would not only benefit patients worldwide, but also provide Cleveland with a much-needed economic boost.

What are some of the challenges facing Cleveland as it works to reimagine itself as a contender in this fast-paced and highly competitive arena? We asked three experts to join in a panel discussion to help pinpoint what Cleveland and the medical school at Case Western Reserve University are doing and what they need to do if they want to get off the starting blocks and have a fast start as a player in the biotech arena.

Joining in the conversation are  Mark Chance, PhD, professor and vice dean for research at the School of Medicine,  Charu Ramanathan, PhD, Co-Founder and CEO at vitalxchange and a biomedical engineering graduate of CWRU ('04), and  Ronn Richard, President and Chief Executive Officer of the Cleveland Foundation. The session was moderated by health care reporter for Crain's Cleveland Business,  Lydia Coutré.

Lydia Coutré: *There was a time when pharmaceutical companies were the only game in town for drug discovery and development. But times have obviously changed. Academic medical centers and research universities are now relied upon to perform a large portion of that work. What accounts for this shift?*

Mark Chance: Pharmaceutical companies have certainly altered their business model over recent years backing away from the discovery and early clinical testing of new drugs to focusing on late stage clinical testing, manufacturing drugs, and marketing to patients. It's too risky for them and they don't see the same return on their investments as they see in other parts of their business. So we in academia see an opportunity, which aligns nicely with our mission, to move cures more quickly from the bench to the bedside. And starting new companies and partnering with small biotech companies is one important part of making that happen.

Ronn Richard: Cleveland's biotech future is at an interesting pivot point. People have said to me that the city could be a capital of drug discovery if it had hundreds of millions of dollars to put into clinical trials. Well, that's the old paradigm. The new paradigm for Cleveland is that we need to grow biotech companies that have great technology and lower the risk of doing so. This opens the door for R&D based at a university or an anchor institution to conduct the necessary preliminary work that enables the technology to move more quickly into the marketplace and be more attractive to investors.

Thinking more broadly, Cleveland doesn't have a unified economic development strategy and it needs one if we're going to be a serious player in the biotech drug discovery arena. Foundations and individual donors need to get behind university-based research not only because drug discovery leads to ameliorating or curing disease, but because our city's future economic and population growth will come with successful biotech startups. Biotech is one area where this city can seriously compete and help it grow.

MC: Our role in academia is to bring along the technologies to a point where a small biotech company can take over the development and attract outside investment. In this process we can answer key questions about the safety and efficacy of the asset so pharma wants to take it and conduct the next phases of development. That's the sort of "build to be bought" strategy we can execute here in Cleveland. We have the novel ideas — the seed corn — being developed in our labs and small biotech firms in the region. And we have a process in which the technology can be developed, converted to companies, optimized, sold, and then the process can be repeated.

LC: *From your experience, Dr. Ramanathan, having built a company in this city and selling it to a large medical device company, what did Cleveland do right and what could it have done better?*

CR: Times have changed since I started the company fifteen years ago. I was pleasantly surprised to learn that in the last three to five years, information of a practical nature about entrepreneurship has been translated into Case Western Reserve's medical school curriculum. But it takes more than a classroom course to really understand the steps towards commercializing an idea. Part of the solution is to use local resources to find entrepreneurs already on the journey. Every day startups are faced with every possible challenge. "We don't have any money." "We don't know what problem to solve first." "What's the technical risk, business risk, market risk?" "Tell me what I should do first and how I should do it." Without meaningful interaction with working entrepreneurs, the information is theoretical.

The second problem is talent. Good people need to be attracted to Cleveland and incentivized to stay. It's not just the technology that's going to drive a company forward, it's the team. The management talent in Cleveland needs to improve. Cleveland cannot compete with the other cities unless young people are willing to step up and be leaders. So we have a people problem as well. And people problems don't solve themselves unless there's a culture change. Cleveland has to embody a culture of innovation, youth and opportunity.

LC: *And how can Cleveland bring about the kind of culture change you are talking about?*

CR: It's not a lever that you can pull today and see an immediate effect tomorrow. But I would suggest investing in opportunities that can be scaled up quickly to give us a presence. Starting with health IT and software applications seems to be a reasonable place to begin. Basically you set the stage for higher risk in the long run and for bigger reward opportunities. It's a process that creates a culture of people wanting to come here, get set up, and be successful. This process will transform Cleveland's reputation as a place where entrepreneurs can get their start. I think we can do it because the innovation in Cleveland is amazing.

MC: One approach we're taking here at Case Western Reserve to create a culture of innovation and risk-taking is implementing a disciplined process to select those ideas with the best chance for success and surround them

DEAN'S DIALOGUE

with the necessary support to move them towards the market. To advance therapeutics in particular we created the Council for the Advancement of Human Health and reached out to our alumni with biotech expertise to participate in advisory panels. They have shown us where to place our financial bets. Since 2012 we have invested about \$1 million in 13 opportunities in therapeutics that have already resulted in the formation of five companies who have raised over \$30 million in professional investment. We're picking up momentum.

At the same time, we believe this process is encouraging a mindset that it's acceptable to try something new and innovative and if it fails, well, something else is just around the corner. I don't think people are quite trusting of that yet. It's failure that creates innovation, not success. It's human nature to want to survive and be successful. We don't need to teach that. But it should be okay to take a risk and possibly fail, otherwise innovation would come to a standstill.

LC: *Turning toward what Cleveland can do to spur its biotech growth, what are some gaps when it comes to funding in both basic and translational research?*

RR: In order to keep really brilliant, risk-taking researchers here in Cleveland we need to help Case Western Reserve and other anchor institutions be even more competitive. These institutions need the funds so they can support their researchers to develop a really hot idea that may or may not succeed on the first try. And so again, the community really needs to get behind this endeavor. The state also needs to do more in this regard, as well as increased funding at the federal level. It will require a full-court press.

MC: One strategy to help put Cleveland on the map right away and attract funding from these three sources is to focus on a few unmet needs where we can have a big breakthrough. Maybe it's multiple sclerosis. Maybe it's neurodegenerative diseases. Maybe it's addiction. But I think a huge advantage we have in Cleveland is cell therapy. There is an enormous amount of this kind of research going on among Case Western Reserve's affiliated hospitals. It's a huge selling point for us both in education and research. So the medical school and the University can provide a neutral space like Switzerland that can interact with all the hospitals cooperatively. When we work together, we're world class every time.

LC: *From your experience, Dr. Ramanathan, what do you know now that you wish you would have known as an early career entrepreneur?*

CR: I wish I had been more aggressive in building a mentor network. Everybody knows that you have to network, but what does that really mean? It means asking yourself "who do I look up to?" "How do I get from where I'm standing now and to where they are?" Everything is in-bounds from leadership and authenticity to managing your emotions.

I also wish I had done more to retain great people. I would have given people who are really talented and want to work for startups a piece of the company. Let's get them here and build a really good culture. Let's say, if you're the best in the business, come work for me. That was not something that I had the audacity to do or say when I started. So we went through so much talent, we kept hiring and firing. It was exhausting. I wouldn't do that now.

LC: *What's your vision for Cleveland's biotech future in five years?*

MC: They say reputation is a lagging indicator. And I think if we could jump five years ahead right now and look back, we'd realize a lot more is happening than we think. If that young person or that not-so-young person would come and take a risk on us, they would find we are very open. It is very easy to do things in Cleveland relative to other cities. You can succeed to a level here that is much more difficult elsewhere. In five years, we're going to say, wow, we've come a long way, let's keep going.

RR: I'm an ultimate optimist. I can tell you in the last five years or so, you really feel that the environment in Cleveland is beginning to support biotech. The Cleveland Foundation has been at the forefront of this effort and we have other great foundations in town that we'd like to see come in. I'd like to see corporate foundations get involved, too. **M**



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With a reputation built on the success of our researchers, the Council to Advance Human Health (CAHH) at Case Western Reserve University is leading an acceleration of bench-to-bedside translation.

With help from generous donors, 15 projects have received funding through CAHH's Accelerator Fund, resulting in 5 spin-out companies to date. These projects have expanded our network of support, totaling over \$75M in new investments for our translational research.

To learn more about the opportunities to support and collaborate with the Council to Advance Human Health, contact Stacy J. Langenderfer, Senior Director of Development, Basic and Translational Sciences, at 216.368.5851 or Stacy.Langenderfer@case.edu.

Searching for solutions

BIOMEDICAL ENGINEERING: A diagnostic test for sickle cell the size of a credit card



Umut Gurkan, PhD

Sickle cell anemia is a rare diagnosis among newborns in the United States, but that's not the case worldwide. In fact, the inherited condition is responsible for millions of childhood deaths globally.

In Africa and many low-to-moderate income countries, between 50 to 80 percent of

babies born with sickle cell anemia die before age 5. However, according to World Health Organization estimates, early diagnosis could prevent 70 percent of those fatalities.

This is where Umut Gurkan, PhD, Warren E. Rupp associate professor of mechanical and aerospace engineering at Case Western Reserve, stepped in. In 2014, Gurkan, who has a secondary biomedical engineering and orthopedics appointment, and his medical school colleagues Connie Piccone, MD, and Jane Little, MD, launched a journey to design a low-cost, portable diagnostic test that accurately identifies the abnormal hemoglobin protein responsible for sickle cell anemia, as well as many other conditions.

"Our main motivation behind this technology was to develop a simple test that would perform an essential blood screening in children — in really young babies — who would otherwise die if they aren't diagnosed with a certain hemoglobin disorder,"

Gurkan says. "We wanted to bring the power of the lab to the people who need this testing. It is essential."

Currently, blood screenings in these countries are cost-prohibitive, averaging \$10 per person per test, he says. A dearth of sophisticated laboratories and trained pathologists also means test processing takes from days to weeks. Consequently, many individuals are lost to follow-up and never receive lifesaving treatment.

Today, Gurkan's test, called HemeChip, solves these problems. The single-use, cartridge-based device, developed by Hemex Health, Inc., from technology licensed from Case Western Reserve, is roughly the size of a credit card and costs less than \$2 per test. With fewer than 30 minutes of training, anyone can perform the test, he says. Results are available in under 10 minutes, can be sent to patients via cell phone, and can be transmitted to electronic medical records using wireless and Bluetooth technology.

To diagnose sickle cell anemia, the test mixes a single drop of blood from a heel or finger prick with de-ionized water and a blue control marker. Existing microchip electrophoresis technology separates hemoglobin variants on cellulose acetate paper based up on their charge. According to field test results with more than 780 individuals in Nigeria, India, Thailand, and the United States, HemeChip correctly identifies those with sickle cell diseases, including patients who only carry the trait, with 100 percent accuracy.

"HemeChip is being called a one-stop shop for diagnosing and treating sickle cell patients," he says. "We would like to make the technology available to everyone for diagnosis and management."

Ultimately, he says, the hope is nations struggling with sickle cell will see screening as a critical part of effective public health programs and establish implementation initiatives.

"The main focus is always on saving the lives of those early sufferers from sickle cell anemia and other diseases," Gurkan says. "In the Western World, these patients can live normally and have a longer life, but right now they're lagging 40 to 50 years behind in having the technology to diagnose and manage these conditions." **M**

Field tests in Nigeria and other countries confirm the HemeChip's 100 percent diagnostic accuracy.



GENE EDITING: Eradicating the T cell reservoirs where HIV hides



Rafick-Pierre Sékaly, PhD

The antiretroviral drugs used to control HIV infection represent one of the major medical advances of the last 25 years. They helped transform what was initially a devastating, untreatable death sentence into a condition that can be managed for most patients. Doing so, however, requires lifelong drug therapy. When antiretroviral therapy is stopped, the HIV infection comes roaring back, released from latent HIV “reservoirs” inside infected immune cells (T cells) where virus particles hide out until immune defenses are weakened. The virus particles then replicate and infect other T cells, causing HIV symptoms to reappear as soon as treatment is stopped.

Researchers have determined that a gene called CCR5 helps HIV particles enter and infect T cells. The finding prompted some intriguing questions: What if a patient’s T cells could be collected, “edited” so that they no longer contained the CCR5 gene, and then were infused back into the patient? Would this help to shrink the numbers of infected T cells and eradicate latent HIV reservoirs? Would this result in something resembling a long-term cure?

These are the questions that Rafick-Pierre Sékaly, PhD, the Richard J. Fasenmyer Professor of Immunopathogenesis at the School of Medicine and one of the world’s leading scientists in AIDS research, human immunology and immunotherapy, has set out to answer in a research collaboration with Sangamo Therapeutics, a biotechnology company based in Richmond, CA, specializing in genomic therapies.

Sangamo’s single-arm studies with CCR5-edited CD4 cells (the type of T cell that HIV targets and destroys) have shown that the process of cell collection, gene editing and onetime re-infusion resulted in a sustained increase in CD4 counts and a significant reduction in the HIV reservoir in vivo (in the body). Meanwhile, Sékaly’s research has demonstrated that a class of anti-inflammatory drugs already FDA approved for rheumatoid arthritis (tofacitinib and ruxolitinib, known as Jak inhibitors) could block the signaling molecules inside infected immune cells that help the cells proliferate. Laboratory experiments confirmed that Jak inhibitors prevent the spread of HIV to nearby, healthy cells.

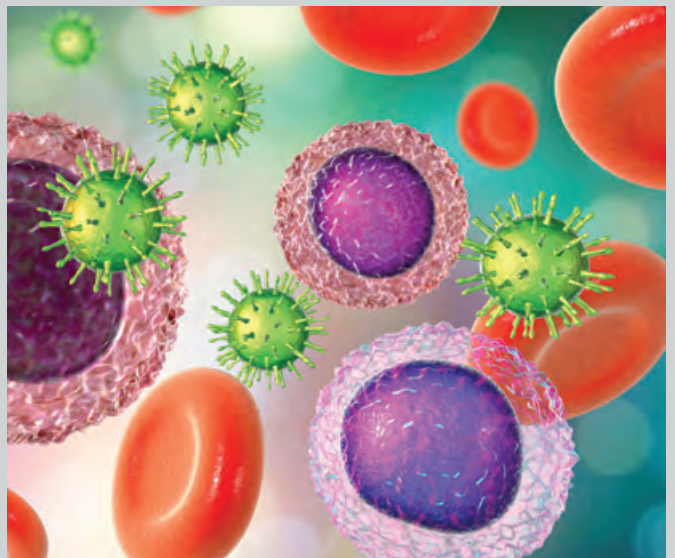
“The existence of the HIV reservoir is one of the biggest impediments to a cure,” says Sékaly. “Sangamo and several collaborators have demonstrated in single arm, non-randomized studies that it is possible to minimize the reservoir using different approaches but through essentially the same

mechanisms, which makes our collaboration with Sangamo a natural one. Our challenge now is to show benefit in a rigorous randomized (two-arm) clinical trial.”

To that end, Sékaly and Sangamo are sharing scientific and technological expertise to compare the outcomes of HIV patients who receive genetically modified T cell infusions to those who receive unmodified T cell infusions. This first-of-its kind clinical trial is being funded by an \$11 million grant from the National Institutes of Health.

For the study, T cells will be collected from the blood of 20 HIV patients. The CCR5 gene will be “knocked out” of these cells using zinc finger nuclease gene editing, Sangamo’s advanced technology platform for developing genomic medicines. Zinc finger nucleases are engineered proteins that can be thought of as genetic “scissors,” designed to enable targeted editing of genes by creating double-strand breaks in DNA at precise locations identified by researchers. The genetically modified T cells will be grown in the laboratory and then re-infused back into the patients they were obtained from. A second set of 10 patients will receive an infusion of unmodified T cells. The clinical study is led by Benigno Rodriguez, MD, and Michael Lederman, MD, from Case Western Reserve and University Hospitals Cleveland Medical Center, and will also include sites in Cincinnati and at the University of California/San Francisco.

“Using a patient’s own T cells as treatment is a perfect example of what personalized medicine can be and, if successful, could provide patients with long-term benefits from a single treatment,” says Sékaly. “Research collaborations like this one are necessary to test our ideas, expand our understanding, and bring creative thinking and innovative technologies to bear on our most difficult challenges.” **M**



BIOMEDICAL ENGINEERING: Boosting the blood's ability to clot



Anirban Sen Gupta, PhD

Each year in the U.S. alone, over 2 million platelet transfusions are given to treat bleeding complications caused by traumatic injury, surgery, and a variety of blood-related ailments. But natural platelet transfusion products have a number of limitations including limited donor availability, need for blood typing and matching, and a three to five day shelf life. Anirban Sen Gupta, PhD, believes he has found a solution by working at the nano-level to develop a synthetic substitute that can mimic the ability of blood platelets to form clots at the site of serious bleeding injuries.

"Platelets are like sandbags that pile up to prevent a flood," says Sen Gupta. "In both cases, you need a critical mass and the right location in order to get the job done. But in severely injured patients, and those diagnosed with certain blood disorders, including cancer, that's not always possible.

The answer may lie in a blood product he and his team are developing whose design principle is inspired by clot-forming mechanisms of real platelets. Sen Gupta, a professor in the Department of Biomedical Engineering – a joint department between the Case School of Engineering and the School of Medicine – and his research team have created SynthoPlate, a patented, intravenously-injected platelet surrogate that can prevent or stop excessive bleeding.

Recently, Case Western Reserve and Haima Therapeutics LLC, a Cleveland-based biotechnology company with offices in the HealthTech Corridor, signed a two-year option to license SynthoPlate. ("Haima" is of Greek origin, meaning blood.)

The company was founded in 2016 by Sen Gupta and Christa Pawlowski, who has a PhD in biomedical engineering from Case Western Reserve. "We are hopeful that SynthoPlate will become a lifesaver in pre-hospital trauma situations," says Pawlowski, who was an undergraduate student, graduate researcher, and postdoctoral scholar in Sen Gupta's laboratory.

SynthoPlate aims to staunch heavy bleeding by binding to the site of an injury to both cooperate with as well as supplement the body's natural clotting mechanisms. Natural platelets have lipid membranes on their surface that present clot-promoting proteins. SynthoPlate features three types of peptides on its surface, enabling these lipid-like nanoparticles to adhere to a bleeding-wound site and aggregate among themselves as well as with adjacent natural platelets to collectively form a clot.

This combined adhesion and aggregation capability renders SynthoPlate unique among current synthetic platelet-surrogate designs.

Natural platelets don't normally cluster in circulation, but at bleeding sites they are catalyzed by injury to the blood vessel wall to activate, adhere, and aggregate. The peptides on SynthoPlate were chosen to purposely adhere to an injury site and only bind with activated platelets. "We want SynthoPlate to interact only with activated platelets at a bleeding-injury site," says Sen Gupta. "We don't want it to clot blood systemically."

Another crucial feature of SynthoPlate is what Sen Gupta calls a "Harry Potter invisibility cloak." Because the nanoparticles are foreign bodies, white blood cells – the body's defenders against invaders – would destroy them in less than 30 minutes. The invisibility cloak, comprising a surface layer of polymers, allows SynthoPlate to remain in the bloodstream for up to three days without prompting a response from white blood cells.

The National Science Foundation, U.S. Department of Defense, and National Institutes of Health have provided early-stage funding for Haima to conduct pre-clinical studies. The licensing agreement with CWRU will support research on lyophilization (freeze drying, which allows reconstituting for injection), shelf-life testing under various environmental conditions, and dosing optimization, all currently being carried out at CWRU and collaborating institutions.

Following successful pre-clinical testing, human trials can begin. If all goes well, it's possible that SynthoPlate will be available for treating humans in three to five years' time.

The potential market for SynthoPlate includes those with a need for a predictable supply of platelet products: small and medium-sized hospitals, first responder units, and the military, where blood products are often unavailable in the field. Even big hospitals and trauma centers, which typically have the greatest stock of donated human platelets, can experience shortages. SynthoPlate's advantages over real platelets include that it has a longer shelf life, there is no need for typing and matching, and contamination risk is minimal due to effective sterilization.

Haima and its SynthoPlate technology are garnering growing attention, including local and industry news coverage. Recently, Ohio Secretary of State Jon Husted featured the company in wits "Ohio's Future" monthly business profile, which cites companies using innovation to drive the economic future of The Buckeye State. **M**

NEUROSCIENCE: Regrowing damaged nerves



Jerry Silver, PhD

While many neuroscience researchers investigate the nervous system to understand how nerves grow, Jerry Silver, PhD, has focused his 40-year research on studying parts of the nervous system where nerves don't regrow. His work has piqued industry interest, led to multiple patents, and now serves as the basis for

NervGen Pharma, a regenerative medicine company that recently began trading on the Canadian stock exchange.

"At the beginning of my career, I was interested in how nerve fibers find their way in the embryo," says Silver, a professor in the department of neurosciences. "They take circuitous routes through the brain and spinal cord to reach their targets, and I wanted to know if there were natural barriers or boundaries that existed."

Silver found that a family of extracellular matrix molecules called proteoglycans form boundary regions, or "guardrails" during development that help turn nerves away from places where they shouldn't grow. At first, the finding was a tough sell. "Nobody believed me because proteoglycans are not supposed to be in the central nervous system. They're supposed to be in connective tissues and cartilage where they belong," he says.

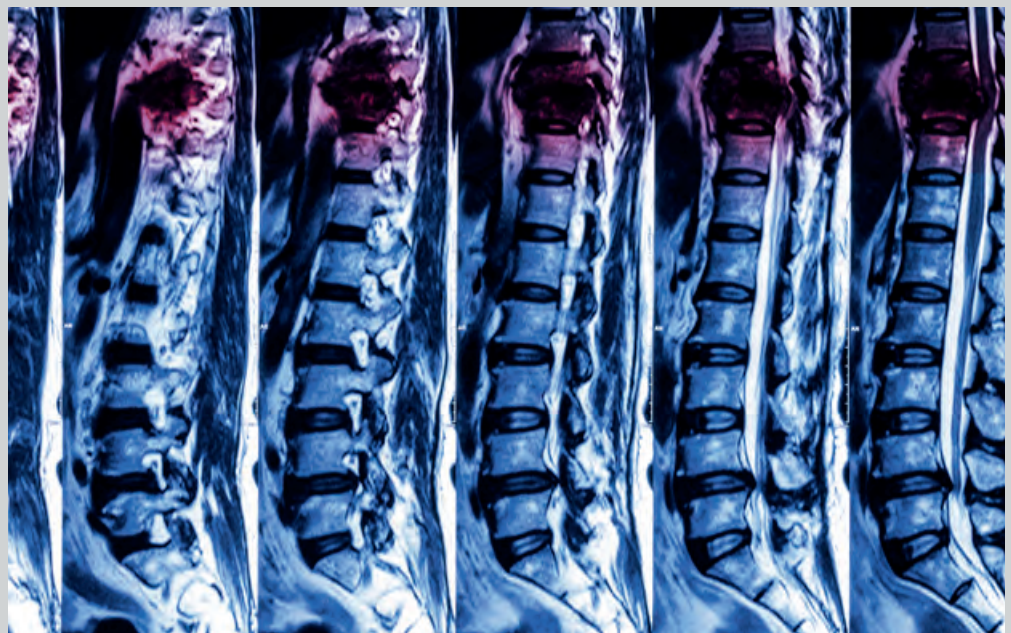
In his first startup biotech venture, instead of focusing on the central nervous system, Silver decided to pursue ways to create therapeutic boundary regions. His first company, Gliatech, Inc., developed a gel containing synthetic proteoglycans. The gel, called ADCON—short for ADhesion CONtrol—prevents nerves from becoming tethered to obstructive and very painful scar tissue adhesions that can form after surgery or traumatic injury. It received FDA approval within three years and has been used in more than 250,000 procedures worldwide.

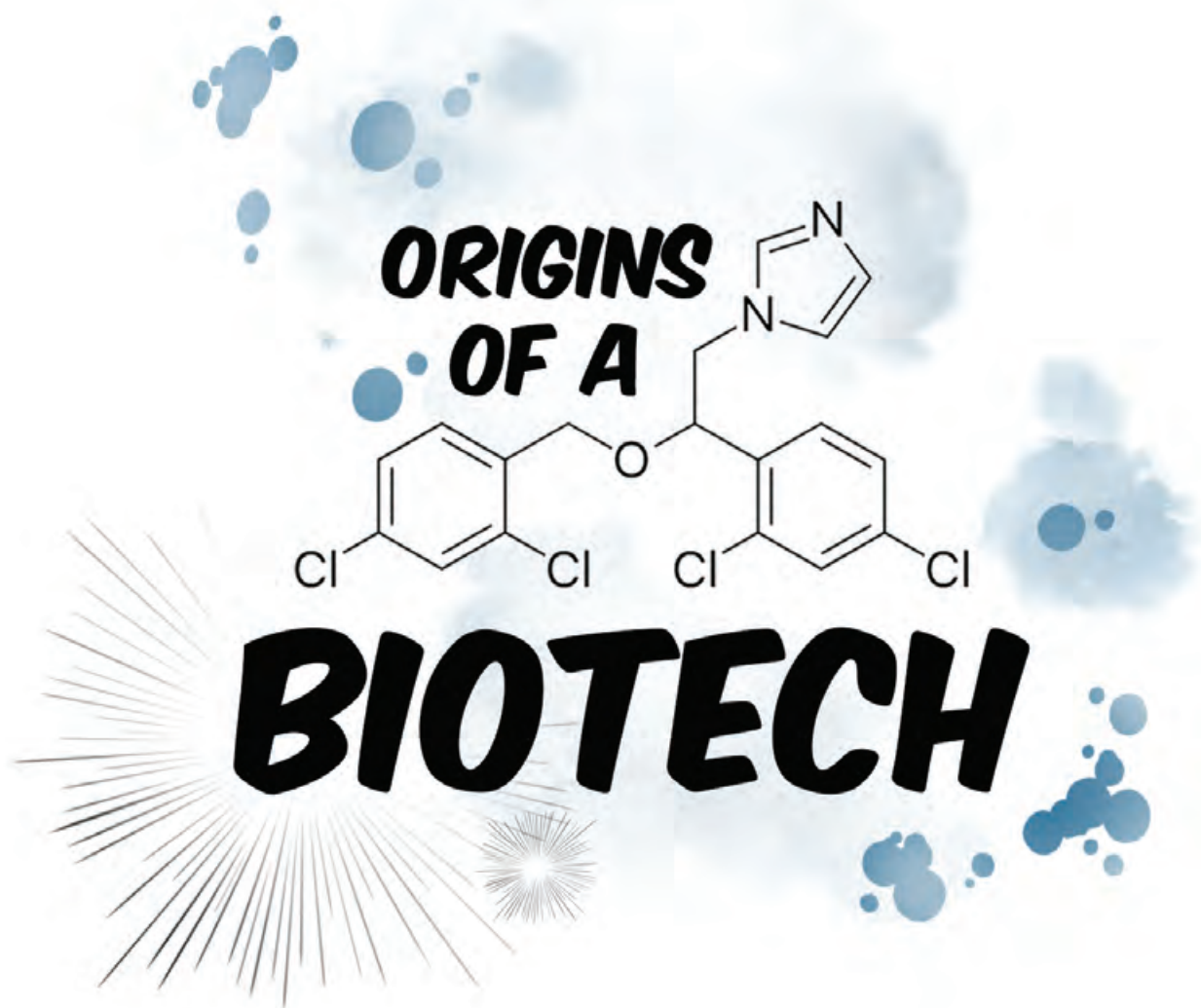
After his early success with ADCON, Silver reframed his research. He began to ask how boundary regions that exist in development can reappear after injury, preventing nerve regeneration and causing paralysis. This question caught the attention of the spinal cord injury community.

With funding from The International Spinal Research Trust, Craig H. Neilsen Foundation, National Institutes of Health, and the Hong Kong Spinal Cord Injury Fund (among others), Silver spent over a decade developing a peptide that blocks proteoglycan receptors on neurons to overcome natural nerve boundaries that form after injury. Most recently, he showed the patented peptide, when delivered systemically, helps regenerate nerves and robustly restores walking and bladder function in rats with spinal cord injury-induced paralysis.

"After our first *Nature* paper, I got a knock on my door," Silver says. The knock belonged to one of the investors from NervGen Pharma and the company wanted to negotiate a deal to bring Silver's peptide to clinical trials. They wanted to see if it could be used to sprout new nerves and overcome scar tissue in humans with nerve damage. Other companies showed interest, too. After several years of negotiations, Case Western Reserve sealed the deal with NervGen.

Part of the peptide's appeal is its versatility. "There are lots of markets where the peptide could play a role. That's a big source of encouragement to the company," says Silver. "They are starting with spinal cord work, but damaging scars occur throughout the body, including after peripheral nerve injury and heart attack." NervGen plans to move the peptide into initial spinal cord injury trials within the next two years. **M**





Every biotech company has its own origin story. And yet, despite all the variables that make each story unique, they all share elements that have helped contribute to their successful launch. There is no better example of how this blend of persistence, ingenuity, teamwork, and luck can work together to help create a biotech than the story of Convelo, a biotech company spun out from laboratories here at Case Western Reserve University School of Medicine.

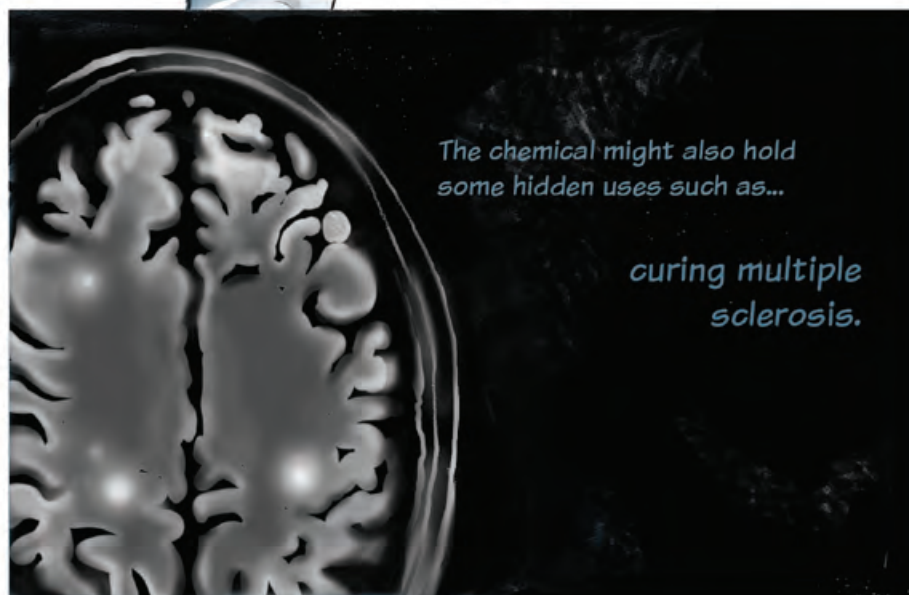
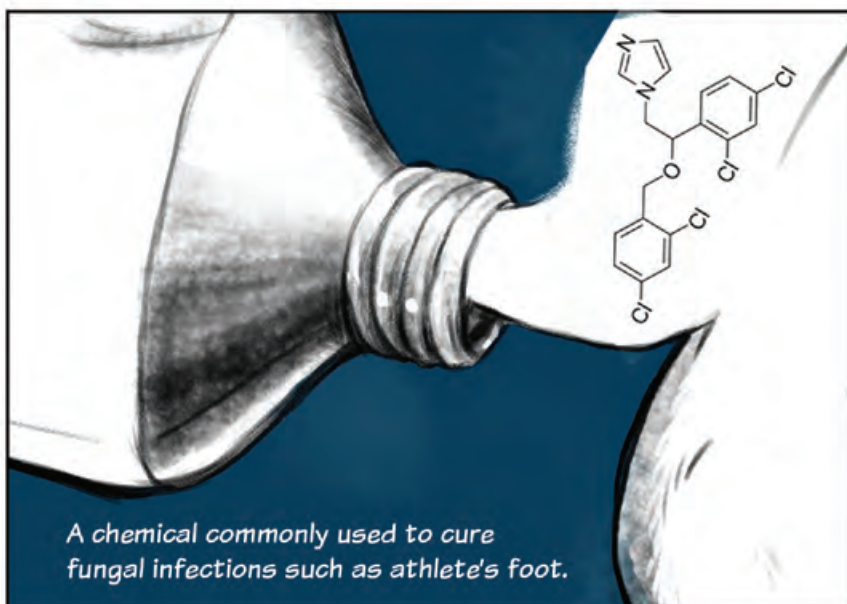
It's a narrative we felt could best be conveyed with both a feature article and a series of sequential illustrations, or a comic.

And so we offer this story of how two researchers led teams of equally dedicated and resourceful scientists through a series of discoveries, combining expertise from within and without academe, to launch a biotech with the mission to cure degenerative diseases of the brain — an adventure that is still unfolding.

But before you begin, you might want to attempt the tongue twister below. It's the name of one of the characters you'll be meeting.



Miconazole



This discovery was made by Paul Tesar, PhD.

You may know it as the key ingredient in medicines such as Desenex and Monistat. It's effective in fighting ailments like athlete's foot and yeast infections. Yet it might wind up having another slightly more significant role to play: curing multiple sclerosis (MS).

Back in the late 1960s when Janssen Pharmaceutica Nv created miconazole, it probably never dreamt that one day the ingredient could play a key role in a potential cure for one of the most disabling neurological conditions of young adults.

That discovery was made by Paul Tesar (CWRU '03), PhD, professor of genetics and genome sciences and The Donald and Ruth Weber Goodman Professor of Innovative Therapeutics. In the decade following his return home to Cleveland after earning his PhD from the University of Oxford, Tesar and his team have contributed groundbreaking

discoveries spanning fundamental aspects of stem cell biology, including development of new stem cell-based therapeutics for clinical application. His pioneering work caught the attention of the prestigious New York Stem Cell Foundation who awarded him of the 2017 Robertson Stem Cell Prize.

In 2015 his lab was conducting research aimed at regenerating the growth of myelin, the protective coating around nerve cells. Made of protein and fatty substances, myelin insulates nerve fibers that allow electrical impulses to transmit quickly and efficiently along the nerve cells.

In diseases such as multiple sclerosis, the immune system attacks and damages myelin, mistaking it for a foreign body, which leads to progressive disability. This immune response also damages the specialized cells that produce myelin, called oligodendrocytes (a tongue-twister from Greek meaning "cells with a few branches").

“The challenge was to find a way to unlock an enhanced regenerative potential within the stem cells.”

Tesar says

When the myelin sheath is damaged, nerves can't conduct electrical impulses normally. The body does some healing on its own by stimulating oligodendrocytes in the area—or by recruiting stem cells from further away—to begin making new myelin at the damaged site. However, this repair process is slow and incomplete.

The clinical need to regenerate these myelinating cells in the central nervous system—in MS as well as many other diseases—is dire. MS is a devastating, highly unpredictable disease, flaring and fading at irregular intervals and producing various symptoms that include problems with mobility, vision, strength and balance. There is no cure. Current medications for MS can help slow or prevent this attack by the immune system, but they don't replace myelin.

Scientists have been investigating different strategies for stimulating oligodendrocytes to produce myelin, including the transplanting of stem cells into the brain—but that's a very invasive and challenging approach.

“We know that there are already stem cells in the brain with the ability to make oligodendrocytes and replace the lost myelin...but when millions of them are being attacked at the same time, the stem cells can't keep up,” Tesar says. “So the challenge was to find a way to unlock an enhanced regenerative potential within the stem cells.”

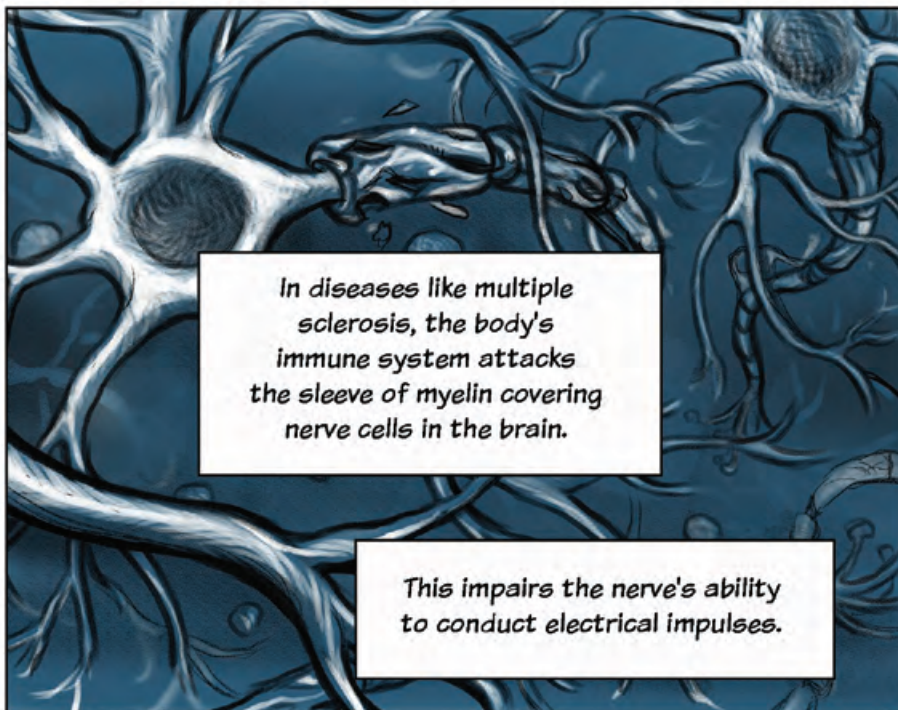
Tesar's lab set out to grow stem cells that are normally in the brain. “That's what the early stages of our lab were built around—generating those cells, and a cellular toolkit

that we could work with,” Tesar says. “The question then became, how can we make these stem cells more efficiently generate new oligodendrocytes? So you plate them in a petri dish, pour a drug on top and see how it reacts.”

Using a novel screening platform developed by Tesar and research scientist Fadi Najm, the team tested a collection of about 700 Food and Drug Administration (FDA) approved drugs in order to pinpoint those with the potential to stimulate the maturation of central nervous system stem cells into myelin-producing oligodendrocytes. (Most of the drugs his lab was screening had previously been used in FDA approved clinical trials, though not specifically for MS.)

The process resulted in the surprise finding that the antifungal medication miconazole, as well as clobetasol, a topical corticosteroid used for various skin conditions, were able to stimulate the differentiation of stem cells into mature oligodendrocytes. Further, these drugs actually stimulated the formation of new myelin, and reversed disease severity in animal models of multiple sclerosis. Paralyzed mice regained the ability to walk. This was big news, and Tesar's lab published a paper disclosing its findings in the prestigious scientific journal *Nature*.

However, the drugs identified in this study were not immediately suitable for use in human multiple sclerosis patients. “To reach patients we needed to understand how the drugs were having such a dramatic therapeutic benefit in animals, and we needed to find better drug candidates,” Tesar says.

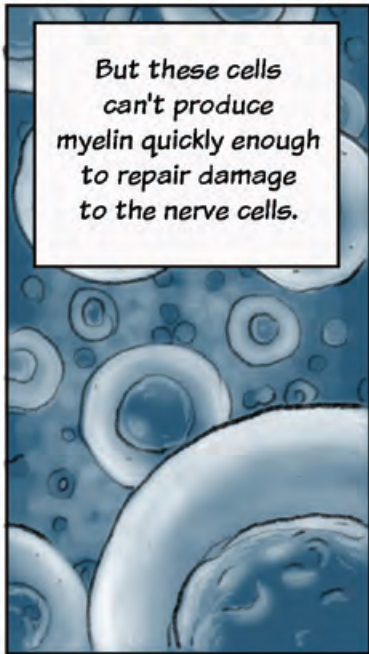


In diseases like multiple sclerosis, the body's immune system attacks the sleeve of myelin covering nerve cells in the brain.

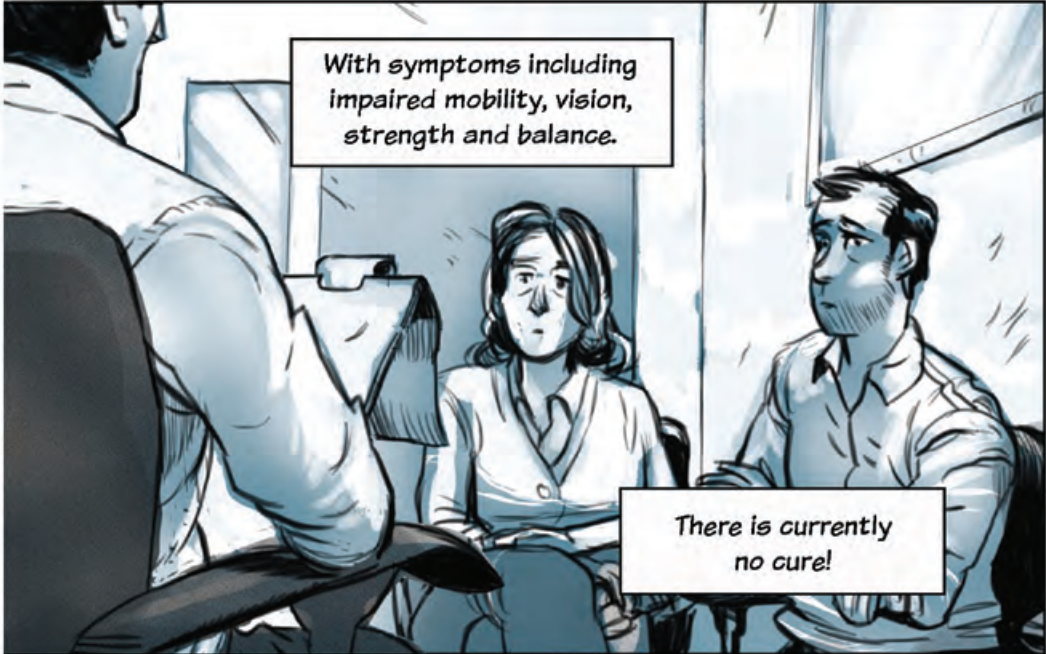
This impairs the nerve's ability to conduct electrical impulses.



Myelin are produced by oligodendrocytes...

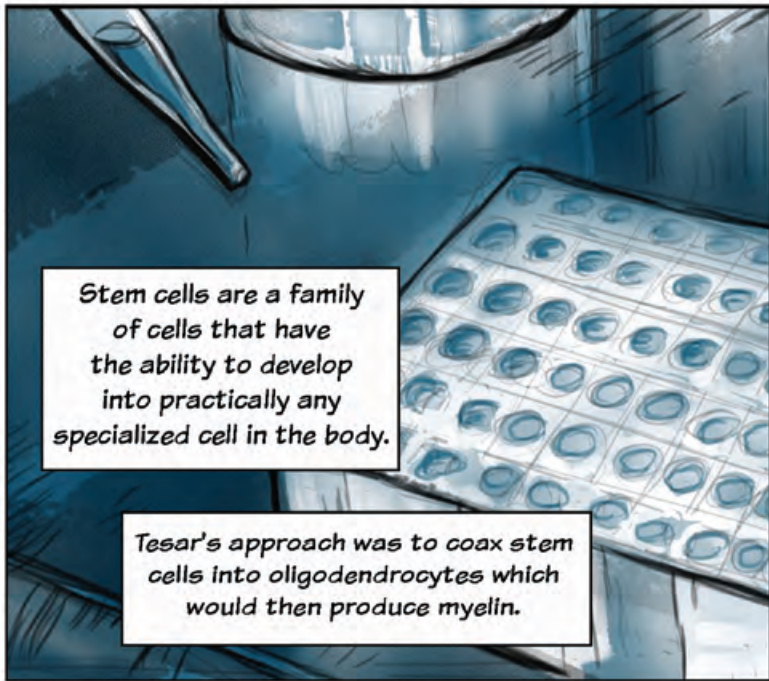


But these cells can't produce myelin quickly enough to repair damage to the nerve cells.



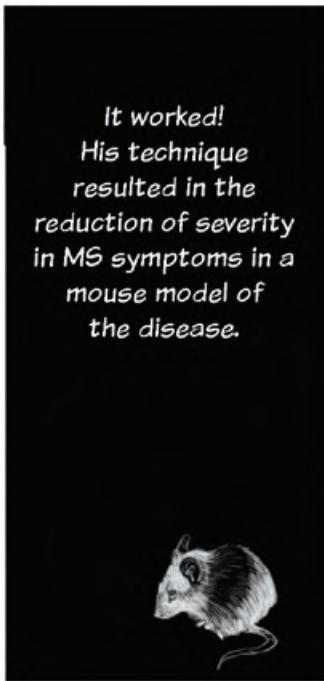
With symptoms including impaired mobility, vision, strength and balance.

There is currently no cure!



Stem cells are a family of cells that have the ability to develop into practically any specialized cell in the body.

Tesar's approach was to coax stem cells into oligodendrocytes which would then produce myelin.



It worked! His technique resulted in the reduction of severity in MS symptoms in a mouse model of the disease.



Exciting news... but working toward a cure required answers to additional questions.

ORIGINS OF A BIOTECH

SCREENING FOR CHEMISTRY

At this point, although Tesar had stem cell and myelin expertise, he saw that taking this work further would require insights from someone with a biochemical point of view. “Our team developed the core biological observation on how to regenerate these myelin-producing cells, but we needed a better understanding of what protein the drugs were binding to in the brain to elicit a functional response,” Tesar says.

He connected with Drew Adams, who had a unique blend of training—a PhD in organic chemistry from Harvard, followed by extensive postdoctoral studies at the Broad Institute of Harvard and MIT within the Center for the Science of Therapeutics.

“It was immediately clear that Drew’s expertise could be a key piece to understanding how our drugs were working,” Tesar says. Adams also had experience in high throughput screening, a method for scientific experimentation that allows a researcher to quickly sift through potential drug candidates and identify those that elicit a desired biological outcome.

“The ability to test thousands of drugs a day allowed us to accelerate our efforts, which in turn uncovered dozens of new lead molecules that ultimately pointed us to new biology,” Adams says.

But it wasn’t just molecular chemistry that played a role in Adams choosing to come to Cleveland. “I wanted a chance to do important work, but when interviewing at institutions I also considered what the fit would be like on a personal level,” Adams says. “Paul and I were on the same wavelength from the start, and between Paul’s stem cell expertise and my chemistry background, I saw an excellent opportunity for a collaboration focused on accelerating the science toward MS patients.”

Adams is now an assistant professor of genetics and genome sciences at the School of Medicine, as well as the Thomas F. Peterson, Jr. Professor of Cancer and Energy Research, and Director of the Small-Molecule Drug Development Core, a newly-built facility enabling high-throughput screening to accelerate academic drug discovery efforts.

A PATHWAY TO ANSWERS

Multiple labs across the globe have identified chemical compounds capable of inducing re-myelination. The challenge has been to understand precisely how each of the small molecules affected brain cell function. Tesar and Adams first sought to understand this cellular mechanism of action of the imidazole antifungals.

With help from colleague Mitch Drumm, PhD, professor of genetics and genome sciences, pediatrics, and the Connie and Jim Brown Professor in Cystic Fibrosis Research, they set about trying to test whether the mammalian form of the enzyme responsible for the antifungal effects of miconazole might be responsible for miconazole’s effects on myelin formation.

One Saturday evening PhD candidate Zita Hubler was using an instrument in Drumm’s lab to monitor whether the antifungal molecules—including other molecules reported by scientists to promote the growth of oligodendrocytes—were inhibiting a specific brain enzyme.

“After dinner I headed back to the lab to see how Zita’s experiment turned out,” Adams says. “What we saw was that not just the antifungal molecules were inhibiting the specific enzyme in the brain that we suspected was important in the formation of oligodendrocytes; all of the molecules we tested were. Right then Zita and I knew something very interesting was going on: if all the molecules were converging on this one brain enzyme, it must be really important for promoting the formation of oligodendrocytes.”

Important enough that Adams interrupted Tesar’s vacation with a call. “I was in the Finger Lakes at the time...Drew called me up and said ‘you’re going to want to see this,’” Tesar recalls. “It was probably the most exciting moment I’d had since Christmas morning of 2009, when I came into the lab early, before all the family festivities, and saw we’d grown our first oligodendrocyte.

“At that point we focused our drug discovery efforts around this enzyme. In all, our team identified more than 20 new drugs that enhance myelin formation by inhibiting this target.” This finding was published in *Nature* last year.

To measure the formation of “human” myelin in the laboratory, the team used a new three-dimensional nerve cell culture model that closely mimics human brain tissue. Sure enough, the drug candidates promoted human myelin formation by blocking cholesterol pathway enzymes. This innovative model was developed in Tesar’s lab by Mayur Madhavan, PhD and Zachary Nevin, PhD, and a study describing it was published in *Nature Methods*.

When in preclinical studies their approach showed regeneration of myelin and reversal of paralysis in MS mouse models, it was time to launch a company. “We had a key disease area, we had drug candidates, we knew how they worked,” Adams says. “You could feel the momentum building.”

Questions like what was the chemistry behind the antifungal's ability to re-populate damaged nerve cells with myelin?



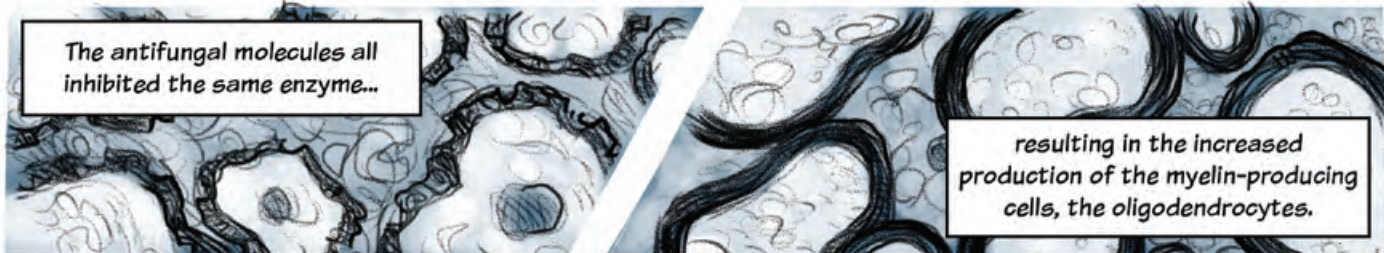
Tesar connected with Drew Adams, PhD, who possessed a special blend of biochemistry and drug development expertise.

One Saturday evening...



While running experiments using several antifungal molecules, among others that were suspected of promoting myelin production, Drew's team made a critical discovery.

The antifungal molecules all inhibited the same enzyme...

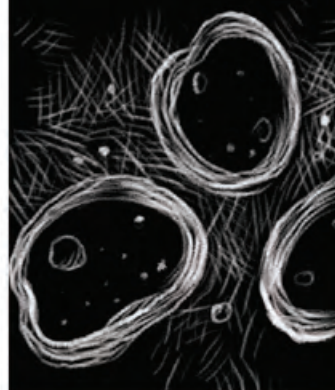


resulting in the increased production of the myelin-producing cells, the oligodendrocytes.

"We now have a druggable target."



Using a new three-dimensional nerve cell culture model that mimics human brain tissue, the lab identified more than 20 new enzyme-inhibiting drugs to enhance myelin formation.



"You're going to want to see this, Paul."



ORIGINS OF A BIOTECH

SCREENING NAMES

“After Drew arrived and we figured out the drug mechanism, we had the foundation to advance the science forward toward clinical testing,” Tesar says. “This necessitated moving the work from our academic labs to the commercial sector where specific expertise and funding streams exist to develop drugs for human clinical testing.”

“We had no expertise in formalizing scientific work into a company, but I had colleagues outside of the University who had started many companies,” Tesar says. “They had seen the science and been helpful about whether there was a commercial opportunity here.” These included several people who were excited about biotech in Cleveland, including Bill Sanford, executive founder, retired Chairman and CEO of STERIS, and Ronn Richard, president and CEO of the Cleveland Foundation. They made initial investments in the company and both thought, “Why put the biotech company in Boston or San Francisco—why not build it here in Cleveland?”

Sanford brought together interested investors. Steven Landau, MD, a Case Western Reserve alumnus and serial entrepreneur who has extensive experience in pharmaceutical development, was named chief of development. Derrick Rossi, PhD, was named president and CEO. Rossi brought a lot of credence as the founder of Moderna Therapeutics, and co-founder of Intellia Therapeutics, Magenta Therapeutics, and Stelexis Therapeutics. He was also a professor at Harvard Medical School and Harvard University, as well as an investigator at Boston Children’s Hospital where he led an academic team working on stem cell biology and regenerative medicine. In 2011 Time magazine named Rossi as one of the 100 most influential people in the world.

At this point the fledgling company needed a name. Adams likens the naming process to that of naming a band. “I was

in an indie rock band with my wife—and that process took quite a while,” he says. “Here, the stakes were much higher...so coming up with “Convelo” took a really long time.” Ultimately Convelo, whose origins are from the Latin meaning “to wrap around”, was a memorable and logical choice.

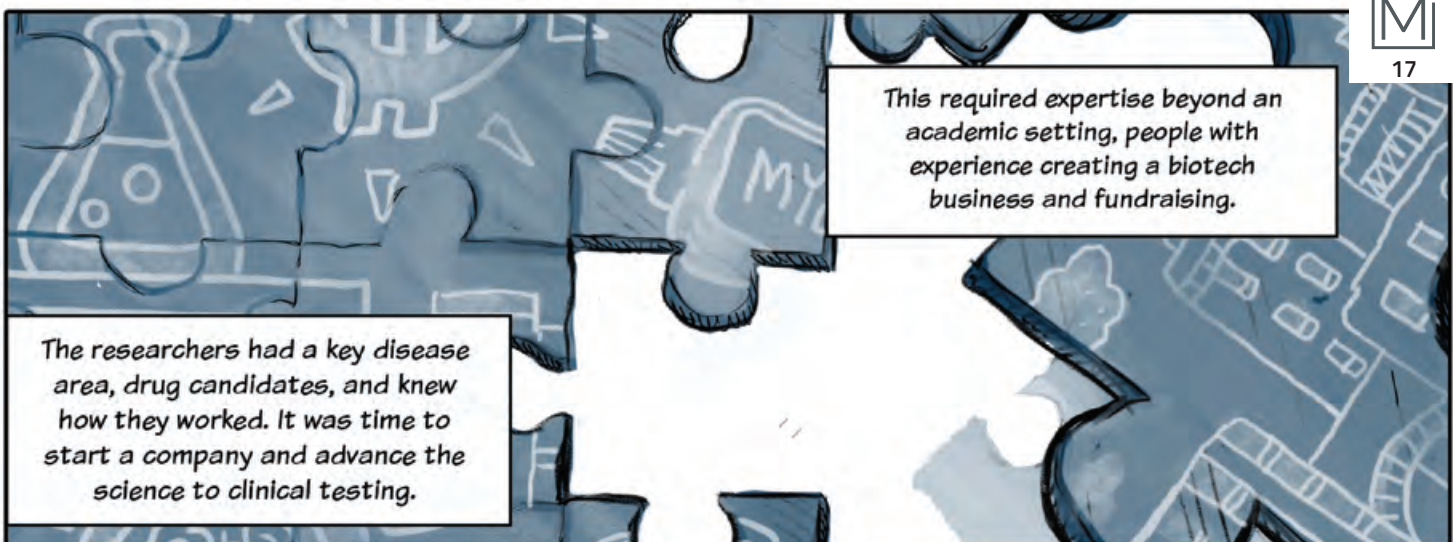
Adams credits Cleveland’s entrepreneurial atmosphere and support in helping him and Tesar form the team to take Convelo forward. “We had to weigh the pros and cons of working with venture capital firms,” Adams says. “They have the resources to make large investments, but on the other hand there would inevitably be a certain loss of control for us. Ultimately we saw the value in keeping the science close to us, and working with local investors.” Convelo’s initial \$7.8 million financing was led by a group of private investors managed by Sanford.

After licensing technology from Case Western Reserve, Convelo set up shop at the incubator site, BioEnterprise. “What’s building in Northeast Ohio is a culture that is friendlier to entrepreneurship and commercialization,” says Adams. “There’s a growing ability to bring in outside experts and foster connections with alumni and friends who’ve done this type of research in the private sector.”

“Moving into the commercial sector requires expertise in basic science, funding to validate hypotheses, and specialized expertise to determine whether a drug discovery is a commercially viable opportunity,” Tesar says. “Through the local community our team got not just funding but the expertise and infrastructure that we needed. Since hiring our first employee, Brad Lang, PhD, who is now VP of research, we’ve built a roster of talent who know how to do this type of research; keeping things local.”

“It feels like a sort of wholesome Midwestern vibe, and we really like that.” adds Adams.

Why put the biotech company in Boston or San Francisco—why not build it here in Cleveland?



This required expertise beyond an academic setting, people with experience creating a biotech business and fundraising.

The researchers had a key disease area, drug candidates, and knew how they worked. It was time to start a company and advance the science to clinical testing.



At this point the fledgling company needed a name. Adams likens the naming process to that of naming a band. (Drew had an indie band in college.)



Settling on the right name was a process of trial and error in itself!



Finally, a memorable and logical choice emerged. The company would be called Convelo, from the Latin meaning "to wrap around."

The Convelo team briefly considered setting up shop in Boston or San Francisco. But then - another Eureka moment: "Why not build it here in Cleveland?"



The city's entrepreneurial spirit and willingness to support Convelo's growth made Cleveland a natural choice.

ORIGINS OF A BIOTECH

MAJOR SHIFTS

Tesar was considering going into veterinary medicine, but when he came to CWRU as an undergrad, began working in a research lab, and found that he loved the problem-solving. Tesar says, "I really enjoyed plotting a path of questions that I could define and structure—and the thing about science is, you can never predict the direction these experiments are going to take...and it's open ended—the work is never really complete."

"A lot of scientists are in it for the discovery; but I'm strongly driven by the translational research aspect—doing work that has a chance to directly benefit patients." There's

something different about an experiment when you come to it seeing the work through that lens."

Adams began at Swarthmore College with an interest in philosophy and political science. "It didn't take long for me to see that it wasn't for me," he says. "So I shifted to biochemistry. Ultimately I was able to do research with an organic chemistry professor and I ended up doing a pure organic chemistry PhD as well. At CWRU, I've really enjoyed applying chemical thinking to biological problems and having the chance to do research that can make a difference for patients."

“I've really enjoyed applying chemical thinking to biological problems and having the chance to do research that can make a difference for patients.”

Adams says

YOU GOTTA BELIEVE

Currently the Convelo team is working to perfect a drug that meets all requirements for efficacy and safety, gets past the blood-brain barrier, and has myriad other properties necessary to advance a drug candidate to clinical trials.

The road to becoming a drug approved by the FDA is a long one, with many efficacy and safety boxes that need to be checked off. Yet the team can't help but feel optimistic, considering the arguably unlikely events that have gotten the project to this point—the stars aligning for Adams to bring his unique expertise to the team, the assembly of stellar investors and biotech leaders, and the surprising discovery of molecules capable of restoring myelin.

But the biggest reason for optimism occurred recently, with the news that Convelo entered into an exclusive

worldwide collaboration with Genentech, one of the world's leading biopharma companies and a member of the Roche Group, to accelerate discovery and development of novel remyelinating therapies.

With such accomplished minds and powerful resources at work to unlock the regenerative capacity of the central nervous system, the world may see a new class of medicines with the potential of helping not just MS sufferers, but a wide spectrum of inherited neurodegenerative disorders, traumatic injury and age-related pathologies such as Alzheimer's.

Now more than ever, for sufferers and families of those with MS and so many other diseases, Convelo's future can't get here soon enough.

The road ahead for Convelo will have many twists and turns as it moves closer to commercializing its technology.

Yet the team can't help but feel optimistic, considering the fortuitous events that have gotten the project to this point.

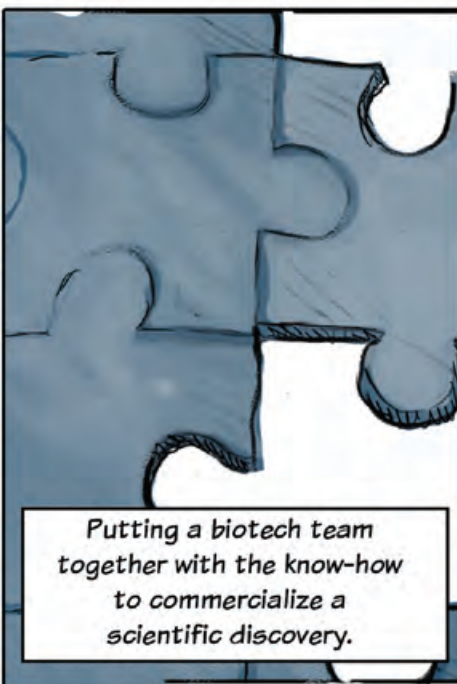


Tesar's expertise in stimulating stem cells to produce myelin.



Using the technique to successfully reverse MS-like symptoms in mice.

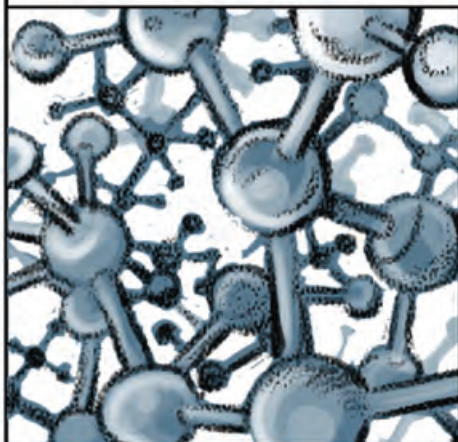
Collaborating with Adams' lab to define the unifying mechanism by which small molecules ultimately repair the loss of the myelin around nerve cells.



Putting a biotech team together with the know-how to commercialize a scientific discovery.



Finding the right entrepreneurial environment to nurture a fledgling biotech.



Additionally Convelo entered into an exclusive worldwide collaboration with Genentech, one of the world's leading biopharma companies.



Convelo may just have the solution to develop a new class of drugs with the potential of helping not just MS sufferers, but those with other neurodegenerative disorders, traumatic injury and Alzheimer's disease.

STAY TUNED!







From bench to board room



Four alumni entrepreneurs share the stories behind their success

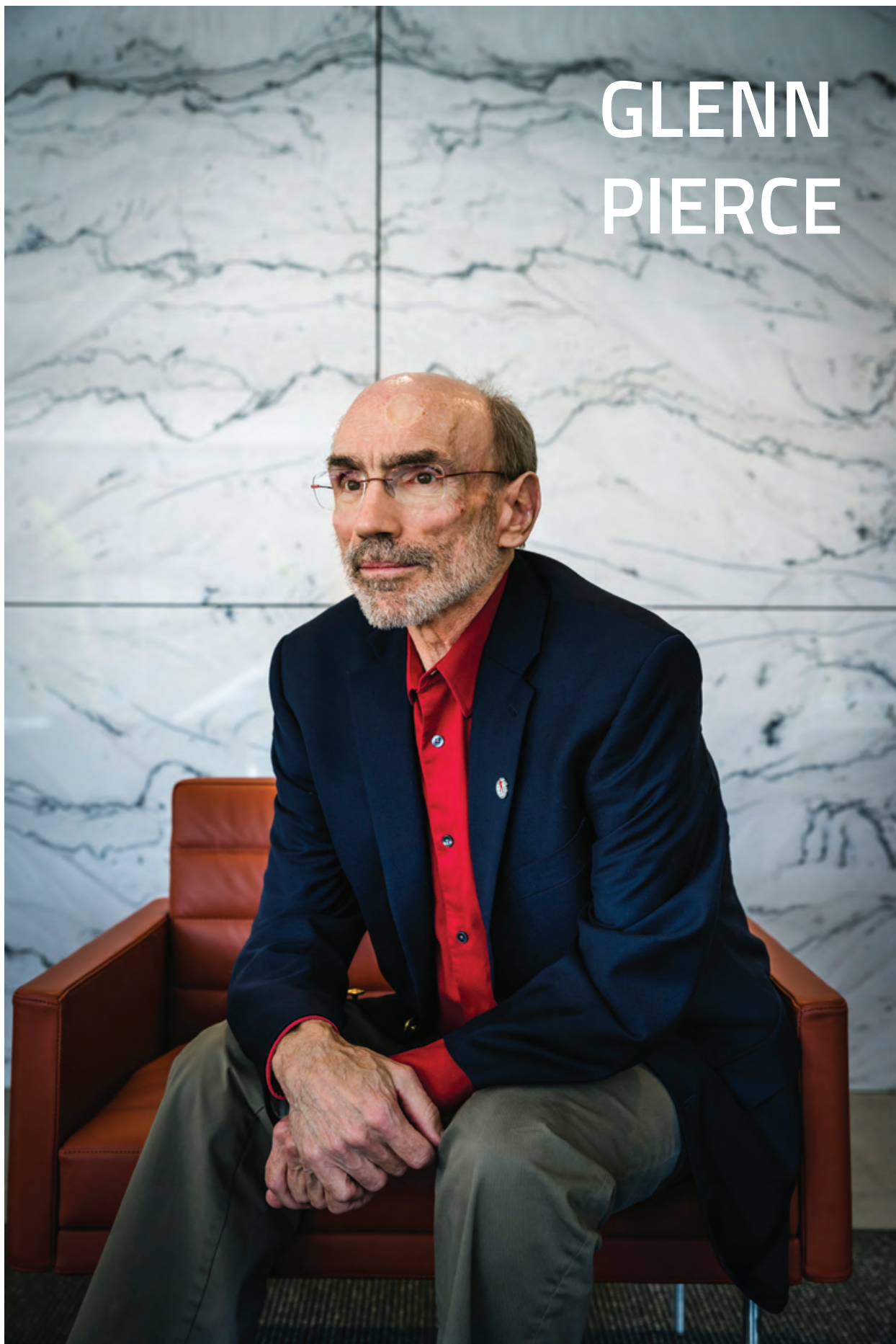
by Dan Morrell

Developing biotech entrepreneurs, says Mark Chance, PhD, requires an integrated business and medical ecosystem. “As a school, we had gotten really good at finding and developing treatments,” says Chance, vice dean for research at the School of Medicine. “But we needed to figure out how to turn those treatments into businesses.” Chance has spent the last several years building the structure to help launch the school’s discoveries into the marketplace. He has helped introduce pilot funding programs that provide early support to promising ideas. He has established programs to mentor aspiring student-led biotech startups, and an entrepreneurship club that allows participants to learn from and network with entrepreneurs and experts in biomedical industries.

But beyond these programmatic elements, Chance says that ecosystem development also requires a mindset shift. “We want an environment where people are taking risks—and are confident about taking risks,” he says. “The future for me is a Cleveland where people aren’t so afraid of failing. And they’re thinking, ‘I’ll take a risk, so I’ll probably land on one foot with a little hand-holding, and then I’ll run off from there.’”

On the next few pages, we trace the stories of four Case Western Reserve alumni who took that risk—and have had the passion to run a path to the top.

GLENN PIERCE



“We’re saving lives every day, and we are improving the quality of life. That’s really rewarding.”

Diagnosed with hemophilia as a one-year-old, Glenn Pierce spent a lot of his childhood at Cleveland’s City Hospital (now MetroHealth Medical Center). During hospital stints, Pierce was sometimes paired with a college student for play time—part of an initiative pioneered by famed Case Western Reserve psychologist Emma Plank to enrich the medical environment for sick children. One day in 1965, while in a playroom with one of the students, he dictated an autobiography, which included a clear goal: “When I grow up, if I get there, I would like to cure hemophilia.”

More than five decades later, Pierce is close to making good on that promise. Confined to a wheelchair at 12, advances in treatment allowed him to slowly ditch his transportation aids—first the wheelchair, then the braces, then the crutches—by the time he was 17, he started at Case Western Reserve without walking aids. His decision to attend medical school was motivated in part by self-preservation. “I had had enough doctors that knew less about my hemophilia than I did, even as a child,” he says. “And so, I thought that the best way I could get better control over my disease was to become a doctor and manage it myself.”

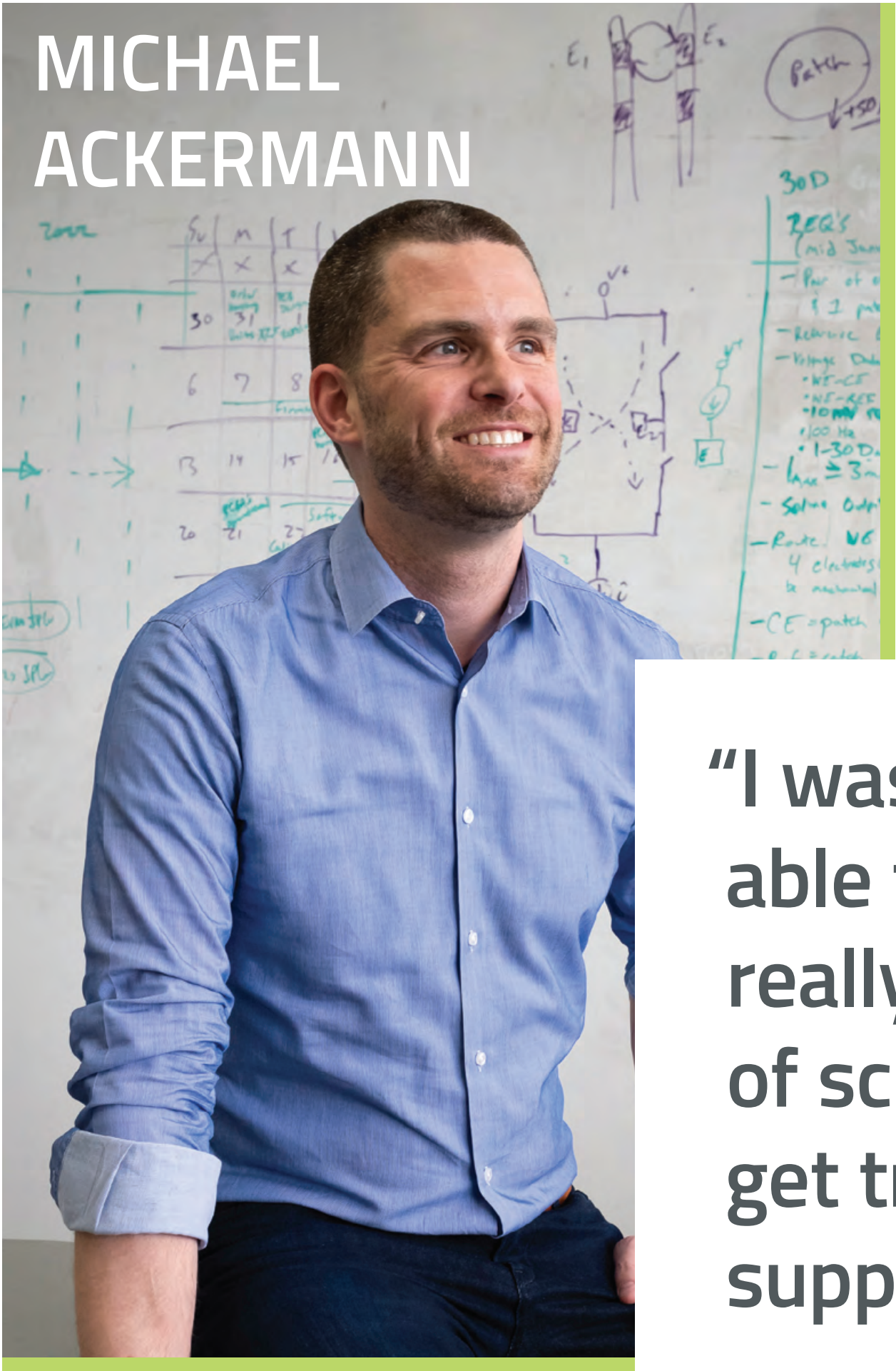
Pierce describes his early career as a dual life: He’d spend his work days on tissue regeneration, and then the rest of his free time volunteering in the hemophilia community, eventually serving as president of the National Hemophilia Foundation three times. “At a certain point, I really no longer had passion from my real work—I really only derived passion from my hemophilia work,” says Pierce. So he made hemophilia his career, starting a succession of jobs at biotech companies that were developing treatments, eventually landing at Biogen in Boston, where Pierce helped bring two new hemophilia drugs to market.

Since leaving Biogen, Pierce has split his professional time between consulting and working as an entrepreneur-in-residence at Third Rock Ventures, a venture capital and private equity firm. As part of that role, he serves as interim Chief Medical Officer of Ambys, a portfolio company working on cell and gene therapy for liver regeneration. “It’s a huge unmet need,” Pierce says. “We have 7,000 liver transplants a year [in the U.S.]. There’s 20,000 people on the waiting list and there’s at least another 20,000 or 30,000 people that can’t get on the list for either medical or social reasons.”

Pierce has also re-immersed himself in the hemophilia community. Last year, he was elected vice president of medical at the World Federation of Hemophilia, where he is focusing on research that could aid hemophilia sufferers in the developing world. It’s long been a focus of his: Before he left Biogen, Pierce worked with senior management to donate \$3 billion of the hemophilia drugs that he worked on to underserved communities globally. “People in the developing world are going without treatment,” says Pierce, who travels several times a year to help train physicians and educate patients in developing countries. “We’ve been treating Syrian refugees in Lebanon and in Egypt. We are getting to a number of people that had never had clotting factor before in their lives. So we’re saving lives every day, and we are improving the quality of life. That’s really rewarding.”

But as meaningful as that work is, he says, it “is like putting your finger in the dike.” The world still needs a permanent solution, and Pierce knows that the answer is gene therapy. He advises a company named BioMarin that he expects to have the first real gene therapy hemophilia treatment on the market in a few years. He’s ever closer, it seems, to making good on the promise he made to himself in that hospital playroom so many years ago.

MICHAEL ACKERMANN



“I was lucky
able to find
really great
of scientists
get tremendous
support

Michael Ackermann has had a wildly successful first seven years as an entrepreneur, founding and then selling his first company to Allergan and co-founding three other biotech companies shortly thereafter. But that personal success, he says, was thanks to the efforts of a wide network of people. "As I look back, it really feels like my career has been characterized by important mentors," he says.

As an undergrad studying biomedical engineering at Vanderbilt, he worked in the lab of a supportive chemical engineering professor for three years, the experience proved profound enough to convince him to pivot from a med school path to a research route. During his graduate studies at CWRU, he worked extensively in neural engineering with Kevin Kilgore, PhD, assistant professor, and Niloy Bhadra, MD, PhD, research assistant professor. "They had pioneered this electrical nerve block technology, which was such a rich area for investigations and innovation," says Ackermann. "I was lucky to be able to fall into a really great area of science and get tremendous support." But before he committed to a life in academia,

he wanted to spend some time in industry, and—with his mentors' blessings—spent a semester at Boston Scientific in Los Angeles. The experience opened his eyes to the thrill of taking a medical solution to market. "It was really impactful to be working on a product that I knew was going to get out and treat lots of people," he says.

After a yearlong postdoc biodesign fellowship at Stanford focused on ophthalmology, Ackermann had a product and a company, Oculeve, which boasted an innovative solution to dry eye disease, an ailment that affects some 33 million Americans. "Treatments addressing dry eye disease were not particularly effective and only addressed inflammation," says Ackermann. The Oculeve device featured a nasal probe that stimulated the lacrimal glands, kick-starting these tear factories that were otherwise idle in dry eye disease sufferers.

But stepping into the CEO role took some adjustment. "It was a very steep learning curve," says Ackermann. Suddenly, he had to master not only the science behind the device, but product development, management, and leadership. "The image I use to describe this period is that I was drinking Red Bull from the firehose for two full years." Ackermann credits getting through the experience to a board-appointed independent director who coached him for nearly 18 months. "I felt like I was getting another PhD in business management," he says.

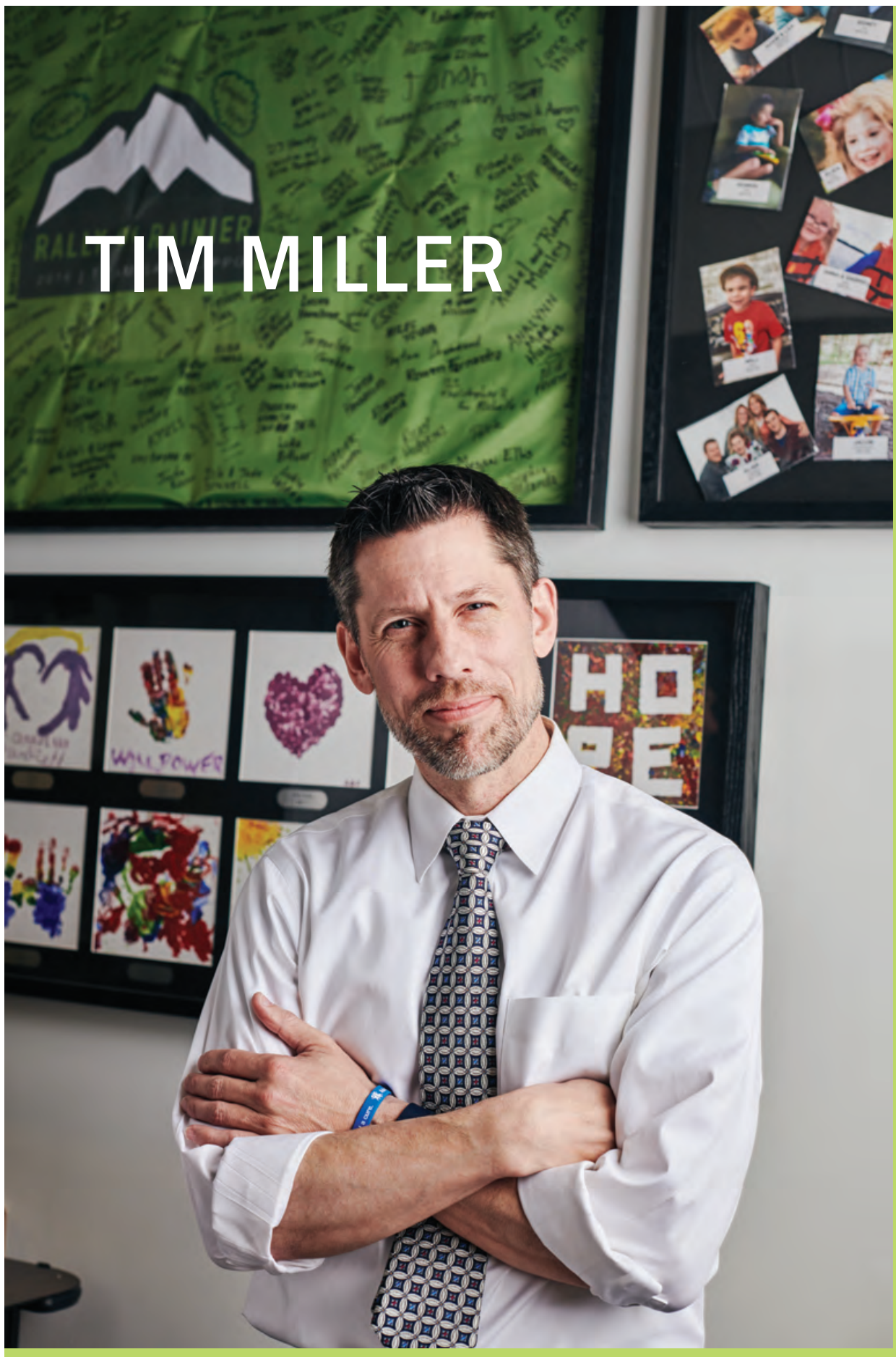
Ackermann stayed with Oculeve for about two years before selling it in 2015. He then co-founded three companies in four months. The first, Presidio, where Ackermann serves as CEO, is developing treatments based on some of the nerve block technology work he did at CWRU, with the first clinical trials expected this spring. Tarsus, where he serves as chairman of the company, is targeting the eyelid inflammation condition Blepharitis, which affects about 19 million Americans, and is in the midst of its first clinical trials. He is also chairman of Oyster Point, which is developing dry eye disease drugs with phase three pivotal trials scheduled for this summer.

His shift to entrepreneurship has taught him something about his strengths as a business person. "I prefer to be in more of a strategic role than an operating role," he says. But his greatest professional lesson? "There's really no substitute for good people and good luck," he says. "I'm trying to do my best to provide both of those things to others now." For instance he is lending his insights to students at the Stanford biodesign program he attended, and making sure he is always available to mentor. "I do my best to try to pay some of that forward."

lucky to be
fall into a
great area
ce and
tremendous

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TIM MILLER



When Tim Miller climbed to the top of Washington's Mount Rainier—one of the country's highest peaks—in 2016, his summit celebration was about more than conquering the 14,417-foot slope. Miller was part of a small

group of people assembled by Carl Kapes, the father of a child suffering from Sanfilippo disease, a rare childhood neurodegenerative disease that causes progressive brain damage and, eventually, death. The climb was intended to both raise awareness and research funding for the disease, while the participation of clinicians, families, and foundations was meant to send a message about solidarity in the mission. "We brought to the top of the mountain a flag that had been signed by about 200 families who had been impacted by Sanfilippo," says Miller. "It was an emotional moment when Carl and I were in the crater at the summit and holding up the flag to take a picture that said we made it."

Miller, president and chief scientific officer of pharmaceutical company Abeona Therapeutics, sees parallels between that climb and his work. "It really reflects the journey of going through drug development—there are certain mountains you have to climb and certain peaks you must reach," he says. Miller's ascent began by earning bachelor's and master's degrees in biology at John Carroll University, where he first began to focus on developing science to find new and better ways to treat patients with disease. At CWRU, Miller dug into gene therapy, focusing his PhD work on cystic fibrosis.

His interest in Sanfilippo started in late 2012, when he was working as a CEO-in-residence at biotech accelerator

BioEnterprise in Cleveland. As part of this work, he would visit families affected by Sanfilippo and other rare diseases to better understand their day-to-day challenges. "Working with many of the families and really seeing the impact on these families fueled my desire to try and do something for them," says Miller.

In 2013, Miller co-founded Abeona Therapeutics with the support of 10 rare disease foundations. "There are over 7,000 rare diseases, and 90 percent of them don't have any product or program that's been approved by the U.S. or European drug agencies," he says. "So our mission is to try and take new products forward, but also use our learnings to develop better products in gene therapy." Abeona currently has three drugs in trials right now—one to treat Epidermolysis Bullosa, which causes severe skin fragility, and two to treat different forms of Sanfilippo. Miller anticipates Abeona will have two more clinical trials starting later this year for new treatments for Batten Disease, a degenerative neurological condition.

As an executive, Miller says that working on cures and treatments for rare diseases keeps employee motivation high. "One of the things you hear a lot about at Abeona is that everyone is grateful to come in everyday, because you're thinking, 'Gosh, I get to work on therapy that may save a child's life,'" says Miller. "I look forward to the day when we have an approved drug to treat infants. A few years later, I'm going to be, I hope, seeing a news report about a family that had their child treated with one of our gene therapies, and see that they're in school—and they're up walking and talking and learning and playing with their friends."

"Our mission is to try and take new products forward, but also use our learnings to develop better products in gene therapy."



CHARU RAMANATHAN

“My businesses are built on access and transparency.”

It was during a device trial at University Hospitals Cleveland Medical Center in 2001 that Charu Ramanathan's future suddenly became very clear. She was the participating cardiologist at a demonstration of a multi-electrode vest which created a detailed map of electrical signals from the wearer's heart. The result simply floored her. The patient was similarly thrilled: “He was super excited that he could see his own heart activity without going through an invasive procedure,” says Ramanathan, who was then just a few years into earning her biomedical engineering PhD at Case Western Reserve. The ultimate goal of these trials were grant funding, but Ramanathan pondered its potential beyond journal articles. “How can we get this to reach millions of patients?” she thought. “That was the aha moment when I realized that I was going to do it.”

In 2007, Ramanathan and her fellow doctoral student Ping Jia launched CardiInsight after many years of tinkering and refining. The early years of the startup were tough. New to the world of entrepreneurship, the duo sometimes had to feel their way through the business side, often defaulting to the advice of high-paid consultants. In the wake of the market crash in 2008, venture funding was scarce. And then her co-founder, Jia, had a catastrophic health event that forced her to step away for an extended period, leaving Ramanathan alone at the helm.

But around 2010, she made a sharp course correction. “I'm going to stop being academic about the company and really start applying some common sense,” she remembers thinking. “That is when things started really changing.”

The product would eventually see a limited launch in Europe in 2012, supported by some \$35 million in venture and government funding. Three years later, medical device giant Medtronic acquired it for \$93 million. She worked within Medtronic as a business unit lead for a while, running CardiInsight product launches, but realized after a few years that it was time to go. “I just said, ‘Okay, the baby's gotten too big,’” she says.

But she didn't stay still. Within a month of leaving Medtronic in the summer of 2017, she founded two startups: Lokyata, a credit-scoring service for microlending, and vitalxchange, a mobile digital platform for connecting patients in search of information about personal health. Ramanathan has helped Lokyata raise a series A funding round, and is structuring a seed round for vitalxchange, which she ultimately envisions as a kind of Angie's List for health care. “We have retail consumer power everywhere else except for health care,” says Ramanathan. “So we've structured vitalxchange around the patient.”

The two companies may seem like divergent pursuits, but Ramanathan notes that there are common themes. “My businesses are built on access and transparency,” she says. With Lokyata, she's helping non-traditional borrowers in Africa and India connect with clear funding channels so they can achieve tangible goals like sending their kids to school or fixing that leaky roof. With vitalxchange, she's empowering health care consumers by breaking down barriers to information. In both cases, she says, the opportunity for impact is enormous. “And I am at a stage in my life where I really want to do this.” **M**

Inside initiatives

An EnRICHing experience

Laimis Belzinskas planned to become a physician after completing a medical physiology master's degree at Case Western Reserve, going so far as to shadow hospital physicians to gain insights into the opportunities of clinical life. But there was an equal tug in a different direction: engineering. A master tinkerer, Belzinskas enjoyed dabbling in 3D modeling, even designing a roller coaster using simulation software. Then he saw an advertisement for EnRICH, the Enhancing Research and Industry Career Horizons Program, which prepares PhD and master's students for careers in the life sciences by connecting them with startups, nonprofits, and established businesses in the Cleveland area. Soon after he contacted the program's founder, Cheryl Thompson, PhD, he was offered two internship opportunities. One at a local hospital and one at Infinite Arthroscopy, a medical device startup focused on producing the world's first fully-wireless arthroscopic camera system.

"Both internships looked great and each addressed one of my two core interests: healing and engineering," Belzinskas says. He deliberated, chose the Infinite opportunity, and has never looked back.

"As an intern at Infinite, I plunged right into the industry. I learned a great deal about 3D modeling, but also research and development, medical device regulatory strategy, and design review," says Belzinskas. Impressed with his skills, eagerness to learn, and commitment to the company's vision of improving health through technology, Infinite offered him a position after graduation, which he accepted. Now rechristened Indago, it offers an arthroscopic camera system that eliminates the weight and entanglements of wires and cables, allowing physicians to focus on patients and procedures, not their tools.

The connections engineered by the EnRICH program take many forms: paid and unpaid internships, mentoring, one-time projects, immersion experiences, and shadowing opportunities. As a result, participants gain access to learning opportunities and professional contacts that serve them in a myriad of ways as they embark on their career trajectories. Hosting forums, making phone calls, and visiting potential



Tessianna Misko, PhD,
executive director of EnRICH

"I enjoyed participating in EnRICH so much as a student that I wanted to lead it."

—Tessianna Misko



Laimis Belzinskas, MS,
physiologist and biomedical engineer at Indago

participating organizations, Thompson—who is also a genetic epidemiologist and director of master's programs in the Office of Graduate Education in the School of Medicine—recruited more than 25 organizations to participate in EnRICH during the program's initial phase.

"I created the program to be flexible and open, so placements can range from one-time sessions to semester and summer positions, to multiyear situations," says Thompson. "We don't impose any demands or limitations. The organization and student agree on the duration of the work experience and work schedule." In addition to many tech startups, participating organizations include the Cleveland Museum of Natural History, Great Lakes Science Center, and University Hospitals. To date, nearly 100 graduate students have taken part in EnRICH.

"I enjoyed participating in EnRICH so much as a student that I wanted to lead it," says Tessianna Misko, PhD, executive director of EnRICH. Misko, whose PhD is in pharmacology, took part in an EnRICH internship in the Office of Research Administration under the assistant director, Anne DeChant. "In addition to my research, which focuses on ribonucleotide reductase as a target for cancer therapeutic development, I'm professionally interested in many things," she says. "Not everyone who earns a doctorate in the life sciences wants to do academic research. I want to help those students identify a career path that they truly love and where they can make an impact." **M**

Guiding entrepreneurs on a pathway to market

How do you go from nothing to something?" Is what Ian Drummond wanted to know. How do you bring an idea to life?

Drummond, faced with the need to choose which medical specialty to pursue, decided to suspend his formal medical school training and take two years to evaluate his options. He was accepted for an internship at a medical device startup and also began audiotaping interviews with physicians about their specialties so he could begin to figure out which path in medicine to pursue.

Drummond decided to edit these two-hour conversations and the podcast, *The Undifferentiated Medical Student*, was launched with the intent to help other students find their path, too. He has developed a following, and released the 69th episode this past April. "Medical students are listening, and I'm getting emails from them and it's motivating me to keep this going," he says. Not to mention, he realized he wanted to pursue a residency in combined pediatrics and anesthesiology.

Still, there was that nagging question of how to do something more with his podcast. The CWRU Venture Mentoring Program (CVMP) unlocked some answers. CVMP provides researchers and aspiring entrepreneurs with unbiased, confidential mentoring to help inspire, develop, and empower their pursuit of commercial opportunities. The program is based on the successful MIT Venture Mentor Service.

The collegial program partners diverse mentor groups with mentees to guide them on a path to market. There's no competition, but instead there's mentoring, structured programming, and support.

"Entrepreneurship and a do-it-yourself startup outlook on life are not only encouraged, they are celebrated in academics these days," says Liza J.M. Heinig, JD, PE, partner at Tarolli, Sundheim, Covell & Tummino LLP. Heinig ('99) is one of Drummond's mentors.

"I can bring some of the lessons I've learned advising clients or other mentees to the program," Heinig relates. "I enjoy speaking with someone who has a new idea they are excited about—they have a vision, and I'd like to support them to make that vision happen."

Drummond's mentors asked him the tough questions. "I needed to find a way to keep doing the podcasts, but with a fraction of the time and energy required," he says.

Samantha Oblander ('08), a CVMP mentee, got involved in CVMP to help move research from the lab to the market. Professor of molecular biology and microbiology, Susann Brady-Kalnay, PhD, invited Oblander to her lab as a postdoctoral scholar. "She has some exciting technology

at the point of getting it to the market, and CVMP was an opportunity for us to help move it forward," Oblander says.

The program gathers together mentees and mentors quarterly.

There's a healthy demand for the type of real-world mentorship CVMP provides. "It's an exciting time to be in biotech development because there are people wanting to invest, develop products and make Cleveland a hub, so there's a lot of energy," Oblander says.

CVMP gives scientist-entrepreneurs a valuable network they might not access otherwise. "Unless you are highly connected, you don't have an advisory board until way after you need one," Heinig points out.

For Heinig, an exciting milestone for the program will be when a mentee becomes a mentor. She adds, "I can see this program being a hallmark of the School of Medicine and of Case Western Reserve as a whole." **M**



Ian Drummond, MD, graduated in May 2019.

Education in action

Finding funding for research? Data analytics can help solve that

Today's biggest biomedical challenge isn't finding the cure for cancer. It's funding the research, says Batula Akhtar-Zaidi, PhD, a Case Western Reserve-trained scientist-turned-entrepreneur.

"There's incredible innovation happening in science and technology, but maybe only 5 percent of it ever gets to market and to the patients that need it," she says.

Universities and academic medical centers know it all too well. Many lament how the National Institutes of Health (NIH) has drastically cut research funding over the past ten to twenty years.

But there's plenty of other money to go around, from private-sector companies and nonprofits, claims Akhtar-Zaidi. Researchers just don't know how to look for it or go about getting it.

That's why, in 2018, Akhtar-Zaidi started FireFly. The Cleveland-based company is part matchmaker, part educator on the art of pitching to non-NIH funding sources.

"Biotech firms, pharmaceutical companies and others are actually looking for labs in academia that they can fund," says Akhtar-Zaidi. "It's less expensive and they get better quality deliverables when they outsource specific R&D."

There are thousands of available funding sources, she says. Rather than searching online for one source at a time, FireFly uses an algorithm to identify a research organization's best options, based on field of study, funder spending trends, geographic area and other criteria.

"It's like match.com for researchers and funders," says Akhtar-Zaidi, who earned her bachelor's degree in biology and chemistry at Case Western Reserve in 2008 and her doctorate in molecular medicine at the Cleveland Clinic Lerner College of Medicine of Case Western Reserve University in 2012.

After graduating, Akhtar-Zaidi moved to Boston, where she helped Massachusetts Institute of Technology launch an initiative to partner with big pharma. She was then recruited by a tech startup in Chicago that designed analytics to match cancer patients with chemotherapy drugs based on the molecular profiles of patients' tumors. There she learned how to build a multi-billion company from the ground up and how data analysis could change medicine. She also learned how badly research labs needed financial support.

"Cancer researchers kept telling me, 'My work could change lives if I could just get funding for it!'" says Akhtar-Zaidi.

In response, she created FireFly, a culmination of her education and work experience.



Batula Akhtar-Zaidi, PhD

After just six months in business, the company has helped guide funding for research institutions in four states.

For example, one lab working on pediatric brain cancer was preparing to close after multiple unsuccessful requests for National Cancer Institute (NCI) grants. An analysis by FireFly revealed that NCI probably wasn't the ideal funding target. Historically it allocated only 4 percent of its budget for pediatric research and only 1 percent of that for brain tumor research. However, there were dozens of relatively small nonprofits, with budgets of \$10,000 to \$1 million, ready and waiting to fund pediatric brain cancer research. Even Akhtar-Zaidi was surprised.

"Once we match scientists to their best-fit funders, we teach how to pitch to them," she says. "Pitching to big pharma or nonprofits is different than pitching to the NIH. Their goals and priorities are different."

The outlook for research funding is brighter than most investigators think, she adds.

"It's not a money problem. It's a data analysis problem — but FireFly is solving it." **M**

For more about FireFly, visit fireflybuzz.com.

The health innovation and entrepreneurship pathway leads students to create their niche

Nearly thirty years ago, life for Mahmoud Ghannoum, PhD, changed in an instant. Iraq invaded his country and his job at Kuwait University disappeared. War turned his quiet, orderly, academic world upside down propelling him to make tough choices for himself and his family. That twist of fate, however, became a fortuitous pathway leading to a successful academic and entrepreneurial career in the U.S.

Ghannoum is a professor of dermatology at Case Western Reserve University School of Medicine and director of medical mycology at University Hospitals Cleveland Medical Center. A serial entrepreneur, he and his son, Afif, launched Cleveland-based Biohm Health LLC, which produces a line of probiotics. And, most recently, Ghannoum has lent his entrepreneurial experience and inclination to train tomorrow's medical inventors.

Ghannoum helped create the medical school's Health Innovation and Entrepreneurship (HIE) Pathway in collaboration with the University's Weatherhead School of Management. The Pathway provides students with in-depth knowledge and focused experience to meet emerging specialties. Ghannoum and Joseph Jankowski, Chief Innovation Officer in the CWRU Office of Research and Technology Management, assembled an advisory board and designed the curriculum for the two-year program, which features a diverse, stellar lineup of speakers experienced in all facets of entrepreneurship.

In the past, medical schools did not require or emphasize business education or entrepreneurship. Ghannoum, who earned an executive MBA from CWRU in 2004, notes that business knowledge is crucial in today's rapidly changing health care landscape.

"We are going to give medical students the basis for entrepreneurship and innovation and networking opportunities," Ghannoum says. "Thirty percent of the students we have are not going to end up seeing patients. But even if they want to focus on treating patients, they must know how to run an efficient office," he explains.

Arming oneself with business knowledge is an advantage. Having a backup plan is essential. Ghannoum knows both these things firsthand.

Ghannoum has raised more than \$25 million in NIH funding and over \$20 million in venture capital for several successful

biotechnology companies over several decades. About ten years ago, he and a team of researchers took the idea of an antimicrobial catheter lock solution, designed to prevent urinary tract infections, from laboratory research to testing and then commercialization.

The HIE Pathway's inaugural cohort of ten first-year students began in September 2018. Each month a well-recognized business leader shares entrepreneurial perspectives on health care innovation, intellectual property, business strategy, venture capital, and other topics. In their second year, the students begin to apply what they have learned through assignments and summer internships. At the end of the Pathway, they face a Shark Tank-like experience where they present a health care-related entrepreneurial idea and business plan to their peers, funders, and established health care entrepreneurs, who provide feedback.

Ghannoum says the students will learn not every idea "takes," and that even good ideas fail. Through the lectures, they will hear not only about the successes, but how and why things went wrong and how the entrepreneurs kept going.

"As an entrepreneur, you fail more than you succeed. But when you learn from your failure, you can move forward and become successful," Ghannoum says. "By the end of the program, the students will not have MBA degrees, but they will know how to ask the right questions. An inquiring mind is key." **M**



Mahmoud Ghannoum, PhD

Honors and accolades

Selected items from August 2018 to June 2019

Honors

Keith Armitage, MD, professor, was awarded the Mastership in the American College of Physicians from American College of Physicians.

Jill Barnholtz-Sloan, PhD, professor, received the 2019 Faculty Distinguished Research Award from Case Western Reserve University.

Kath Bogie, PhD, associate professor, received the Best Overall Contribution to the Field Award from the National Pressure Ulcer Advisory Panel.

Brian Cobb, PhD, professor, received the John S. Diekhoff Award for Graduate Student Mentoring from Case Western Reserve University.

Monica Gerrek, PhD, assistant professor, received the J. Bruce Jackson, MD, Award for Excellence in Undergraduate Mentoring from Case Western Reserve University.

Mark Griswold, PhD, professor, was named a Siemens Inventor of the Year in the Open Innovation category.

Jonathan Haines, PhD, professor, received the 2019 Faculty Distinguished Research Award from Case Western Reserve University.

Clifford Harding, MD, PhD, professor, was named a Distinguished University Professor by Case Western Reserve University.

Insoo Hyun, PhD, professor, was named a Fellow of The Hastings Center.

Ahmad Khalifa, MD, PhD, research fellow, received the Dr. Mohamed Ghoneim Award for Young Urologists - Silver Medal from the Arab Association of Urology.

Anant Madabhushi, PhD, professor, was named a Fellow of the Institute of Electronics Engineers.

Heidi Moawad, MD, clinical assistant professor, was named Editor in Chief of Neurology Times.

Clare Rimnac, PhD, professor, was named a Distinguished University Professor by Case Western Reserve University.

Sharon Stein, MD, associate professor, was appointed President-Elect of the Association of Women Surgeons.

Nicole Ward, PhD, associate professor, received the Research Achievement Award in Psoriasis from the American Skin Association.

Grants

William Bush, PhD, associate professor, was awarded a \$1.2M grant from the National Institutes of Health and National Institute of General Medical Sciences.

Case Comprehensive Cancer Center was awarded \$8.9M from the National Cancer Institute.

Darcy Freedman, PhD, associate professor, received a \$936,418 grant from the Foundation for Food and Agriculture Research.

Sanjay Gupta, PhD, professor, received \$962,000 over three years from the Department of Defense.

Jonathan Haines, PhD, professor, received a \$14.6 million grant to be awarded over multiple years by the National Institute on Aging within the National Institutes of Health.

Alex Huang MD, PhD, professor, was awarded a three-year \$1.35 million grant from the St. Baldrick's Foundation and the Osteosarcoma Collaborative.

Alissa Huth-Bocks, PhD, professor, received a \$4.5 million grant from the National Institute for Child Health and Human Development within the National Institutes of Health.

Mukesh Jain, MD, professor, and colleagues were awarded a five-year \$6M grant from Foundation Leducq.

Gunnur Karakurt, PhD, associate professor, was awarded a four-year \$1.3M grant from the National Institutes of Health.

Ahmad Khalil, PhD, assistant professor, was awarded a five-year \$1.85M grant from the National Institutes of Health.

Jayne Knutson, PhD, associate professor, received a \$3.2M grant from the National Institutes of Health.

Tomoaki Ogino, PhD, assistant professor, received a \$1.8M grant from the National Institute of Allergy and Infectious Disease within the National Institutes of Health.

Parameswaran Ramakrishnan, PhD, assistant professor, received a \$440,000 grant from the National Institutes of Health.

John "Chip" Tilton, MD, associate professor, was awarded \$300,000 from the Dr. Ralph and Marian Falk Medical Research Trust.

Edward Yu, PhD, professor, received a \$3.34M grant from the National Institute of Allergy and Infectious Diseases within the National Institutes of Health.

Publications

Kumar Alagramam, PhD, associate professor, was senior author of "Unconventional secretory pathway activation restores hair cell mechanotransduction in an USH3A model," published in *Proceedings of the National Academy of Sciences*.

Sandip Basak, PhD, postdoctoral fellow, was lead author and **Sudha Chakrapani, PhD, associate professor**, was senior author of "Cryo-EM reveals two distinct serotonin-bound conformations of full-length 5-HT3A receptor," published in *Nature*.

Andrew Blum, MD, PhD, assistant professor, was lead author and **Kishore Guda, DVM, PhD, associate professor**, was senior author of "Systems Biology Analyses Show Hyperactivation of Transforming Growth Factor- and JNK Signaling Pathways in Esophageal Cancer," published in *Gastroenterology*.

David Buchner, PhD, assistant professor, was senior author of "Mutations in PIK3C2A cause syndromic short stature, skeletal abnormalities, and cataracts associated with ciliary dysfunction," published in *PLoS Genetics*.

Mark Chance, PhD, vice dean for research, and **David Lodowski, PhD, assistant professor**, were co-senior authors of "Assembly of a GPCR-G Protein Complex," published in *Cell*.

Mahmoud Ghannoum, PhD, professor, was senior author of "Effects of a Novel Probiotic Combination on Pathogenic Bacterial-Fungal Polymicrobial Biofilms," published in *mBio*.

Michael Greenberg, PhD, adjunct instructor, was lead author and **Menachem Shoham, PhD, associate professor**, was senior author of "Small-molecule AgrA inhibitors F12 and F19 act as antivirulence agents against Gram-positive pathogens," published in *Scientific Reports*.

Kishore Guda, DVM, PhD, associate professor, was senior author of "Systems Biology Analyses Show Hyperactivation of Transforming Growth Factor- and JNK Signaling Pathways in Esophageal Cancer," published in *Gastroenterology*.

Christopher King, MD, PhD, professor, was lead author and **James Kazura, MD, professor**, was senior author of "A Trial of a Triple-Drug Treatment for Lymphatic Filariasis," published in *New England Journal of Medicine*.

Siran Koroukian, PhD, associate professor, was senior author of "Access and Affordability in Low- to Middle-Income Individuals Insured Through Health Insurance Exchange Plans: Analysis of Statewide Data," published in the *Journal of General Internal Medicine*.

Zhonghua Liu, PhD, postdoctoral fellow, was lead author and **Tsan Sam Xiao, PhD, associate professor**, was corresponding author of "Crystal Structures of the Full-Length Murine and Human Gasdermin D Reveal Mechanisms of Autoinhibition, Lipid Binding, and Oligomerization," published in *Immunity*.

Anant Madabhushi, PhD, professor, and **Satish Viswanath, PhD, assistant professor**, were senior authors of "Multisite evaluation of radiomic feature reproducibility and discriminability for identifying peripheral zone prostate tumors on MRI," published in *Journal of Medical Imaging*.

Shigemi Matsuyama, DVM, PhD, associate professor, was senior author of "Epigenetic age is a cell intrinsic property in transplanted human hematopoietic cells," published in *Aging Cell*.

Krisztina Papp-Wallace, PhD, assistant professor, was lead author of "Ceftazidime-Avibactam in Combination With Fosfomycin: A Novel Therapeutic Strategy Against Multidrug-Resistant *Pseudomonas aeruginosa*," published in *The Journal of Infectious Diseases*.

Clara Pelfrey, PhD, associate professor, was an author of "Scope, Influence, and Interdisciplinary Collaboration: The Publication Portfolio of the NIH Clinical and Translational Science Awards (CTSA) Program From 2006 Through 2017," published in *Evaluation & the Health Professions*.

Joseph Rathkey, MSTP student, was lead author and **Derek Abbott, MD, PhD, professor**, was senior author of "Chemical disruption of the pyroptotic pore-forming protein gasdermin D inhibits inflammatory cell death and sepsis," published in *Science Immunology*.

Jacob Scott, MD, DPhil, clinical assistant professor, and **Robert Bonomo, MD, professor**, were co-authors of "Antibiotic collateral sensitivity is contingent on the repeatability of evolution," published in *Nature Communications*.

Xinglong Wang, PhD, associate professor, was lead author of "Mitofusin 2 regulates axonal transport of calpastatin to prevent neuromuscular synaptic elimination in skeletal muscles," published in *Cell Metabolism*.

Zerui Wang, MD, PhD candidate, was first author of "Early preclinical detection of prions in the skin of prion-infected animals," published in *Nature Communications*.

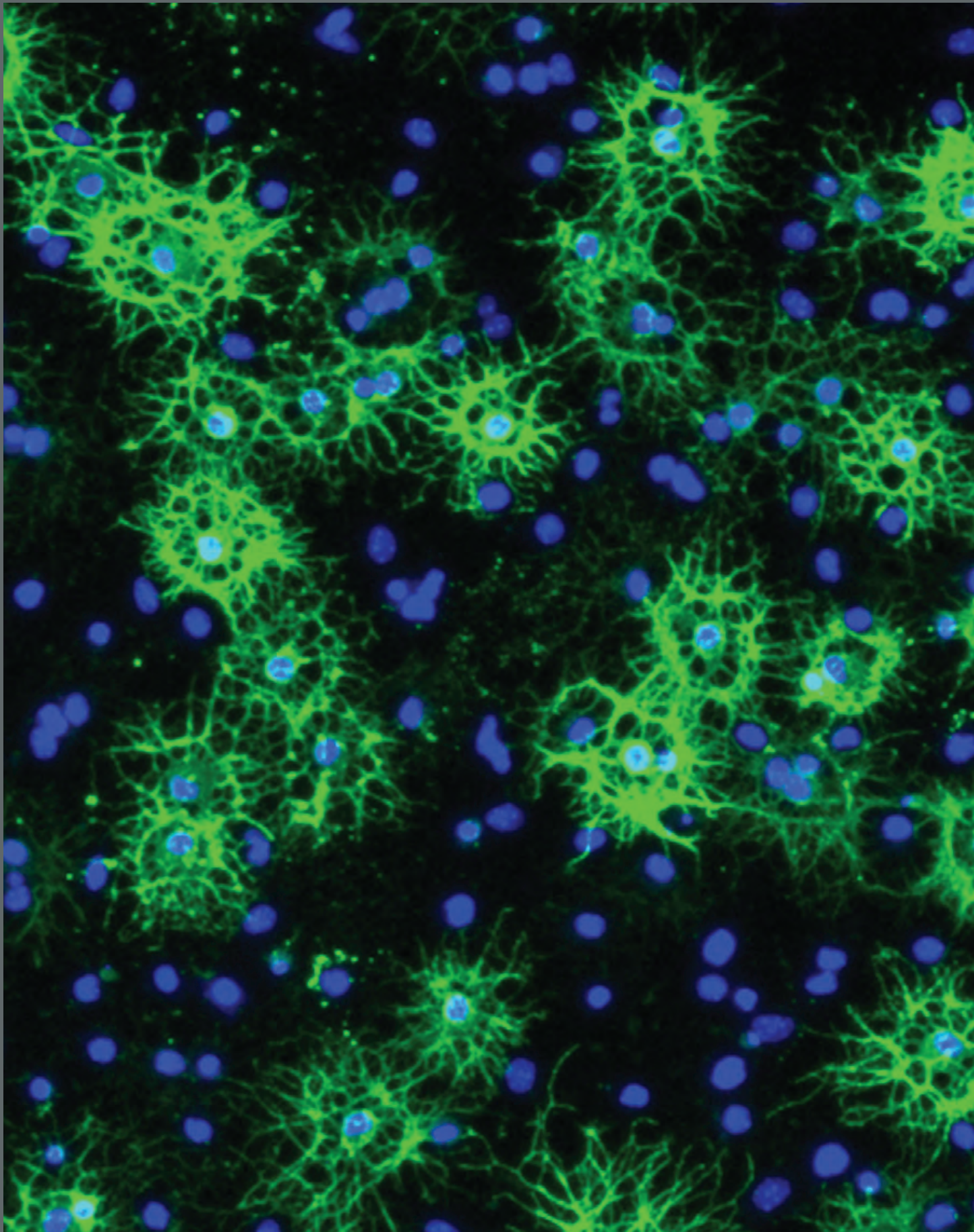
Sichun Yang, PhD, associate professor, was senior author of "Multidomain architecture of estrogen receptor reveals interfacial cross-talk between its DNA-binding and ligand-binding domains," published in *Nature Communications*.

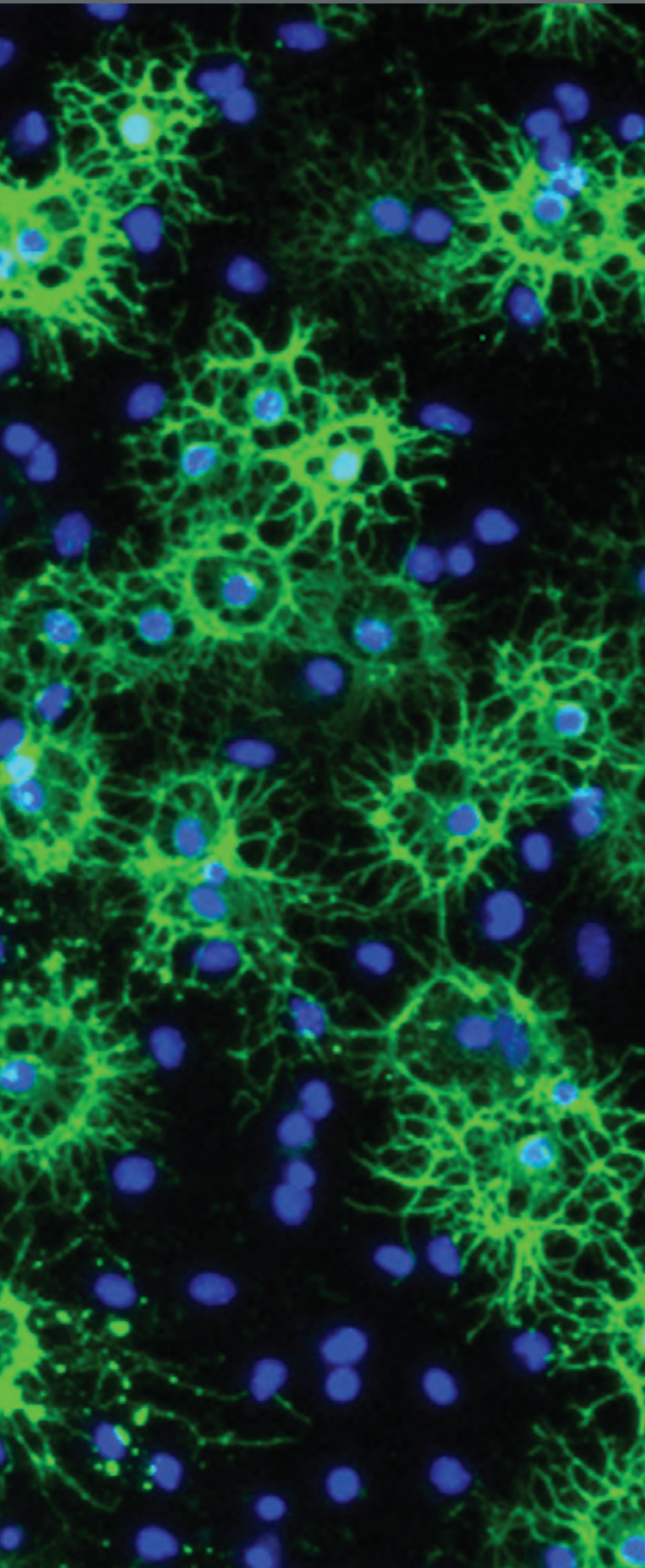
Stewart Youngner, MD, professor, and **Insoo Hyun, PhD, professor**, were co-authors of "Pig experiment challenges assumptions around brain damage in people," published in *Nature*.

Leah Zagore, PhD candidate, was lead author and **Donny Licatalosi, PhD, assistant professor**, was senior author of "DAZL Regulates Germ Cell Survival through a Network of PolyA-Proximal mRNA Interactions," published in *Cell Reports*.

Left brain | Right brain

The art of science





Birthing brain cells

Generating myelin-producing brain cells (oligodendrocytes) using new early stage medicines.

Credit: Ben Clayton, PhD,
Tesar Laboratory, CWRU
School of Medicine

School of Medicine
Office of Marketing and Communications
2109 Adelbert Road, Wood Building, G-37
Cleveland, Ohio 44106

Non-Profit
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