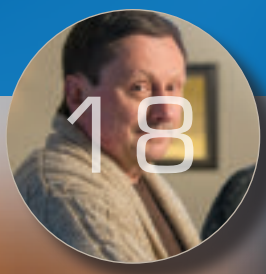
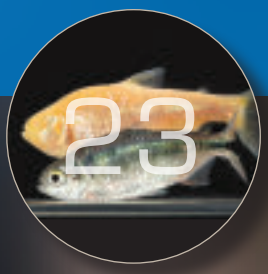
2 **FUNCTIONAL AMYLOIDS**
HOW MUCH-MALIGNED AMYLOIDS MAY BE THE KEY TO OUR MEMORIES

# STOWERS REPORT

NEWS AND INSIGHT FROM THE STOWERS INSTITUTE FOR MEDICAL RESEARCH 2020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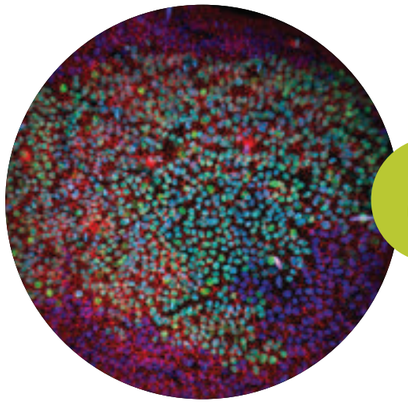





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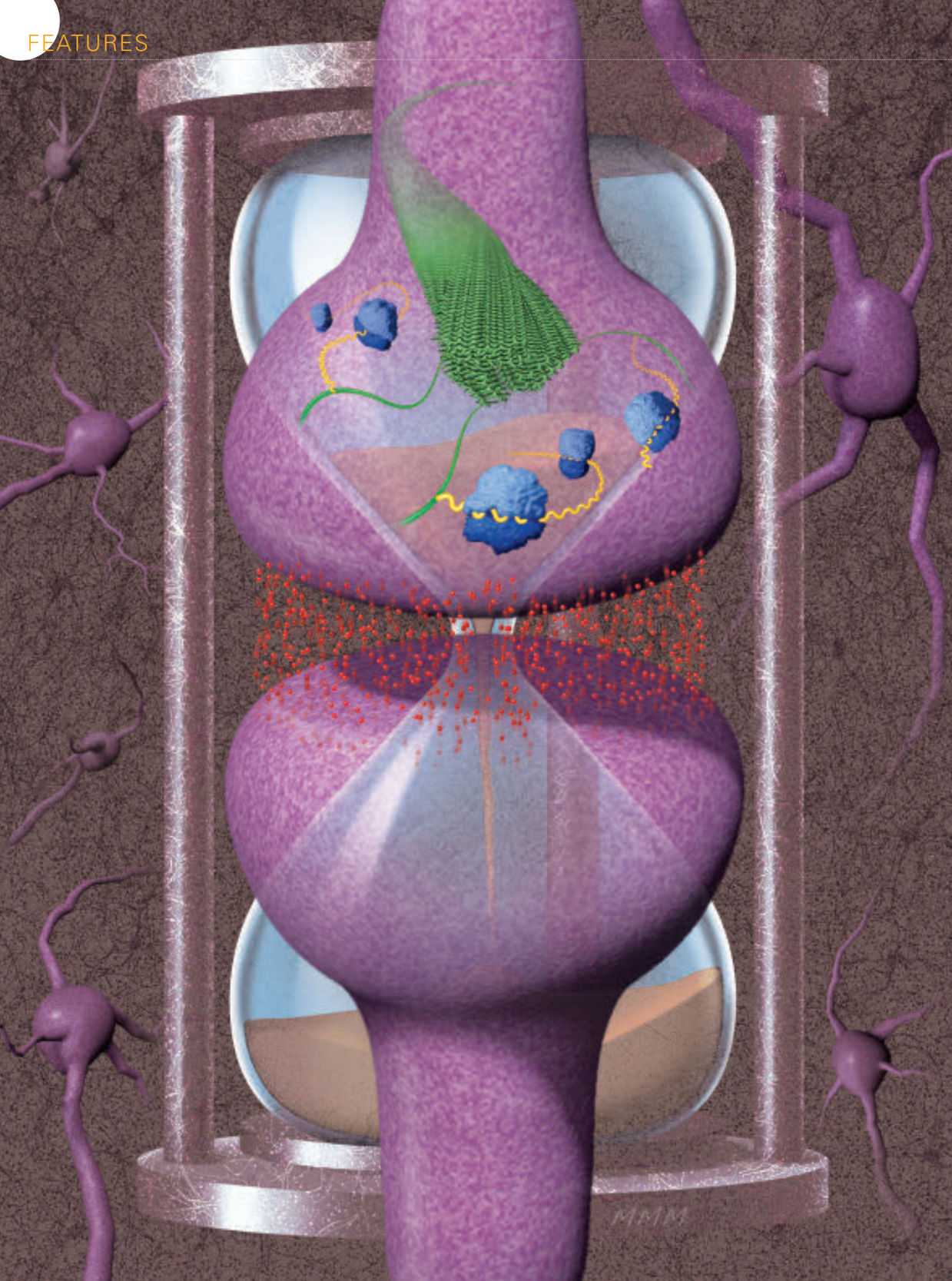


*By Melissa Fryman*

# Functional amyloids: A "magical" protein state

## How much-maligned amyloids may be the key to our memories

**Memory. For the majority of us, it is a constant companion, at times uninvited, and at others, cherished. Sometimes we strain to make and retain a fleeting memory, and at others, a memory seems nothing short of automatically installed, enduring a lifetime in our minds.**

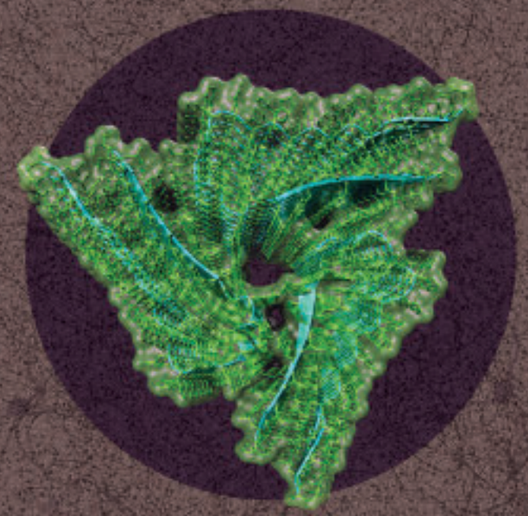
It's still mysterious, but the biological process that underlies memory persistence is better understood now than ever, thanks to researchers from the Si Lab at the Stowers Institute.

"In a general sense, memory is the ability of a system to experience something and then somehow maintain a signature of that experience, even after the experience has disappeared," explains Investigator and Associate Scientific Director Kausik Si, PhD. In many biological entities, this capacity is centered in the nervous system, and in particular at synapses, which are the connection points between nerve cells.

Indeed, it was work done on the sensory-motor neural circuit of the sea slug *Aplysia californica*, by Si and Eric Kandel, MD, at Columbia University nearly twenty years ago, that led to the initial surprising discovery about the molecular requirements for memory maintenance. Their discovery was twofold—an RNA-binding protein called CPEB (cytoplasmic polyadenylation element binding protein) is required for long-term synapse-specific modification, and in order to perform its full function in that capacity, CPEB has to self-assemble to form a functional protein aggregate that can self-renew, effectively acting like a prion.

Prions are self-renewing protein aggregates, often amyloid aggregates, that have a deservedly frightful reputation. Perhaps the best-known prion in relation to human health is an infectious prion, the hallmark of Creutzfeldt-Jakob disease, which can arise from a genetic origin, or via transmission from an animal, as in the human form of "mad cow" disease.

Amyloids are protein aggregates with characteristic structural features and have an equally bad reputation, being associated with such devastating neurodegenerative pathologies as Alzheimer's and Parkinson's diseases, as well as Lewy body dementia. "The central hypothesis is that the protein misfolds and forms an amyloid—either a smaller structure of repeating units or a larger assembly that forms a fibril or fiber—and that it's a toxic entity," says Si.



Of their original finding in *Aplysia*, "that a protein in the nervous system can aggregate in a very specific situation and can be a substrate of something that is stable yet dynamic such as memory—that's just completely counter to what people were describing," Si reflects. "Essentially the idea bumped into a hundred years of studies on protein aggregation and amyloids in the brain that suggested one possibility—and then our finding suggested something radically different."

Over the years, Si and his team have built a strong case for amyloids as a substrate for memory. They showed that CPEB proteins exist in the brains of mice and the fruit fly *Drosophila melanogaster*, where it is known as Orb2. Importantly, they found that as single units, Orb2 binds to specific protein-encoding mRNA messages, important for memory, located at synapses, acting to repress protein production. As an amyloid assembly, by contrast, Orb2 binds those mRNA messages at synapses and promotes production of those key synaptic proteins, leading to a persistent alternation in synaptic transmission that allows memory persistence.

Using memory assays, they have shown not only that self-aggregated Orb2 is required for long-term memory in adult fruit flies but also that already-formed memory is still dependent upon the Orb2 protein.

Most recently, Ruben Hervas, PhD, a postdoctoral researcher in the Si Lab, and collaborators determined the 3D structure of endogenous Orb2 aggregates from fruit fly heads, at near-atomic resolution. Using a technique called cryo-electron microscopy where low-temperature samples (such as small pieces of tissue or purified proteins) are imaged by electron microscopy, followed by computer-assisted reconstruction of the resulting images, they confirmed that, indeed, the state of Orb2 necessary for memory persistence is an amyloid. The implications are vast.

## A LONG HISTORY OF AMYLOID RESEARCH

The term "amyloid" first appeared in the scientific literature in 1838, when it was used to describe the amylaceous, or starch-like, makeup of plants that stained blue when exposed to iodine and sulphuric acid. It wasn't until 1854 that the term was popularized medically, by the "father of modern pathology" Rudolph Virchow, to describe small white deposits in the brain that stained blue the same way starch did.

"In some sense," says Si, "from inception, amyloids were associated with the wrong thing—the term was coined to describe something that was supposed to be starch-like, but now we know amyloids are made up of proteins."

The molecular definition of amyloid emerged from the work of biophysicist William Astbury, continues Si. "He saw that denatured, or unfolded, albumin protein could form fibers in a particular arrangement—layered zigzag-like structures called stacked β-sheets—with a standard distance between the stacked layers forming the β-sheets of 4.7 angstroms."

A complementary definition of amyloid was derived from the fact that plaques isolated from the brain could be stained with Thioflavin T and Congo Red dyes. "In the 1950s and '60s, Alan Cohen and colleagues connected the two. He isolated dye-stained material from the brain, looked at it under an electron microscope, and found that some of the material had similar fibrous appearance."

Researchers then found that amyloid plaques isolated from the brain were resistant to protein-destroying enzymes and detergents. "This led to the idea that the amyloid state is an unintended consequence of proteins being misfolded or unfolded, shortened, or otherwise degraded or mutated—and that once an amyloid forms, because it's so stable, it's an irreversible state that leads to disease. People of course got stuck on this."

## FUNCTIONAL AMYLOIDS HIT THE SCENE

"In the late 1980s and early 1990s, when yeast fungal prions were discovered, people saw that prions exist in other species, without killing them, and the aggregates of these prions fit the definition of amyloids. But these amyloids were not biochemically active," Si explains.

"Around 2000, researchers coined the term 'functional amyloid' because bacteria or fungi utilize the amyloid to do things—but the protein is not biochemically active. It's supporting and acting as a stable matrix that provides rigidity, or the ability to stick to things."

Together, the emergence of functional amyloids in yeast and bacteria suggested the possibility that amyloids could be non-pathogenic. But nobody had ever thought that amyloids could be the substrate of memory.

## "THEY THOUGHT I WAS OUT OF MY MIND"

"When I thought about it and talked to some people, they thought I was out of my mind. First of all, it's a prion in the nervous system. Secondly, if it's forming an amyloid in the nervous system, it cannot be doing anything good. Thirdly, people thought if amyloids are so stable, how can memory be reversible? After all, memory does change and seemingly disappear."

"I was trained as a physical chemist in India," Si recounts. "I wanted to switch fields and move to neuroscience, but nobody wanted to take me. So, I actually went to a meeting where I talked to Eric, and I convinced him that he should let me join his group."

"I was interested in a profound observation that Eric's group had made. They had discovered if you stop protein synthesis in the synapse, the synapse can still change but it cannot maintain that change over time."

"That finding suggested that the formation of memory and its subsequent maintenance have distinct requirements," Si continues. To study how memory sticks around, one must first understand how, and which proteins are made in the synapse.

"When I started out, I never thought it would lead me to prions and amyloids."

## "MAGICAL" PROTEIN STATE

That functional amyloids could exist in the nervous system "provided a very simple solution to one of the most complex biological processes," says Si. "Our findings suggested that a protein could be used like flipping a switch. By changing the conformation of a protein, the nervous system can encode information on to a stable, yet changeable, physical substrate to achieve something seemingly magical, such as memory."

"There was a time when people debated," says Si. "Are there magical genes or magical proteins that the nervous system utilizes to create memory? This discovery suggested there are not, but that instead, there are magical protein states."

## STUCK

The loss of memory can be tragic, and many biomedical efforts are underway toward treating or preventing devastating pathologies such as Alzheimer's disease and Lewy body dementia. The vast majority of potential therapies are designed to dissolve or prevent the formation of amyloids. Those that have progressed to phase 3 clinical trials have failed to cure memory loss.

"This would imply that the amyloid formation that we see in the nervous system sometimes either is an intended consequence, or, that the mere presence of amyloid is not bad even if its presence may indicate an undesired situation," says Si.

When I thought about it and talked to some people, they thought I was out of my mind. First of all, it's a prion in the nervous system. Secondly, if it's forming an amyloid in the nervous system, it cannot be doing anything good. Thirdly, people thought if amyloids are so stable, how can memory be reversible? After all, memory does change and seemingly disappear.

*– Kausik Si, PhD*

## SOLVING FOR THE STRUCTURE OF ORB2

"The very first time I talked with people at Columbia University—some of the most accomplished neurobiologists—they told me, 'Kausik, the day you solve the structure, come and talk to me.' They also warned me it wasn't going to be easy."

Fast-forward 20 years. In a study published in the March 13, 2020, issue of *Science,* Si and Hervas have done just that.

"We knew that the Orb2 protein can adopt multiple conformations," says Si. But, he explains, "often, researchers solve the structure of a protein where it is convenient to get as opposed to where it actually functions." By expressing a protein in bacteria, for example, "it might form an amyloid, but biochemically it does not function the same way it does in its native context." Thus, Hervas and Si agreed that although it would be much more difficult, using Orb2 from its original source to solve the structure would be the most meaningful way to proceed.

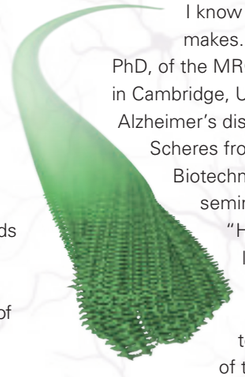
Because X-ray crystallography—a traditional method for determining protein structures—has limitations when applied to crystallizing large proteins in their native states, solving the structure with that method was unlikely, according to Hervas. And because they could harness the explosive improvements in imaging technology of recent years, they knew that cryo-EM could be the perfect tool.

## ENTER THE COLLABORATORS

"This was a really challenging problem, and it exemplifies what I view as the future of science, which is team science," says James Fitzpatrick, PhD, professor and scientific director of the Washington University Center for Cellular Imaging (WUCCI).

The work is a result of "people with backgrounds in different fields—computational biology, wet lab biology, neuroscience, physics, microscopy, and structural biology—coming together to do this kind of cryo-EM," says Fitzpatrick.

Leading up to the collaboration, WUCCI at the Washington University School of Medicine in St. Louis had acquired a powerful cryo-EM. Fitzpatrick recounts, "I felt it was important, as there weren't many of these instruments at all in the Midwest, and particularly in Missouri, that we should try to reach out and engage our regional community. I had gone to Stowers to give a seminar," Fitzpatrick added. "I love to visit Stowers—it's such fun."



Although Fitzpatrick studies pathological amyloids, he admits, "this is the first time I had heard the term 'functional amyloid.' Having spoken with Kausik, he had talked about functional amyloids, and he told me he was very interested in cryo-EM. Afterward, I did a bit of reading and I got really excited about this. I told him to send Ruben over for a visit."

After transporting themselves and their samples by car and train back and forth across the state, Hervas and members of the Si Lab, with the help of Fitzpatrick, developed a process to seamlessly prepare, transport, and then cryogenically freeze and image the samples using the machine at the WUCCI.

It was during this time, Fitzpatrick says, "a cryo-EM legend gave a talk at Stowers."

## THE LEGEND, THE MATCHMAKER

When Hervas told Eva Nogales, PhD, professor at the University of California, Berkeley, senior scientist at the Lawrence Berkeley National Laboratory, and Howard Hughes Medical Institute investigator, about his interest in using cryo-EM to solve the structure of the Orb2 amyloid, she said, "I know exactly the person to put you in touch with."

"There is an interesting Spanish connection," says Nogales. "I don't work with amyloids, but because I work on Tau protein when it is bound to microtubules, I know about the fibrillary tangles that Tau makes. Because of that, I know Sjors Scheres, PhD, of the MRC Laboratory of Molecular Biology in Cambridge, UK, and his work on Tau amyloids in Alzheimer's disease." Nogales adds that she knew Scheres from his time at the National Center for Biotechnology in Madrid, where she often gives seminars while she's there visiting friends.

"He speaks Spanish better than me," she laughs.

"Scheres developed a program that most of the cryo-EM community uses to process the raw data that comes out of the machine into the 3D density maps," says Fitzpatrick. "From those maps, we build the atomic-scale models. He's like the expert in amyloid helical reconstruction."

"Sjors is an absolute star. Lots of people want to collaborate with him," says Nogales, "but he can only spread himself so thin. In this case, I'm talking to Ruben, and I'm from Spain, and he's also from Spain, and we have this special connection. Plus, the project is super cool. It's easy to get excited about this work."

"I told him, because Sjors works on amyloids, he will know exactly how to process the samples. So I put them in touch, and then really quickly, they had determined the structure."

Being their matchmaker, Nogales says, "I actually found out before anyone else. They were complementary and they work well together. It's a happy story—I wish it worked out like this all the time!"

Kudos goes to Hervas, who had to screen hundreds of buffer solutions, as well as isolate a huge amount of ultra-pure Orb2 protein. "Ruben extracted protein from three million fruit fly heads. If that doesn't deserve some kind of award, I don't know what does!" exclaims Fitzpatrick.

"One of the things I deal with all the time is, for lack of a better phrase, 'crap in, crap out'—so if you have a bad sample, you're going to get bad data," says Fitzpatrick. That certainly was not the case here. "One of the reasons they had such a high-resolution structure is because the quality of the sample going in was just so pure, it was easy to track the fibrils."

"This is an example of people doing work that opens the mind to think of things in a new way," says Nogales. "I'm not a neurobiologist, but memories last much longer than the "lifetimes" of individual proteins. At a cellular and molecular level, how can that be?"

This work provides one possible solution to that question: That the form of Orb2 required for memory persistence is an amyloid, and that Orb2 amyloid has such slow turnover as well as the capacity to incorporate newly generated protein into that form, "not as a way of taking away functionality, but as a way of *creating* functionality—that's what I think is cool," says Nogales. "It's not a pathological state, it's just a functional state."

Another important question is—if amyloids are so stable under physiological conditions, how can memory be dynamic? One potential clue can be found in the central core of the amyloid structure. Unlike the hydrophobic, or water-repelling, core of pathogenic amyloids, the hydrophilic, or water-loving, core of Orb2 amyloids suggests how some neuronal amyloids could be a stable yet regulatable substrate of memory. The hydrophilic surfaces of the Orb2 amyloid fold could be susceptible to modification in a way that's fundamentally different than hydrophobic core amyloids. "From a structural point of view, that is also very cool," says Nogales.

## WHAT'S NEXT

The exploration of functional amyloids in neurobiology has only just begun. "Studying this problem has led us to areas of study that I never thought I'd be working in. Now we study gene splicing and protein chaperones, as well as how many shapes a protein can take and how." The Si Lab is also studying the molecular basis of forgetting. That is, does the dissolution of Orb2 amyloid dictate when a memory disappears? If so, does it just disintegrate, or is that process also tightly regulated?

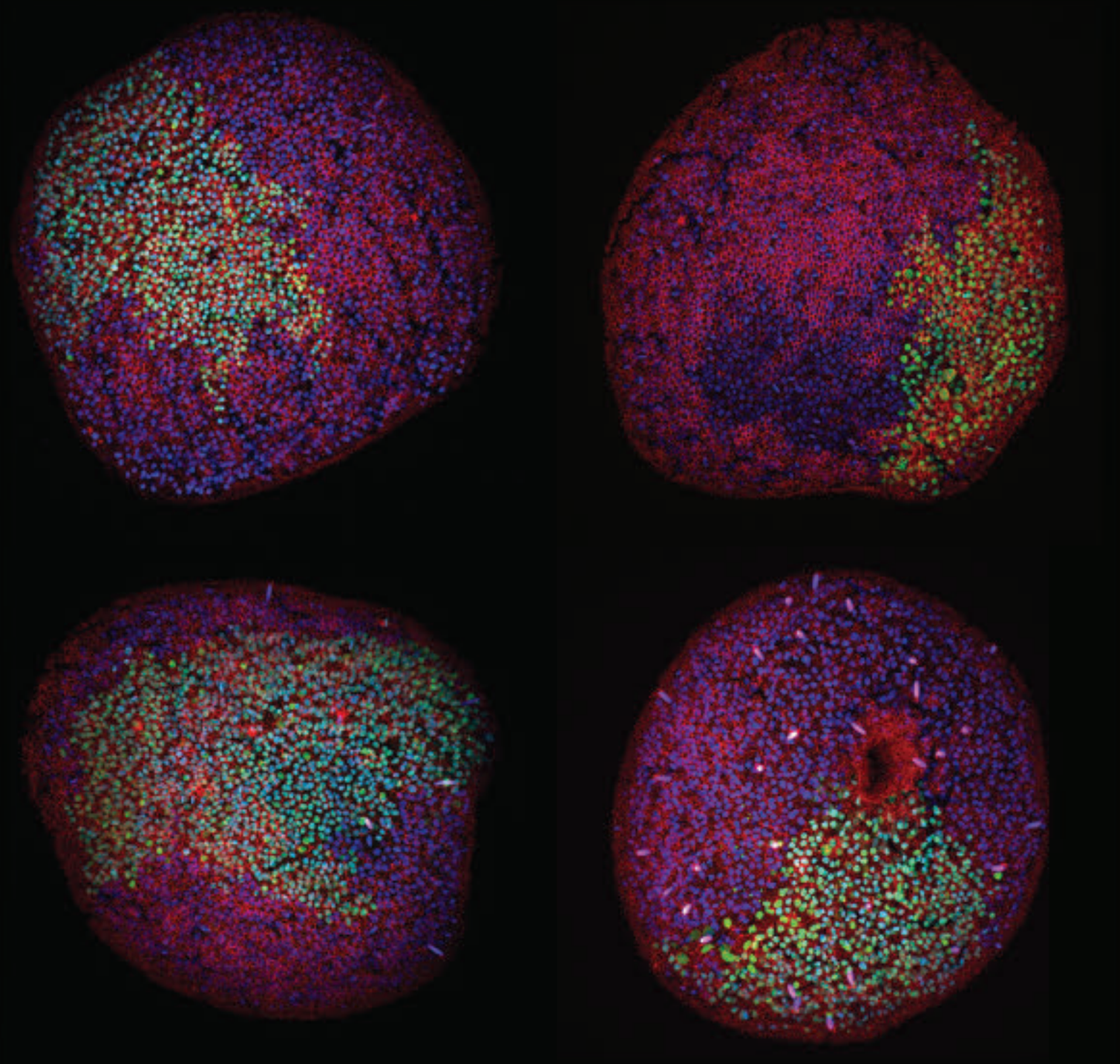
Among many other projects, the Si Lab is now working on a mouse model to test whether CPEB is required for long-term memory, and whether it also self-aggregates as an amyloid.

"The key question is moving this line of research from fruit flies to mice to humans," says Si. Although the possibility exists that something in the vertebrate or mammalian nervous system doesn't allow the use of functional amyloids as a mechanism of information storage, "it would be very hard to imagine that this process of memory, which has evolved to be utilized by so many biological organisms, is suddenly not utilized in humans."

Once again, proving it will not be trivial.

"The challenge is whether the methods that they developed for working in fruit flies—for extracting the purified protein—will be easily applied to human biopsy samples," says Fitzpatrick. "We have a lot of the data processing hurdles sorted out. I think once we get a good sample, we'll be able to generate data pretty quickly."

"Ultimately, it's science," says Si. "It's not what we think, it's what is. We'll keep working to figure out what's going on."



# WHEN SCIENCE MEETS ART

*By Marla Broadfoot*

Stowers Institute researchers explore the interplay between the scientific process and the artistic method as they endeavor to understand and describe the world around us.

When Julia Peloggia de Castro was working in a biochemistry lab as an undergrad at the University of São Paulo, her boss used to tape pages from Nikon's Small World calendar over every bench. One image featured a close-up of a bee eye dotted with dandelion pollen grains. Another highlighted individual nerve fibers in an array of pastel colors. Yet another zeroed in on a snowball of mold accumulating on an overripe tomato.

"I was always so fascinated by those images," says Peloggia de Castro. "I looked at them and thought, one day I want to do that. I want to be the person who takes an image that will inspire someone else."

Then in 2017, while interviewing for the PhD program of the Graduate School of the Stowers Institute, Peloggia de Castro received a colorful calendar showcasing winners of an Institute-wide scientific image competition. Her reaction? "Oh yeah." She promised herself that she would participate in the image competition every year, no matter what.

At Stowers, incorporating scientific images into an annual calendar is just one way to explore the intersection of science and art. By commissioning illustrations and artwork, supporting artists-in-residence, and creating library and art museum exhibits, the Institute is helping people see science through a different lens, celebrate its accomplishments, question its assumptions, and understand its impact.

These efforts ultimately demonstrate that scientists and artists are not all that different. Both seek to create something new, to better the understanding of life, and to depict some version of reality. Their work—regardless of whether it comes from a laboratory or a studio—shows that truth and beauty can coexist.

It does remind me of how we as scientists make discoveries. It involves a lot of practice, and trial and error. Sometimes accidents are made. Sometimes it turns out beautifully.

*– Robb Krumlauf, PhD*

## An homage to science

"Some people tend to picture scientists as white males in lab coats with pencils sticking out of their pockets who think about science all the time," says Robb Krumlauf, PhD, an investigator and scientific director emeritus at Stowers. "In fact, many scientists come from diverse backgrounds, and many scientists have diverse interests."

Krumlauf says that though he possesses no artistic skills himself, he has always appreciated art and has been friends with artists throughout his life. He loves to visit local galleries when he travels around the world to scientific conferences to present his groundbreaking work on developmental biology. In 2016, Krumlauf was elected to the National Academy of Sciences, considered to be one of the highest honors given to a scientist in the United States. To celebrate the occasion, his wife, Leanne Wiedemann, commissioned their friend and Kansas City artist Kathy Barnard to create a piece of stained-glass art.

For inspiration, Barnard visited Stowers, where she learned that Krumlauf's work is as philosophical as it is scientific. His research revolves around one central question—how can the creatures roaming this earth come in such a wide variety of sizes, shapes, and forms when their underlying genetic makeup is often so similar? Outwardly, fruit flies and humans could not seem more different. Yet they share a whopping 60% of their genomes. A mere 2.5% of DNA separates mice and men.

Krumlauf discovered that a set of genes called homeobox genes appear again and again in evolution, determining how the patterns of various tissues and structures unfold to give rise to each unique living and breathing organism. In fruit flies, mutations in these genes can create an extra pair of wings or prompt a leg to grow in place of an antenna. In mice, alterations in these genes can generate new pairs of ribs.

During Barnard's visit, she noticed a delicate little pen-and-ink drawing of a mouse with wings hanging on the wall of Krumlauf's office. The picture was a gift from Rosa Beddington, a friend and fellow scientist, who was inspired by Krumlauf's work to draw the fanciful creature.

"I knew I had to start with that mouse with wings," says Barnard, "but what else could I put in it? What kind of story could I tell in this piece of glass?"

Then Krumlauf explained to her that even though he began his research in mice, over the last several decades he had expanded his studies to include other experimental models like zebrafish, African frogs, and lamprey. In doing so, his studies have uncovered how the mechanisms controlling brain development differ between species, and how they can be disrupted in human diseases.

"I decided to incorporate all of these animals into the piece and have them interact to make the piece come alive," says Barnard. The resulting piece features some playful mice with wings, frogs, fish and a lamprey swimming in the pond, along with a few insects buzzing around the flowers of an echinacea plant. The borders are etched with patterns reminiscent of the nerves branching out of the brain region Krumlauf studies. At the top of the piece, a curious mouse peers into the scene below. "I included that element to bring you in," says Barnard. "You are that mouse, observing it all."

Early in the process, Krumlauf visited Barnard in her studio to observe the artist at work. He watched as Barnard employed chemistry, heat, and color to immortalize his model organisms in glass, using a technique she had honed over the years. "I loved seeing how she developed things, how it all came together," says Krumlauf. "It does remind me of how we as scientists make discoveries. It involves a lot of practice, and trial and error. Sometimes accidents are made. Sometimes it turns out beautifully."

Today, the stained-glass piece—which turned out beautifully—hangs in Krumlauf's office at Stowers. Sometimes, like when it catches the midafternoon light, Krumlauf says he finds it hard not to daydream. "To me it is a celebration of creativity and discovery for both art and science."

## Science simplified

While science often inspires art, as it did when Barnard etched a menagerie of model organisms into stained glass, art can also inform science. Such is the case with Darrick Hansen, a predoctoral researcher working in Linheng Li's lab at Stowers. Hansen has been studying adult stem cells that reside deep inside the gut, in millions of small pits or "crypts." These amazing regenerative cells respond to a multitude of signals from the environment and other cells in the crypt as they rebuild the entire lining of the gut, a feat they perform every few days.

"There ends up being so many players that using words alone to describe them starts to feel impossible," says Hansen. Li suggested that Hansen reach out to Mark Miller, a science and medical illustrator at Stowers, to create a visual depicting the "wild, wild West" of the intestinal stem cell niche. "Though there are lots of images out there already, they aren't very aesthetic," says Hansen. "And they don't give a good sense of what is going on in this complex structure."

The duo began meeting in 2017 to develop the illustration, which they wanted to serve as a living resource that could be built upon as knowledge grew. Miller started out with what was known about the structure historically, drawing upon histology and anatomical studies of the architecture of the niche. Then he brought in the new data Hansen had gathered about the types of cells that had been discovered lurking in the specialized space.

As Miller reconstructed the scene, it became clear where gaps in his own knowledge—and sometimes that of the field—remained. He began peppering Hansen with questions. How big is this cell type? How far away is it from that structure? Where are the blood vessels? "Some of these questions might be considered ignorant, but I needed to answer them to create the illustration, as it's really difficult to draw what you don't understand."

*Darrick Hansen*

*Mark Miller*

Hansen says those questions forced him to look at the data in greater detail, and to question some of the assumptions in the field. "When you are always talking to the same people, you assume certain things," he says. "But then when someone from the outside asks a question, you say, wait a second, is there data to support that? Or is that just something that we pass down anecdotally or a term that we've used incorrectly all this time?"

After nearly two and a half years of back-and-forth discussions, the team developed an illustration that is complex, brightly colored, and, not surprisingly, difficult to put into words. At first glance, the looping, invaginated forms of the crypts might resemble a roller coaster running on a network of circuits embedded underneath. But with closer inspection, the interactions between 15 different types of cell types begin to emerge.

Hansen says his conversations with Miller have helped him grow as a scientist. He says he is no longer afraid to ask questions or to risk appearing stupid in his quest for the truth. “I think presumed knowledge causes far more problems in science today than ignorance does,” he says.

Though the illustration has not been published yet, Hansen has shared it with other members of the NIH-funded Intestinal Stem Cell Consortium, of which the Li Lab is a member. He says, while several researchers have commented about learning something new, a couple have pointed out something they thought was wrong.

“I said no, that’s right,” says Hansen. “Look at the data.”

## Worth a thousand words

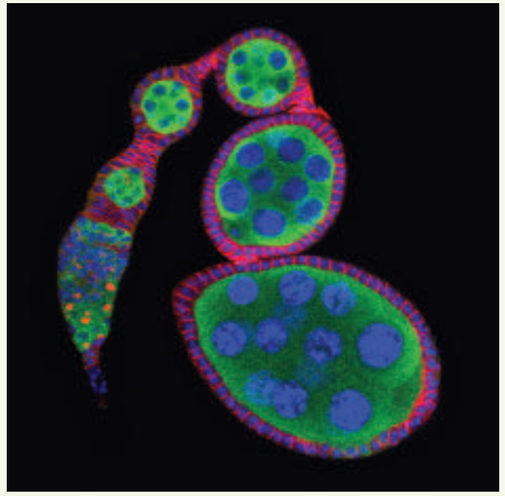
While scientific images convey valuable data to researchers, their simple beauty can sometimes transcend the information they contain and transform them into objects of art. Once a year, Crossroads, an organization of postdocs, students, and staff scientists, asks researchers to enter their best photographs, data visualizations, and videos into a scientific image competition held as part of the annual Young Investigator Science Retreat (YISR).

“We set up Crossroads to help advance the careers of young scientists, to help them develop the soft skills they need to succeed,” says Krumlauf, who oversaw the program when he was Institute director. “But one of the things we discovered when talking with trainees was how proud they were of the data coming off their microscopes or the drawings they created on their computers. You would see their work framed in their offices or posted in the hallways.”

Krumlauf decided to compile Stowers researchers’ most visually appealing work in one place, by showcasing the YISR images in its “Images of Discovery” calendar. The calendar features not only photographs but also intricate illustrations and data visualizations created by trainees to communicate their science. “It’s the whole idea of a picture being worth a thousand words,” he says.

One image, reminiscent of a busy map of airport hubs, actually depicts a constellation network of gene expression in Mexican cavefish and surface fish. Another that looks like orange and yellow pinwheels is in fact a series of rose plots representing the number of Stowers-affiliated publications per month over the course of four years.

Stowers Predoc Peloggia de Castro made it into last year’s calendar with an image that features four bright red and blue balls of cells covered in smatterings of green, showing the starlet sea anemone at early stages of



development. When she traveled home to São Paulo, she took a handful of copies of the calendar with her to share with her grandmas. The calendar not only gave them bragging rights but also served as a conversation piece for her to talk to people in her community about science.

“My family loves it,” she says. “They don’t understand anything that is written there, but they always leave that month up all year long. When anyone came to visit the house, they would see the picture and I would explain to them what I do. It makes me really happy because it helps me connect with people who are not scientists.”

## In the eye of the beholder

Microscopists Jay Unruh, PhD, and Brian Slaughter, PhD, both grew up on farms in the heartland, where the houses were far apart and there were no scientists as far as the eye could see. Yet they both loved science, and visited their neighborhood libraries to pick up fun facts about biology and physics or pore over biographies of famous inventors. Today, as co-directors of the Stowers Microscopy Center, they help organize events at local Kansas City libraries to expose the public to science and the scientists that conduct it.

“We were raised in communities that didn’t necessarily know or trust scientists,” says Slaughter. “We think it is important for the public and scientists to interact as much as possible, and we use art as a way to do that.”

For the “Beauty of Biology” exhibit, the pair curated some of the Institute’s most eye-catching images—many winners of the image competition—and printed them onto large sheets of high-gloss metal. They then arranged the images into a series, first depicting whole organisms, then parts of organisms, and finally cells and structures that are invisible to the naked eye. Unruh said the exhibit was designed to draw people in, to wonder and to ask questions about the meaning underlying the beauty.

Dani Wellemeyer, head of outreach and community engagement at the Miller Nichols Library at the University of Missouri-Kansas City (UMKC), recalls being captivated by the larger-than-life views of biology afforded by the traveling exhibit. Her favorite image depicted the ovaries of a fruit fly as a cobblestone path of green blobs, each outlined with red and blue hatch marks and filled with bubbles of blue material. Wellemeyer was not the only one picking favorites; people often asked her if they could buy copies of the images to take home with them.

In addition to the Miller Nichols Library, the exhibit has made the rounds to four community libraries, each for several weeks to a few months at a time. At most of the libraries, “show-and-tell” receptions were held, featuring Stowers research trainees to work microscopes they brought for the occasion or to answer questions from the attendees.

“The big questions that we always try to prepare our students for are ‘Why do you care about what happens in a flatworm or a sea anemone or a mouse? How does this relate to human health?,’” says Unruh. “I think those are hard questions for students to answer, but they are important.”

Through the process, the organizers found that they often disagreed with members of the public about what was beautiful about the works on display. One time, they heard some people commenting on the juxtaposition of vibrant reds, yellows, and greens in a particular image, and all Unruh and Slaughter could see were the underlying scientific ideas that it portrayed.

“We’re thinking about the cool processes of science that are represented here, that we don’t completely understand,” says Slaughter. “And we can think of all the fun experiments we’d like to try to understand them. We think it is beautiful, but from a different perspective.”

## Bridging disciplines

Science prizes objectivity, while art works to the opposite effect. Still, both can tickle the intellect and stir the emotions. Labeling science and art as separate entities belies the fact that these two drivers of human innovation have been intertwined for centuries, in the mind’s eye as well as on the world stage. The epitome of this interplay is the Renaissance artist and scientist Leonardo da Vinci, whose studies of anatomy and physiology brought the Mona Lisa to life.

Steph Nowotarski, PhD, a postdoc in Alejandro Sánchez Alvarado’s lab at Stowers, considers herself to be both an artist and a scientist. She went to college planning to double major in her two loves but quickly found there were not enough hours in the day for her to spend in the lab training to be a scientist and to spend in the studio training to be an artist. “As society accumulates knowledge at an exponential rate, we are asking people to learn things very quickly, and so you have to stay in your lane to keep up,” she says.

Though Nowotarski made what she considered the pragmatic choice to stay in the science lane, she kept looking for opportunities to veer into art. One day she met Mol Mir, a student at the time at the Kansas City Art Institute (KCAI) who was touring Stowers with classmates. Mir asked an insightful question about how the detector worked on the high-powered microscope Nowotarski was using. That question led to a conversation about how Mir’s art focused on generating 3D renderings of cells, a technique Nowotarski had just begun to explore for her own work on the planarian flatworm. That summer, Mir joined the Sanchez lab as Stowers’ first art intern, later staying on as a lab assistant.

*Mol Mir*

"The science that I do mostly involves looking at electron micrographs of planaria and building models off of them," says Mir. "So my art is constantly inspired by what I am seeing every day."

Mir and Nowotarski teamed up with retired KCAI fiber chair Jason Pollen and recent KCAI graduate William Plummer to launch an immersive art exhibit inspired by planaria, a model organism made famous by its regenerative properties. The team met once a week to brainstorm ideas and play around with different mediums and experiences, all exploring what the minuscule aquatic creatures could teach us about being human.

The exhibit, which was displayed at the UMKC Gallery of Art from January through early March 2020, took viewers through two separate rooms—one dark, one light. The dark room explored the concept of observation, the first step in any scientific or artistic process. Viewers strolled past giant projections of planaria, blown up hundreds of times their actual size. They saw photos of the arrow-shaped flatworm cut into pieces, alongside photos after these pieces morphed into full-sized clones. They were captivated by the 16-minute video A Drawn Line, in which the animals undulated and moved with perfect symmetry, as if trapped in a kaleidoscope.

In the second room, people were treated to wall-to-wall canvases featuring interpretive works of art by Mir, Nowotarski, Pollen, and Plummer. Each of these static paintings evoked a sense of movement, either by a maze, a mass of overlapping circles, or an elaborate mandala. In the center of the room, a single pendant light hung over three cylindrical tanks displaying the planaria. The tanks were perched on a table crafted in the shape of a planaria cut into three pieces, left over from Mir's thesis project. The room had plenty of space for people to interact and interpret the artwork, and peer at the animals with magnifying glasses, marveling at how small they were in real life.

"Science and art can both have a lot of jargon. I was excited to see scientists asking questions about art, and artists asking about science," says Nowotarski. She said the experience taught her there are many ways to communicate one's place in the world. And to remember to tap the same creativity she channels through her art to fuel her pursuit of science.

## Truth and beauty

Science and art both take creativity, curiosity, and persistence. These seemingly disparate disciplines emphasize the importance of observation and interpretation, often leading to big ideas that force us to shift our worldview. It is hard to imagine where we would be today without the knowledge gained by science or the inspiration gained by the arts.

Peloggia de Castro, who has spent two years working as a predoctoral researcher in Tatjana Piotrowski's lab, hopes to have a lab of her own one day. But she worries if that will be possible, given the ever-shrinking number of tenure-track academic jobs available. On bad days, when the failures that are a regular part of the scientific process get her down, she waits until everyone has left before firing up the microscope to take beautiful pictures.

There, she takes close-ups of phenomena most of us will never see, much less appreciate. The tiny heart of a growing zebrafish, whose body is almost entirely transparent. The migration of a hundred specialized cells from the head of that remarkable organism all the way to the tip of its tail. The "zebrabow," whose cells light up with the colors of the rainbow.

After a couple of hours lost in that hidden world, Peloggia de Castro remembers why she went into science. "Life is beautiful," she says. "This is beautiful. This is what I fell in love with."



*By Anissa Anderson Orr*

# New osteoporosis advance rooted in Stowers research

**Pioneering research from the laboratory of Stowers Investigator Robb Krumlauf, PhD, helped lay the groundwork for a new approach to treating osteoporosis—an often debilitating disease that affects millions of people worldwide.**

Osteoporosis thins out and weakens bones, making them more prone to breaking. About 10 million people in the United States have osteoporosis, and postmenopausal women with the disease are particularly susceptible to fractures, which can be life-altering events leading to the loss of mobility.

While standard treatments help stave off bone loss, they don't replace lost bone. The new drug romosozumab, approved by the US Food and Drug Administration in January 2019 and developed by Amgen in collaboration with the Belgian biopharmaceutical company UCB, is the first drug that promotes bone growth. The injectable monoclonal antibody, sold under the brand name Evenity, works by blocking a protein, sclerostin, that inhibits the buildup of bone.

This new treatment for osteoporosis was made possible in part by an unexpected discovery made by Stowers researchers nearly two decades ago. The researchers uncovered a mechanism that controls bone growth. Krumlauf and former lab member Debra Ellies, PhD, published the work, which the Institute also patented. The intellectual property was licensed to Amgen in 2005.

## FOUNDATIONAL RESEARCH PAVED WAY FOR NEW DRUG

The discovery that guided the development of romosozumab arose out of basic research into Hox genes, which play a key role in the formation of body structures, including bones.

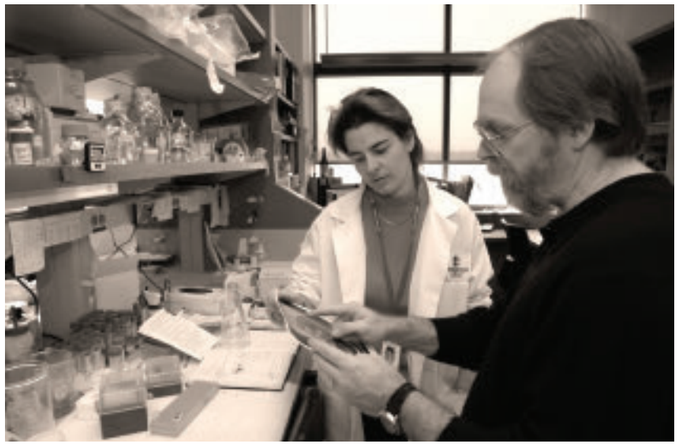
In the early 2000s, Krumlauf's team identified a specific signaling pathway that regulates Hox genes and found that the same pathway also controls the buildup of bone. The researchers discovered a protein related to sclerostin, called Wise, and showed that both proteins inhibit the Wnt signaling pathway by binding to co-receptors on the surface of cells. This finding was unexpected because work on related molecules suggested that they were likely to block a different pathway.

Over the next decade, the lab conducted experiments to deepen their understanding of how Wise and sclerostin controlled bone loss. They knew they were on the right track when a mouse model they developed that lacked the gene for Wise had much stronger bones than mice with functional copies of the gene.

"That was the 'Aha!' moment for us. The Wnt signaling pathway looked like it was playing a really critical role in laying down new bone. We thought this could be a really important discovery," Krumlauf says.

In addition to Krumlauf's research, scientists from other institutions had spent decades studying Afrikaner patients who had bones that didn't break. This condition caused health problems ranging from overgrown skulls, deafness, and severe headaches to fingers that fused together. In 2001, the scientists reported that these effects resulted from a single gene mutation that blocked expression of sclerostin.





*In a photo from 2003, Robb Krumlauf and Debra Ellies were captured discussing their Hox gene research.*

According to Krumlauf, Wise is important for laying down new bone during early development while sclerostin is important for laying down bone in adults. Findings about both of these related proteins have been instrumental in understanding how the body builds bone.

## STOWERS ENABLES FINDINGS THAT STIMULATE MEDICAL ADVANCES

Krumlauf says Stowers' support was critical for translating his findings from a laboratory discovery to a potentially life-changing therapy for osteoporosis. With the freedom to pursue foundational research and follow the new directions it might take instead of focusing on a narrow line of study, his lab made an unexpected discovery that has great potential for improving human health.

The Institute also leveraged its relationship with BioMed Valley Discoveries, a discovery development organization co-founded by Jim and Virginia Stowers, to shepherd the discovery through the patenting and licensing process, which can be time-consuming and expensive for researchers to handle on their own.

"What I'm proud of is that the Institute helped us protect our discovery and understand its value. The BioMed Valley Discoveries team found a way to guide it to the right people, with interests in developing and using it, and now we're on the threshold of it being able to make a difference in human health," Krumlauf says.

Amgen spent the next decade conducting additional preclinical studies and human clinical trials to take Krumlauf's discovery and others' findings about bone growth to the next level. Romosozumab is an antibody that mimics the mutation found in the Afrikaner patients by blocking sclerostin from binding to its receptor.

The FDA based its approval of Evenity on the results of two Phase 3 clinical trials, which showed a significant reduction of fractures. One year of treatment with the drug lowered the risk of new spinal fracture by 73% compared to placebo. The drug also increased bone density in the spines of study participants by around 15%, which is significant and similar to spurts of growth in adolescence.

The approval of Evenity represents the first new drug aided by research from Stowers and reinforces the Institute's core belief that unexpected connections resulting from basic research have practical benefits in supporting the development of new medicines and therapies. Krumlauf and Ellies did not seek to study osteoporosis when they were trying to understand the mechanism by which sclerostin acted. Their fundamental studies led to unexpected insights into how a potential treatment for osteoporosis could work.

In addition to Krumlauf and Ellies, the research was assisted by former Stowers researcher Youngwook Ahn, PhD. Contributors from other institutions included Nobue Itasaki, PhD, at MRC National Institute for Medical Research UK, and Scott Saunders, MD, PhD, at Washington University Medical School. The Krumlauf Lab continues to investigate how the pathway that controls bone buildup may potentially affect other organs and tissues.

The approval of Evenity represents the first new drug aided by research from Stowers and reinforces the Institute's core belief that unexpected connections resulting from basic research have practical benefits in supporting the development of new medicines and therapies.

# RON CONAWAY, PHD

By Cathy Yarbrough

Ron Conaway, PhD, taught himself calculus when he was a high school student in his hometown of Sidney, Montana. "My teachers did not know calculus," says Conaway. So Conaway's parents, who were bookkeepers, drove their son to Billings, Montana—a four-hour trip each way—to purchase books about calculus and the other subjects that fascinated him.

"When I was growing up, I also wanted to learn more about chemistry, physics, and philosophy. Even then I was interested in thinking about solving problems," he says.

Conaway's study of calculus often led to questions for which answers were not readily available. The internet didn't exist then. "Nowadays students can find answers to their questions by turning on a computer and searching online," he says. But Conaway had to wait until he arrived at Indiana University (IU), where he found "a whole new world, including an extensive library and people who could answer my questions."

Conaway earned a BA degree in physics and chemistry at IU and was one course short of also obtaining a bachelor's degree in philosophy. While a freshman, he decided to pursue a career in biomedical research. Because his mother had died from cancer, Conaway considered studying the biological processes disrupted in the disease.

"Oncogenes had not yet been discovered," Conaway explains. "However, it was known that cancer cells had different phenotypes, or observable features, that had something to do with DNA replication and transcription." During transcription, a gene's DNA instructions for a specific protein are transcribed into a format (messenger RNA, or mRNA) that can be "read" by the cell's protein manufacturing machinery.

To gain experience in biomedical research, Conaway interned in the laboratory of IU Professor of Chemistry John P. Richardson, PhD, who was searching for the mechanism by which the Rho factor enzyme terminated transcription in bacterial cells. "Although I didn't make a major contribution, the research was a blast because it was like detective work," he recalls.

Although he enjoyed the research, Conaway felt that something was missing from the experience. The Rho factor had been identified many years before Richardson investigated its role in transcription. "I decided that it would be more fun to conduct mechanistic experiments on a new enzyme activity that I had helped to discover," he says.

During their careers, Conaway and his research partner and spouse, Joan Weliky Conaway, PhD, who he met when they were graduate students at Stanford University and who also is a Stowers investigator, discovered and determined the mechanisms of action of numerous molecules that influence transcription. "Joan and I have been able to do this enough times to keep me really happy," he jokes. And indeed, that productivity has resulted in over 180 co-authored scientific papers.

**WHAT DID YOU ENJOY MOST ABOUT GROWING UP IN SIDNEY, MONTANA?**

Only in retrospect, when I was at IU, did I realize that I had liked living in Sidney because my family and I knew everyone there including the ranchers and farmers in the area. During my first months as a freshman at IU, I was anxious because I had never lived any place with so many people. On campus, I would walk by people whom I would never see again. That was a new experience for me.

**SOME SCIENTISTS REGARDED YOUR AND JOAN CONAWAY'S DECISION TO WORK TOGETHER AS UNUSUAL. BUT YOU DO NOT. WHY?**

Where I grew up, it was very common for a husband and wife to work together. Many of the ranches and farms were operated jointly by married couples. When Joan and I began working together over thirty years ago, there were not that many married couples in science.

With one exception, we've held equal positions and shared the same lab. After completing our postdoctoral studies, I was briefly a faculty member in the chemistry department at the University of Texas at Austin. Joan was a research associate and did not apply for a faculty position. We left about a year later to join the Oklahoma Medical Research Foundation, where we each had a faculty position but shared one lab. We've had a similar situation at Stowers.

**YOU HAVE WITNESSED AND CONTRIBUTED TO THE DEVELOPMENT OF STOWERS INTO ONE OF THE NATION'S LEADING BIOMEDICAL RESEARCH INSTITUTES. WHY HAS STOWERS SUCCEEDED?**

I see the reasons for the Stowers Institute's success starting with Jim Stowers Jr., who not only conceived of the Institute but also paid for it. Jim was a great judge of character, which partly explains why he was able to start with virtually nothing and build American Century Investments into a successful and thriving asset management firm. He hired good people to staff the company.

Jim also picked good people to build the Institute. One of Jim's brilliant decisions was to hire Bill Neaves, PhD, the first president of Stowers, and Robb Krumlauf, PhD, the first scientific director. They were extraordinary leaders who provided a foundation of research excellence. As a result, Stowers has been a great place to conduct research.

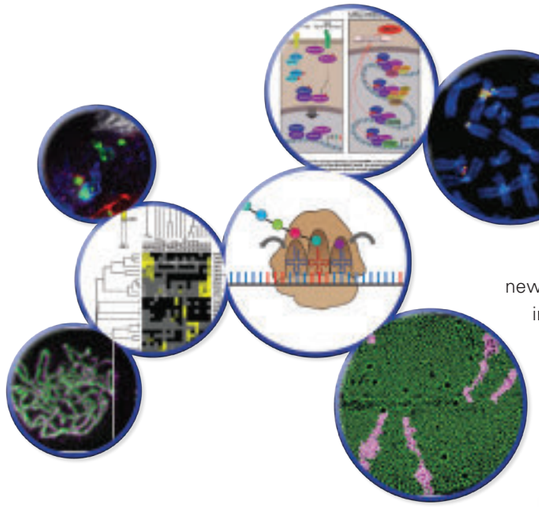
**YOU AND JOAN PLAN TO RETIRE IN 2021. WHAT ARE YOUR PLANS?**

We likely will stay in Kansas City. However, we've been so focused on our predocs and postdocs that we've not decided what we'll be doing after we retire. Joan and I have been helping our trainees finish their research projects and training and then line up their next position so that they will have the best chances of having a happy and productive future in science.

**WHAT WILL YOU MISS MOST ABOUT CONDUCTING RESEARCH?**

When I was growing up, I liked thinking about chemistry, physics, and math, but it was not satisfying because I could not test my ideas in a lab. As a scientist, I have been able to talk about research problems with other people in the lab and conduct experiments to determine whether my ideas were correct. I'll likely miss that.

# RESEARCH ROUNDUP



While 2019 may seem a distant memory, it is worthwhile to reflect on the scientific progress that Stowers scientists made that year because the very nature of research at Stowers is one that builds upon itself. Each new bit of discovery adds a piece to the puzzles that our scientists are trying to solve, but also adds to the larger collection of knowledge that advances our understanding of the complicated processes of life.

In 2019, our researchers produced seventy-four original research papers as well as thirty-four review papers, commentaries, and book chapters.

Included in the discoveries of this impressive body of work are findings from the Li Lab that indicate a way in which blood-forming adult stem cells, despite being sensitive to DNA damage, manage to repopulate blood cells after chemotherapy or injury has depleted their numbers, which advances the understanding of blood-forming adult stem cell biology and may open new avenues for treating blood diseases like leukemia and autoimmune disorders.

The Washburn team created a topological scoring (TopS) algorithm, which allows scientists to look at big sets of data in new ways that may help them uncover more details about how proteins interact and understand more precisely how certain activities on the cellular level happen. They also discovered new details about several proteins implicated in cancer that suggest treatments targeting these proteins, which are present in more than 85% of breast cancer tumors, may help by reducing or stopping tumor growth.

The Bazzini Lab found ribosomes play an active role in regulating mRNAs—the messages that ribosomes read to make proteins. Understanding the regulatory function of ribosomes in modulating gene expression in human cells can provide insight about causes of gene misregulation, which can sometimes lead to human diseases.

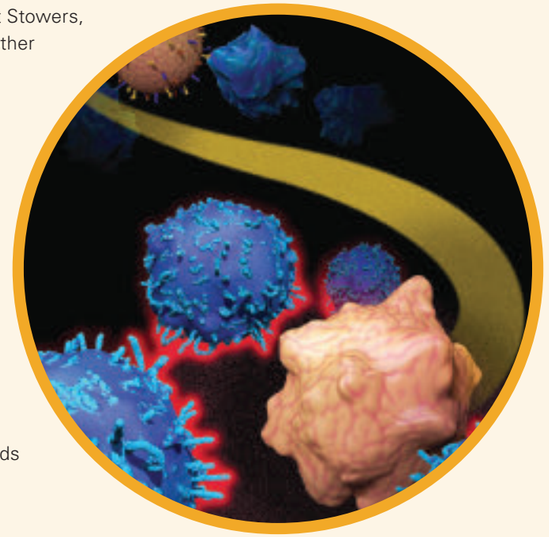
Research from the Gerton Lab solved a mystery to a half-century-old observation of connections between particular human chromosomes by uncovering how the chromosomal connections might be built. This discovery provides clues about the origins of chromosomal fusions associated with infertility and developmental disorders in humans.

The Gibson Lab team highlighted the importance of uniform cell size in maintaining the architecture of epithelial sheets. They showed that small epithelial cells can dissociate from each other and disperse among normal cells. They are continuing to explore whether abnormally small cells may have a role in disease initiation or progression, such as in tumorigenesis.

And the Hawley Lab reported the importance of the structure of a large protein complex called the synaptonemal complex in the process of meiosis, a special kind of cell division that gives rise to reproductive cells. This finding may help further researchers' understanding of the causes of human miscarriage.



## WHAT'S OLD IS NEW AGAIN



Evolving from studies in the lab of Linheng Li, PhD, researchers at Stowers, Children's Mercy, The University of Kansas Cancer Center, and other institutions reported on a promising new strategy to overcome drug resistance in leukemia, using targeted doses of the widely used chemotherapy drug doxorubicin.

The researchers found that low doses of doxorubicin, a standard treatment for several types of cancer including leukemia, inhibits two molecular pathways, Wnt/beta-catenin and PI3K/Akt, which work closely together to promote tumor growth and resistance to therapy. The team also found that low-dose but not high-dose doxorubicin activated anticancer immunity against therapy-resistant leukemia stem cells, an unexpected and novel discovery. The research holds promise as a more effective strategy to overcome cancer therapy resistance and stimulate immunity that can be used in combination with other cancer therapies including chemotherapy, radiation, and immunotherapy for patients with leukemia and other types of cancer. Low-dose doxorubicin also avoids the harsh side effects of high-dose doxorubicin, potentially offering patients a better quality of life.

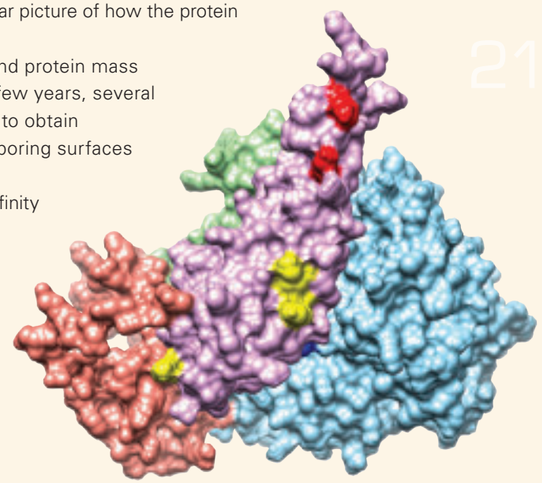
*This study was first published online April 20, 2020, in* Nature Cell Biology.

## TECHNOLOGIES CONVERGE

Sin3/HDAC is a large multiprotein complex that is normally responsible for "turning off" a specific set of genes that, when mutated, is also implicated in cancers like triple negative breast cancer and pancreatic cancer. Although Sin3/HDAC components have been well-studied, getting a clear picture of how the protein complex subunits assemble has been difficult.

Michael Washburn, PhD, and his lab have long used proteomics and protein mass spectrometry to study complexes in protein networks. Over the last few years, several technologies have improved and, when combined, allow researchers to obtain unambiguous information regarding the spatial arrangement of neighboring surfaces within multiprotein complexes.

Recently his team described the use of three existing approaches—affinity tag protein purification, chemical crosslinking with high-resolution mass spectrometry, and computational molecular modeling with protein docking—to pinpoint specific surfaces, within the intact protein complex, that are in very close proximity to each other. These capabilities can be further combined with other powerful techniques such as cryogenic electron microscopy to provide an even higher-resolution picture of the interactions at interfacing surfaces within intact protein complexes.



*This research was published online April 14, 2020, in the journal* Cell Reports.

# SURVIVAL OF THE FIT-ISH

The Zanders Lab recently provided surprising insight into meiotic drivers and how they can be suppressed that could help researchers better understand the forces that shape the evolution of gamete formation, as well as those underlying human infertility.

In a study led by Sarah Zanders, PhD, her team describes a strategy that the *S. pombe* fission yeast genome can use to mitigate some of the worst effects conferred by parasitic gene elements known as meiotic drivers.

The meiotic drivers analyzed are able to short-circuit the conventional law of Mendelian segregation, which usually ensures that each gamete (reproductive cell) receives one of two copies of each chromosome from the parent cell with equal transmission. Meiotic drivers instead can poison gametes that do not contain their genetic sequence, thereby swinging the transmission rate in their favor.

As a way of enabling the survival of some gametes that would otherwise die, the *S. pombe* genome can employ variants of other genes to create a situation that "protects" them, even if it comes at a cost to fitness. For example, a mutation in *rec12*, a gene responsible for proper chromosome segregation, can lead to gametes having extra chromosomes. While extra chromosomes are usually undesirable, in this scenario they actually enable more gametes to survive.

*This study was published online August 13, 2020, in* eLife.

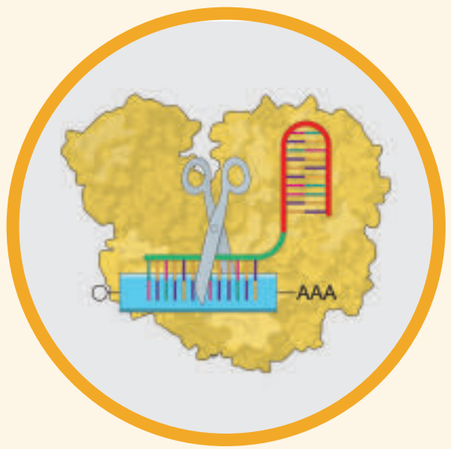
# CAVEFISH PROVIDE IMMUNITY INSIGHT

Similar to people, cavefish live in an environment with a reduced number of parasites. Unlike people, however, cavefish have had much more time—about 150,000 years—to adapt to these conditions. To learn more about how a low-parasite environment may shape the evolution of a host's immune system, researchers from the laboratory of Nicolas Rohner, PhD, and collaborators examined the impact of decreased parasite abundance and infection on the evolution of the cavefish immune system.

The study characterized the cavefish immune system and how it responds to threats, compared to that of closely related river fish from a parasite-rich environment. Their findings show that cavefish differ in their sensitivity toward immune stimulants and have a different composition of immune cells, including a reduction of the immune cells that play a role in inflammation. In future studies, the scientists hope to identify genetic factors involved in cavefish immune system evolution that could provide clues about the development of immune system disorders and potentially human autoimmune diseases, where the immune system attacks its own body.

*This report was published online July 20, 2020, in* Nature Ecology & Evolution.






# CRISPR KNOCKDOWN

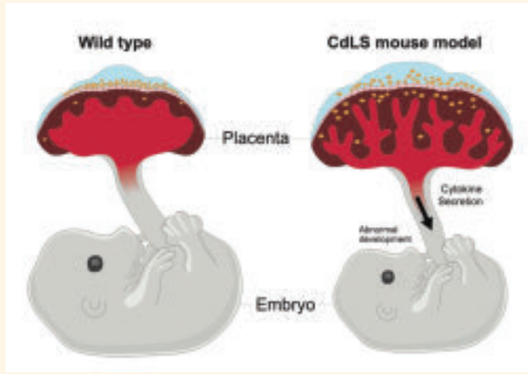
CRISPR is a gene-editing tool that has enabled researchers to study the function of different genes in model organisms. Scientists have now harnessed this powerful technology to target gene messages in animal model embryos to gain a better understanding of the genetic programs that direct early stages of vertebrate development.

The Stowers team, led by Assistant Investigator Ariel Bazzini, PhD, and their collaborators show that the technology, called CRISPR-Cas13, is able to target RNA—DNA's chemical cousin that carries messages needed to construct proteins—in embryonic animal models in a specific and systematic manner, allowing researchers to study the role of RNA in the earliest hours of development. The researchers show that the CRISPR-Cas13 method is effective in zebrafish, killifish, medaka, and mouse embryos, and thus could be used to explore early developmental genetic programs in a broad range of animal species.

*This work was first featured online in* Developmental Cell, *August 7, 2020.*

# PERSISTENT DNA DAMAGE AND PREGNANCY OUTCOMES

Cohesins are ringlike proteins that are essential for chromosome segregation, gene expression, and repair of DNA damage. Mutations that affect these proteins cause the human developmental disorder Cornelia de Lange syndrome. Jennifer Gerton, PhD, and her team describe a detailed study of the placentas of mouse models of the syndrome.



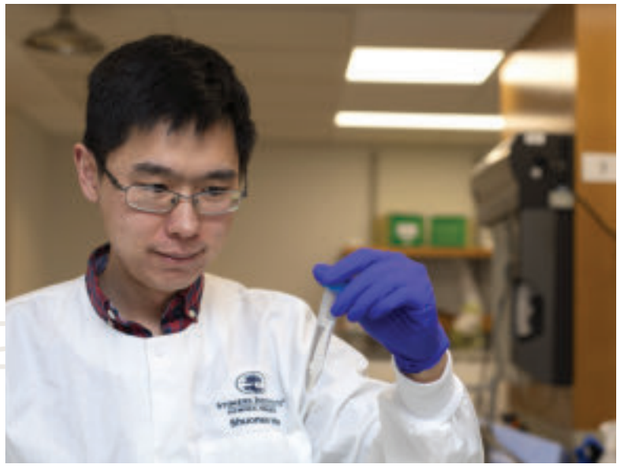

They discovered that the Cornelia de Lange mouse model placentas accumulated damage to their DNA, entered a permanent growth-arrested state known as senescence, and churned out pro-inflammatory cytokines that affected the growth of the embryonic mice. These findings have important implications for understanding the crucial role that the placenta plays in mammalian development.

*This study was published in the June 16, 2020, issue of* Developmental Cell.

Shuonan He

# FINDING EVOLUTIONARY BIOLOGY IN THE WEIRD

*By Jen A. Miller*



Shuonan He has a simple explanation for why he studies sea anemones: they're weird. "When I started to get into biology in college, I looked for unusual animals or the ones that people don't know much about," he says.

His fascination paid off. In 2014, he became a predoctoral researcher at the Graduate School of the Stowers Institute, studying just that "weird" animal. In 2018, he was the first author on a paper published in *Science* about how Hox genes, already well-known for their roles in the formation of bodies of bilaterally symmetrical animals, are important regulators of the body plans of radially symmetrical animals like sea anemones.

"The sea anemone has the perfect system for studying evolutionary biology. I fell in love with the system first and then that question of 'how do Hox genes work here?' became the most obvious avenue to pursue," he says.

Sea anemones weren't the first animal to fascinate him, though. Shuonan started out studying zebrafish, working in a zebrafish laboratory at the Peking University in Beijing while an undergraduate student.

He learned about the Stowers Institute when Alejandro Sánchez Alvarado, PhD, scientific director of the Stowers Institute, gave a presentation there about sea anemone regeneration.

"Sea anemones seemed way more interesting than zebrafish," he says, "and I wanted to be where I could study them." He realized that place was the Stowers Institute only three days before the Graduate School's application deadline. "I read a lot in those three days to help enhance my application to the program and show I wasn't completely off base," he quips.

He had his heart set on studying sea anemones, and after the usual Grad School lab rotations, he joined the Gibson Lab to do just that. "The discovery of Hox genes is one of the first major milestones in the development and the advancement of modern development biology," he says. "We've been able to start picturing development as a process that can be modulated and understood in a series of events that's precisely regulated by genes."

The Hox family of genes is also special because it spans so far across the evolutionary tree of life. "Hox genes play that crucial role in the development of fruit flies all the way to humans. It's a super deep evolutionary root that we've discovered," he muses.

Even though Kansas City is the only place he's lived in in the U.S., He said he enjoys the size, scope, and vibe here. "It's a pretty peaceful, quiet city, which is what I wanted," he says. When not unearthing the secrets of evolutionary biology in "weird" animals, he says he spends much of his free time cooking and walking his girlfriend's dog, Sticker, a six-year-old Chihuahua mix of indeterminate origin. "She's a super cute and scrappy dog," he shares.

He is taking a long-term view of his future career in terms of what he wants to study, and what that research will contribute to scientific knowledge overall. "Right now, as part of my graduate research, we're trying to push the field more toward the era of genomics." After that, He sees himself homing further in on evolutionary biology, in whatever animal he finds most fascinating at the time. "Hopefully I can find something equally cool or even more fascinating than the sea anemone," he says. "I'm pretty sure the sea anemone is not the only species that we can find some cool biology in."

He hasn't forgotten an important lesson learned in that first zebrafish laboratory, either. In 2013, a fire at Peking University all but destroyed the lab. After watching the fire online and getting over the shock of what happened, he and his fellow lab mates worked together to reconstruct the lab and re-establish lost zebrafish lines.

"It was a huge setback at the time, but in the long term, it has shown me it's possible to overcome unexpected and sometimes devastating events in research," he says.

Despite the fire, in 2014 as an undergraduate, he was the first author on a paper published in *Nature Communications* about how zebrafish can regrow lost heart tissue while mammals cannot.

Maybe he'd have done that research without having to re-establish the zebrafish lines, maybe not. "It's like they say—it's 99% hard work, but you really need that 1% luck sometimes."

> Hopefully I can find something equally cool or even more fascinating than the sea anemone. I'm pretty sure the sea anemone is not the only species that we can find some cool biology in.
>
> *– Shuonan He*

# POSTDOCS NAB NIH FUNDING

Two postdoctoral researchers received notice of an F32 fellowship from the National Institutes of Health in 2020. The F32, or the Ruth L. Kirschstein Postdoctoral Individual National Research Service Award, provides up to three years of funding to enhance the research training of promising postdoctoral candidates.

Joseph Varberg, PhD, postdoc in the Jaspersen Lab, received support for his research on the nuclear pore complex in fission yeast from the National Institute of General Medical Sciences. Nuclear pore complexes (NPCs) span the inner and outer nuclear membranes of cells and are the gatekeepers that regulate the movement of proteins and RNA across the nuclear envelope. Varberg aims to define the mechanisms that control NPC assembly and to determine how distinct populations are established and maintained. This work may provide insight into cancers that originate from changes in the number and function of NPCs.

Piotrowski Lab Postdoc Jeremy Sandler, PhD, received his F32 award from the National Institute on Deafness and Other Communication Disorders. His project will focus on studying the gene regulatory network underlying sensory hair cell regeneration in zebrafish. He will study the genetic interactions and processes that regulate genes involved in the regeneration response, in order to learn about why hair cells in the inner ear of mammals do not regenerate. This research could provide clues to eventually help restore hearing.

# TRAINEES RECOGNIZED WITH FUNDING

The beginning of 2020 brought funding announcements for three trainees. University of Kansas Medical Center PhD student Jianzheng Wu was awarded the Mabel A. Woodyard Fellowship in Neurodegenerative Disorders from the KUMC Institute for Neurological Discoveries. This competitive award provided $30,000 for one year of support for research geared toward understanding, preventing, and curing Progressive Supranuclear Palsy and related neurodegenerative disorders. Wu is conducting his research in the Halfmann Lab.

Natasha Shylo, PhD, a postdoctoral researcher in the Trainor Lab, received the Emerging Research Organisms grant from the Society for Developmental Biology. The one-time award will help support her research on early development of veiled chameleons, specifically how they develop left and right sides.

At the end of January, former GSSIMR predoctoral researcher Cassandra Kempf received a Travel Stipend Award from the US Human Proteome Organization, a scientific organization that encourages the use of proteomics technologies and the dissemination of knowledge pertaining to the human proteome and that of model organisms. Kempf's work focuses on identifying direct interactions in the Sin3/HDAC protein interaction network using biochemical approaches and quantitative imaging.

# NIH K99 FUNDS AWARDED TO TWO HAWLEY LAB POSTDOCS

The Hawley Lab has seen two postdoctoral researchers receive prestigious Pathway to Independence (K99/R00) fellowships from the National Institutes of Health recently. This five-year award is designed to support researchers as they transition from postdoctoral researcher roles into independent research positions.

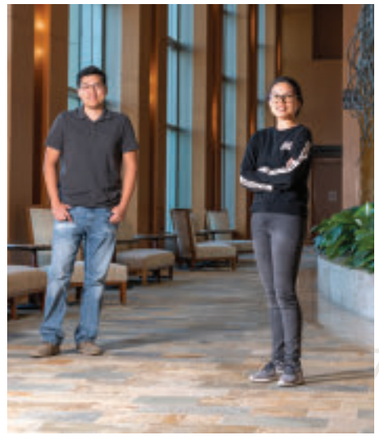
Stacey Hanlon, PhD, received her award from the Eunice Kennedy Shriver National Institute of Child Health and Human Development for her research of small supernumerary marker chromosomes (sSMCs). sSMCs are structurally abnormal chromosomes that can result in infertility and intellectual and developmental disabilities. Hanlon seeks to define the mechanisms of sSMC disruptions during complex developmental processes. However, this requires an effective model system that does not currently exist. Hanlon plans to develop this model in fruit flies so that she can probe the dynamics and formation of these chromosomes.

Katie Billmyre, PhD, was awarded her fellowship from the National Institute of General Medical Sciences. Billmyre's study will investigate the molecular and cell biological mechanisms behind chromosome-specific recombination events in the fruit fly, which will provide insight into the proper segregation of chromosomes during meiosis in higher organisms. Her work has the potential to identify the importance of chromosome structure in meiotic chromosome behaviors, which has implications for infertility. Billmyre also received a 2019 DeLill Nasser Award for Professional Development in Genetics from the Genetics Society of America.

# TWO GSSIMR PREDOCS RECEIVE TRANSITION FUNDING

In late summer of 2020, two Stowers predoctoral researchers were awarded prestigious fellowships from the National Institutes of Health. The NIH Predoctoral to Postdoctoral Fellow Transition Award (F99/K00) provides two years of funding for predoctoral research, with four years' additional support for a postdoctoral position.

For Qiushuang Wu, a member of the Bazzini Lab, the fellowship will support her research on post-transcriptional regulation, specifically downstream open reading frames (dORFs). dORF represents a new, strong, and universal translation regulatory mechanism in vertebrates. This research could support the possible clinical impact of dORFs to detect and treat cancer, providing new diagnostic regions of the mRNA as potential targets for drug design.



In the Halfmann Lab, Alejandro Rodríguez Gama is studying the role of protein self-assembly in the innate immune system. Aging in humans leads to a chronic inflammatory state, known as inflammaging, which increases the risk for age-related diseases such as type 2 diabetes, atherosclerosis, and Alzheimer's disease. Results of this research could advance our understanding of aging and potentially illuminate new opportunities to combat age- and disease-associated autoinflammation.

# Zanders named one of ten 'scientists to watch'

Assistant Investigator Sarah Zanders, PhD, has been named to *Science News*' 2020 SN 10: Scientists to Watch list. She is one of ten early- to mid-career researchers recognized for having already made big contributions in their fields.

Zanders joined the Stowers Institute in 2016 and shortly thereafter was awarded an R00 grant from the NIGMS, the second phase of the NIH Pathway to Independence Award. Since then, she has been named a Basil O'Connor Scholar and a Searle Scholar. She also received an NIH New Innovator Award in 2018. She was named Vice Dean of the Graduate School of the Stowers Institute in 2019.

Zanders' research focuses on selfish genes in gametogenesis, a process that gives rise to reproductive cells such as eggs and sperm. By studying the *wtf* family of meiotic drive genes in the fission yeast *Schizosaccharomyces pombe*, Zanders and her lab aim to uncover the self-survival strategies used by *wtf* genes and explore how they have affected genome evolution.

Now in its sixth year, this award recognizes young stars, all age forty and under, in scientific research who have proved their potential for much greater impact in the years to come. Each of the SN 10 was nominated by a Nobel laureate, member of the National Academy of Sciences, or SN 10 alumni.

# Banner year for Halfmann

Assistant Investigator Randal Halfmann, PhD, was the recipient of two grants in 2020. Effective in January, Halfmann received a grant from the NIH National Institute of General Medical Sciences. This award, spread over four years, provides $1.2 million for his project titled "Elucidating mechanisms of amyloid nucleation in vivo."

This research looks closely at amyloids, protein aggregates that influence both physiological and pathological processes, including cellular memories and differentiation on one hand, and aging and neurodegeneration on the other. Results from this work could offer insight into how the kinetics of amyloid assembly influences the time scales of those processes. With that goal in mind, Halfmann is focusing on the first step of amyloid formation, nucleation, and has developed cell-based tools to analyze nucleation data. His results could reveal critical mechanisms of nucleation in living cells, and ultimately yield a deeper understanding of, and possibly new therapeutic options for, age-related and neurodegenerative diseases.

Also in January, the American Cancer Society awarded him a Research Scholar Grant, providing $700,000 over four years to support his project on the role of protein aggregation in cancer-promoting inflammation.

To grow and divide quickly, cancer cells upregulate the process of protein production called translation. This increases the chances that newly produced proteins will aggregate with each other, leading to changes in their activity. Cancer cells also persistently turn on a program called inflammation, which helps them grow even faster and evade signals to self-destruct. Exactly how they do this, and whether that decision is related to protein aggregation, is unclear. Halfmann's study aims to uncover the biological mechanism for how translation rate controls these proteins' aggregation, as well as determine if the aggregates themselves can cause inflammation and some of the associated changes that facilitate cancer progression. This research could lead to a fuller understanding of cancer progression, which may in turn reveal new vulnerabilities of cancer that can be treated therapeutically.

Additionally, in April the Stowers Scientific Advisory Board recommended Halfmann be promoted to Associate Investigator, effective January 2021.

# New NIH funding

Two Stowers investigators were awarded five-year grants from the National Institutes of Health (NIH) in 2019. Investigator Ting Xie, PhD, received a $1.7 million grant from the Eunice Kennedy Shriver National Institute of Child Health & Human Development. More recently, Investigator Linheng Li was awarded $2 million from the National Institute of Diabetes and Digestive and Kidney Diseases.

The aim of Xie's project is to investigate how niche-mediated interactions control stem cell lineage differentiation. Stem cells have the ability to continuously self-renew and produce differentiated progeny. The mechanisms controlling stem cell lineage differentiation are critical for using stem cells in treating human diseases, such as Parkinson's, Alzheimer's, and diabetes. Xie's team will use fruit fly germline stem cells (GSCs) to gain a better understanding of how the cellular microenvironment controls differentiation. The knowledge gained from this study could provide critical information for treating human degenerative diseases, alleviating cancer, and promoting healthy aging.

Li's study also involves the niche, though his research centers on the mouse intestinal system to study stem cell development. Many intestinal disorders are due to defects in intestinal stem cells or progenitor cells, or to misdirected signals provided by the niche. This research into defining the essential niche components, and the associated signals that direct these stem and progenitor cells to proliferate and differentiate, could be an important step toward treating intestinal disorders with regenerative medicine. Li, who joined the Institute in 2000, was renewed as Investigator at the 2020 meeting of the Stowers Scientific Advisory Board.

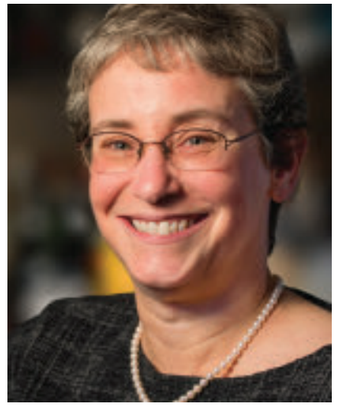
# Additional NIH funding

Two Stowers investigators with ongoing grants from the National Institutes of Health (NIH) were awarded additional funding in 2020. The National Institute of Mental Health renewed a grant for Investigator and Associate Scientific Director Kausik Si, PhD, while Investigator Ron Yu, PhD, received a one-year supplement for his NIH R01 grant from the National Institute on Deafness and Other Communication Disorders.

The renewal for Si extends funding for another five years to support his research on long-term memory in the adult brain. Si's research uses the fruit fly to look at intron retention (IR), which is believed to modulate gene expression. Si's prior research has suggested that the nervous system utilizes IR to control expression of proteins that are important for formation and stabilization of long-term memory. This project could shed insight on the functional relevance of IR in memory, and could be an important step toward understanding how IR in the adult nervous system can be employed to integrate environmental and internal cues to govern protein expression, synaptic function, and memory.

For Yu, the extension allows him to expand his project on the mechanisms of developmental plasticity in the mammalian olfactory system to include studying the function of proteins APP and AB42. AB42 has been associated with Alzheimer's disease pathology and neuronal death in Alzheimer's patients, and problems with the sense of smell are one of the earliest manifestations of the disease. Using the mouse olfactory system to examine the pathways that process and interact with APP could increase understanding of the molecular and cellular bases of Alzheimer's disease.

# Joan Conaway elected to National Academy of Sciences



Joan W. Conaway, PhD, a Stowers investigator since 2001, was elected a member of the prestigious National Academy of Sciences (NAS) for her distinguished and continuing achievements in original scientific research. The recognition reflects the exceptional productivity and impact of the research program co-led by Conaway and her lifelong collaborator and husband, Ron Conaway, PhD, also a Stowers investigator.

Through their thirty-year scientific partnership, the Conaways have significantly advanced scientific understanding of one of life's most fundamental processes—how information encoded in the DNA of our genome is transcribed into a blueprint that is then used to make proteins involved in virtually every biological process. The Conaways' discoveries have shed new light on the molecular mechanisms of transcriptional regulation—the complicated biological process that transcribes a gene's DNA instructions for a specific protein into a format (messenger RNA, or mRNA) that can be interpreted by the cell's protein manufacturing machinery. In addition to revealing how gene transcription occurs at the molecular level, the Conaways' research has highlighted some of the steps in the process which, when disrupted, can play a role in cancer and other diseases.

Conaway was awarded an AB degree in chemistry and biology from Bryn Mawr College and completed her PhD in cell biology at Stanford University School of Medicine. Prior to joining Stowers, Conaway was interim head and member of the Program in Molecular and Cell Biology at the Oklahoma Medical Research Foundation and Adjunct Professor in the Department of Biochemistry and Molecular Biology at the University of Oklahoma Health Sciences Center. She was also an Associate Investigator at the Howard Hughes Medical Institute until relinquishing the position for her move to the Stowers Institute.

Membership in the NAS is considered one of the highest honors given to a scientist in the United States. Conaway joins Scott Hawley, PhD, Robb Krumlauf, PhD, and Alejandro Sánchez Alvarado, PhD, as Stowers investigators elected to the society of distinguished scholars. Founded in 1863, the NAS includes more than 200 living Nobel laureates and such historic figures as Alexander Graham Bell, Albert Einstein, Thomas Edison, Barbara McClintock, and Orville Wright.



# Bazzini collaboration selected for Pew funding

The Pew Charitable Trusts selected Assistant Investigator Ariel Bazzini, PhD, to join the 2019 class of Innovation Fund Investigators. This fund was launched in 2017 to encourage collaborative projects among Pew's existing biomedical network of over 1,000 scientists and researchers from the United States and Latin America. The six pairs of investigators chosen for this award, all alumni of Pew's biomedical research programs, partner on interdisciplinary research to tackle some of the most complex questions in human biology and disease.

Bazzini is collaborating with Diego E. Alvarez, PhD, Adjunct Professor at the Universidad Nacional de San Martín in Argentina. Bazzini and Alvarez, both Pew Latin American Fellows, worked together during their postdoctoral training at Yale University. For this project, they received $200,000 over two years to investigate how the dengue virus manipulates host cells in order to replicate during infection.

Both labs seek to understand how dengue regulates or affects gene expression of viral and host genes in mammalian and mosquito cells. The Bazzini Lab approaches this problem from a gene regulatory point of view and the Alvarez Lab approaches it from the angle of viral-host interactions, allowing a complementary approach to study how translation affects mRNA stability. Due to the high levels of viral translation and tRNA demand, as well as the need to replicate within two hosts, dengue infection provides a unique opportunity to study the interplay between tRNAs, translation, codon composition, and mRNA stability. Results from this research could aid in the rational design of attenuated viruses with application as safe vaccine candidates.

# Rohner receives New Innovator Award

In October 2020, Assistant Investigator Nicolas Rohner, PhD, received a prestigious and highly competitive National Institutes of Health (NIH) Director's New Innovator Award. This five-year award, which provides up to $2.5 million, supports unusually innovative, high-impact research from exceptionally creative early-career investigators.

Rohner's research focuses on metabolic dysfunction and adaptation in cavefish and its implication for metabolic diseases. The cave-dwelling *Astyanax mexicanus* have adapted to the conditions of their limestone caves: absence of light, lack of predators, and no reliable food sources. Available food arrives mainly through seasonal floods, meaning the fish experience starvation conditions for most of the year.

The cavefish have a surface-feeding cousin, a population with ample food supply, that Rohner uses for comparison. Having multiple subpopulations of the same species make the cavefish a powerful genetic model system for studying fasting resistance and the resulting resilience mechanisms to metabolic stress.

Rohner's project aims to uncover the mechanisms and novel pathways of how cavefish are able to withstand long starvation periods. Understanding how these fish tolerate such harsh conditions will lead to a better understanding of fundamental principles of metabolic homeostasis, with far-reaching implications for treating metabolic diseases such as metabolic syndrome and diabetes.

The Stowers Scientific Advisory Board approved Rohner's promotion to Associate Investigator, effective January 2021.

# UNCOMMON TIMES REQUIRE UNCOMMON EFFORTS

As the novel coronavirus disease, COVID-19, took hold and spread through populations around the globe in early 2020, communities scrambled to mitigate its impact. The Stowers Institute was no different, and when quarantines were imposed that sent researchers home and essentially put most research on a temporary hold, protective measures were implemented to initially allow for critical operations to continue. But as the quarantine wore on, additional creative and adaptive measures were implemented to allow the science to resume and proceed as fully and safely as possible.

The Institute established a COVID-19 Response Committee and an Infection Control group that created rigorous standards to minimize safety risks in the work environment and support members' safe return to campus. Collaborating closely with Operations, Security, and Environmental Health and Safety teams, their efforts included a systematic health screening and virus testing program combined with providing personal protective equipment and executing enhanced cleaning and disinfecting protocols.

In addition to these rapid responses, the collective deep biological research and biotechnology expertise of Stowers scientists was harnessed for COVID-19 diagnostic testing development efforts. A team led by Investigator Jennifer Gerton, PhD, collaborated to develop a more highly automated and cost-efficient saliva-based viral detection test. Utilizing a partnership with neighboring research institute MRIGlobal, the weekly Stowers employee testing program adopted the internally developed enhanced testing method. At the same time, another Stowers team led by Investigator Joan Conaway, PhD, assembled to develop an enhanced COVID-19 antibody detection test, intended to provide information about past exposure and potential immunity to the virus.

Throughout the Stowers campus, rotating lab schedules were developed to minimize the number of individuals in the research areas at any given time. Contactless research sample submission processes for scientific support facilities were established. Food operations shifted to prepackaged items and contactless service. Teams like Information Technology worked quickly to deploy resources that would support remote work. Lab and departmental meetings, speaker presentations, conferences, and thesis defenses moved to online virtual formats.

And behind the scenes, every remote operation, including finance and accounting, grants, human resources, communications, and library services, adapted to ensure that research and organizational support continues as seamlessly as possible. While it may not be business as usual and campus activities have been altered for the time being, members across the Institute have demonstrated extraordinary flexibility, perseverance, and positive spirit while facing challenges of the pandemic and preparing for the eventual return to full operations.

# WELTE SAILS INTO RETIREMENT

In May of 1994, David Welte, a managing partner in a prominent Kansas City law firm, was hired to establish the Institute as a Medical Research Organization, a little-known and often overlooked type of tax-exempt entity that offered its founders many of the advantages of a public charity and very few of the restrictions of a private foundation. Through this role, Welte became part of the early management of the Institute and would later become the Institute's Executive Vice President and General Counsel.

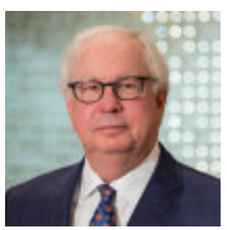
Welte recalls that in those early days, some individuals scoffed at the idea of creating a premier medical research institute in Kansas City, saying it would not amount to anything more than a pretty brick building with the Stowers name engraved on it. "But Jim and Virginia never wavered from their commitment to succeed in Kansas City. And they were right." says Welte.

In tribute to his lasting legacy, Co-founder Virginia Stowers reflects, "I have greatly valued David's counsel through the years. His commitment to realizing our vision has been an important element of the Institute's success." And Stowers Chairman of the Board Richard Brown shares, "David has served alongside the leadership teams at both the Stowers Institute and American Century Investments, and I am very proud to have been his colleague over those many years. He has served with distinction in every arena in which his leadership was needed, with wisdom, calmness, and grace."

Welte himself once said, "Jim Stowers had very fundamental beliefs in how to build an organization and build it well. You hire the very best people, you turn it over to them, you don't get in their way." Indeed, that is exactly what our founders did when the hired Welte.

# NEW LEADERSHIP TEAM HIRES

To meet the evolving needs of the Stowers community, several new positions have been added to the slate of leadership at the Institute. These individuals bring not only experience and talent, but also a passion for the mission of the Institute.



Vice President of Finance and Treasurer Penny Spence joined the Institute in 2019 and in early 2020 assumed additional responsibilities including accounting, payroll, benefits, and finance systems. Director of Human Resources Patrick Mitchell was promoted to Vice President of Human Resources, Diversity, Equity, and Inclusion. Mitchell leads the Institute's ongoing efforts to promote a culture that values the differences, similarities, and complementary strengths of a diverse workplace.

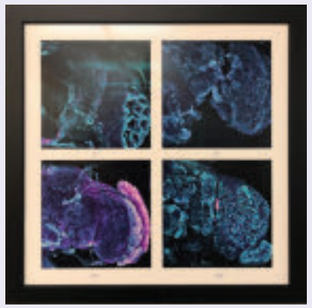
With a renewed commitment to community and educational outreach, Steve Bellis was appointed as the vice president of external relations and communications. He leads the Institute's efforts to engage with the Kansas City community through Institute initiatives. Additionally, he oversees the educational outreach program and communications efforts.

In May 2020, it was announced that Charles German had joined the Institute as co-general counsel. His primary practice areas have been internal and governmental investigations, corporate governance, biotech, capital markets, and professional liability.

# OUTREACH AND COMMUNITY ENGAGEMENT EFFORTS EXPANDED

With increasing public interest in science, the Stowers Institute is spurring new opportunities for its researchers to educate and inform while showcasing the Institute's own research.

The Office of External Engagement, led by former Head of Molecular Biology Karen Staehling, PhD, is spearheading efforts to broaden opportunities for exposing interested groups to the research programs at the Institute. This initiative is focused initially on teacher outreach and public education.



The teacher outreach efforts are aimed at enhancing science education in the Kansas City area by empowering teachers through training opportunities and access to industry experts. Stowers has partnered with and provided content to the Connector, a virtual classroom administered through PREP-KC. Stowers researchers were involved with the 2019 KC STEM Alliance's Mentor Day that was hosted at the Institute. Stowers also hosted science education powerhouse HHMI BioInteractive for a one-day professional learning workshop for high school science educators. And, while temporarily on hold due to COVID-19 restrictions, the Institute hosts tours that introduce high school classes to the inner workings of a biomedical research facility.

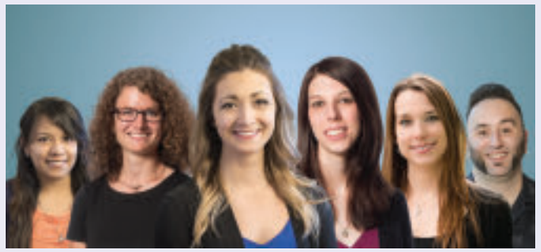
The BIG IDEAS @ScienceStowers lecture series and the popular traveling scientific image exhibit are pillars of the Institute's public education efforts. Both are designed to inspire a thirst for scientific knowledge and bring scientific ideas in an engaging and accessible way to the greater Kansas City community. More information about these events can be found on stowers.org.

# COVID-19 CLAIMS GSSIMR GRADUATION CEREMONY

While the COVID-19 pandemic of 2020 affected the Graduate School's ability to host a graduation ceremony, it did not stop several predoctoral researchers from completing the requirements for their PhD degree.

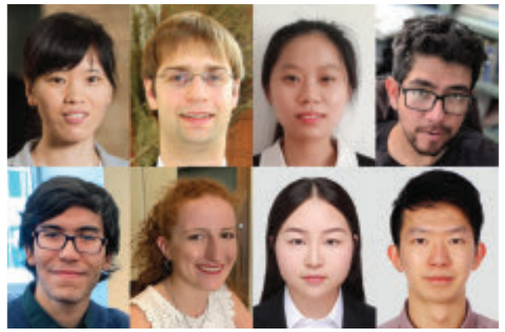
Raquel Barajas Azpeleta and Joaquin Navajas Acedo completed their degree requirements at the end of 2019. Both earned competitive placements as postdoctoral researchers, Barajas Azpeleta at the Champalimaud Centre for the Unknown in Portugal, and Navajas Acedo at Biozentrum at the University of Basel in Switzerland.

Only a few days into the pandemic remote work period, Zanders Lab Predoctoral Researcher María Bravo Núñez successfully defended her thesis by videoconference on March 19. She began her postdoctoral position at Harvard University in July.



***GSSIMR graduates, left to right: Bravo Núñez, Soffers, Nuckolls, Bauerly, Azpeleta, Navajas Acedo***

Three other Graduate School predoctoral researchers effectively defended their theses over the summer months. In June, Gibson Lab Predoc Beth Bauerly and Workman Lab Predoc Jelly Soffers successfully completed this requirement. Bauerly is now a postdoctoral researcher at Dartmouth College in New Hampshire. Soffers is heading to Harvard University for her postdoctoral research. And in August, Zanders Lab Predoc Nicole Nuckolls successfully defended her thesis. She began a postdoctoral research position in October at the University of Colorado Anschutz Medical Campus.



# SCIENTISTS IN THE MAKING

Meet this year's ensemble of predoctoral researchers and find out some of what spurred their scientific curiosities.

### Minling Hu

***Beijing Normal University***

Minling Hu worked as a research technician in the Halfmann Lab for two years, so when she decided to pursue a PhD, she knew she wanted it to be at the Stowers Graduate School. Hu attended Lanzhou University for her undergraduate work and Beijing Normal University for a master's program in translational science.

### AJ Treichel

***Winona State University***

As a child, AJ Treichel spent a lot of time outdoors watching tadpoles and caterpillars transform into frogs and butterflies. Later, watching a zebrafish embryo divide again and again, he realized he could make a career out of being curious about the natural world. Treichel attended Winona State University in Minnesota where he received a Bachelor of Science in cell and molecular biology.

### Fanning Xia

***Wuhan University***

Fanning Xia has been fascinated by biology since high school and originally planned to go into the medical field, but discovered she was afraid of holding a scalpel. Shifting to biology and research felt like a natural choice. She attended Wuhan University for her Bachelor of Science degree.

### Carlos Barradas Chacón

***National Polytechnic Institute of Mexico***

Carlos Barradas Chacón grew up in León, Mexico, where he found peace watching nature documentaries. He hopes to someday study regeneration in *Ambystoma mexicanum*, the axolotl. Barradas Chacón attended Autonomous University of Queretaro and National Polytechnic Institute of Mexico.

### Pablo Guzmán Palma

***Pontifical Catholic University***

Pablo Guzmán Palma chose his career path when he learned how to use a microscope in high school. He was "fascinated by the shapes and colors of plant cells, by how microorganisms move under the lens." Guzmán Palma earned his Bachelor of Science and post-bachelor's degrees in biochemistry at Pontifical Catholic University.

### Camila Behrensen

***Universidad Argentina de la Empresa***

Camila Behrensen might have Isaac Asimov to thank for her love of science. While growing up, Asimov was her favorite author, in part because of how he was able to explain complicated concepts in ways that everyone could understand. She received her Bachelor of Science in biotechnology from the Universidad Argentina de la Empresa.

### Kaili Li

***Sun Yat-sen University***

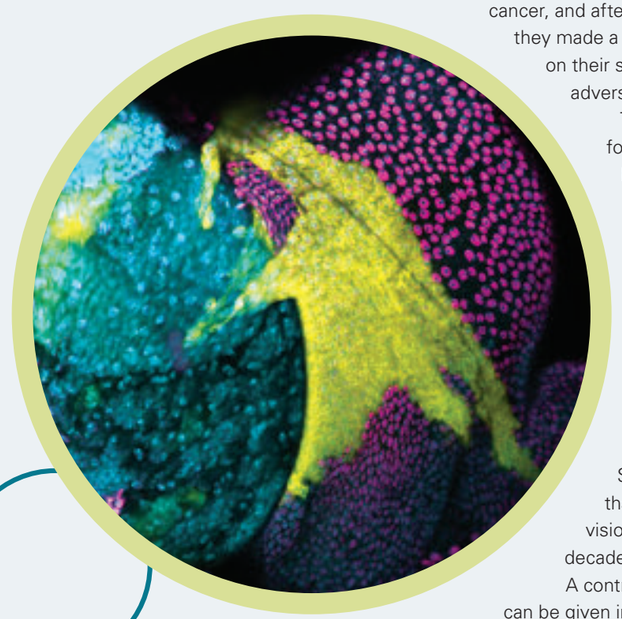
Kaili (pronounced Kelly) Li first became interested in science when she participated in a biology competition during high school, then got really hooked after reading "On the Origin of Species." Li earned her bachelor's degree in bioengineering from Henan Agricultural University and her master's in cell biology from Sun Yat-sen University.

### Haining (Frank) Jiang

***Shanghai Jiao Tong University***

Haining (Frank) Jiang was the type of kid who loved to take things apart just to see how they work. That same curiosity led him to study biology and medicine in high school and at Shanghai Jiao Tong University, where he received a Bachelor of Science in biomedical science and experience working on cancer epigenetics.

# INVESTING IN TOMORROW'S CURES:
# The Hope Shares® Endowment



Cancer. Alzheimer's disease. Diabetes. Cardiovascular disease. Birth defects. Chances are, you or someone you know has been affected by at least one of these conditions, which are all too common in our society.

For Jim and Virginia Stowers, the challenge was cancer, and after successful treatment and recovery, they made a momentous decision: They would draw on their substantial fortune to transform their own adversity into Hope for Life® for millions.

Today, Stowers scientists are at the forefront of unraveling the mechanisms behind health and disease and preparing the groundwork for novel treatments and cures. Their work is made possible by the Hope Shares Endowment—the lifeblood of the Stowers Institute.

Unlike most research programs at universities, which immediately spend their donors' contributions, the Institute uses every gift, no matter how big or small, to add to its endowment. As the capital invested in the Hope Shares Endowment grows, it ensures that Jim and Virginia Stowers' extraordinary vision continues to gain momentum for decades to come.

A contribution to the Hope Shares Endowment can be given in the donor's name or in memory or honor of someone they love.

We are fortunate to have the support of many loyal donors who know their generous contributions to the Hope Shares Endowment help secure the Institute's future and accelerate our researchers' life-changing contributions to human health. It's an investment that will pay dividends in improved health and well-being for decades to come.

The following pages pay homage to all the visionary men and women who believe in our mission and are convinced that an investment in the Stowers Institute is the best way to advance knowledge and provide Hope for Life®.



## Lifetime Contributions

*Lifetime Contributions through November 2020*

### $10 Million+

Pamela Stowers

### $1 Million+

American Century Investments Foundation
William and Priscilla Neaves, *including*
*In Memory of Robert Dornhoffer*
*In Memory of Betty Mae Patterson*
*In Memory of Neal and Jeanne Patterson*
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Every Wednesday during the academic year, the Institute's auditorium – or, during the COVID-19 pandemic situation, the Institute's webinar channel – comes alive with the very latest in hard-hitting science. This ongoing public seminar series was developed to host distinguished researchers from institutions across the country and around the world for scientific talks covering an array of research topics. From Nobel Laureates to newly-minted lab heads, a broad cross-section of scientists share their research with Stowers researchers and the local scientific community. These talks serve to spark scientific ideas and facilitate dialogue among diverse researcher areas.

## WEDNESDAY LECTURE SERIES BY THE NUMBERS

**624**
**Scientific talks**

**166**
**Different organizations or institutions represented**

**148**
**Speakers hold National Academy of Sciences membership**

**49**
**Foreign organizations or institutions**

**41**
**Howard Hughes Medical Institute speakers**

***Most frequently represented organizations by number of talks***

**41**
**Harvard University**

**25**
**Stanford University**

**25**
**Washington University**

**24**
**Stowers Institute for Medical Research**

**9**
**Nobel Laureate speakers**

**4**
**Speakers who would later join the Institute as investigators**

*(2000-2020)*

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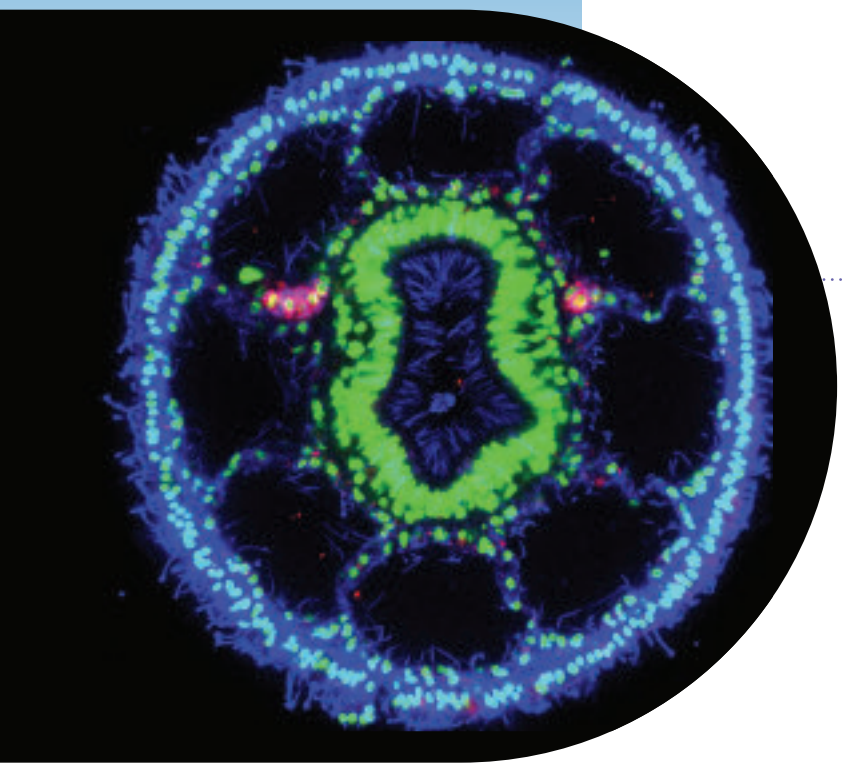
TO MAKE A SIGNIFICANT CONTRIBUTION TO HUMANITY THROUGH MEDICAL RESEARCH BY EXPANDING OUR UNDERSTANDING OF THE SECRETS OF LIFE AND BY IMPROVING LIFE'S QUALITY THROUGH INNOVATIVE APPROACHES TO THE CAUSES, TREATMENT, AND PREVENTION OF DISEASES.



Sometimes called "flowers of the sea," sea anemones are beautiful marine animals that also display stunning views under a microscope. Stowers scientists study the species *Nematostella vectensis* to explore how tissues and organs develop and assemble. Researchers in the Gibson Lab are especially interested in how this ancient sea animal uses many of the same key molecules found across the animal kingdom—in similar and different ways—to regulate its development and build its unique adult form. This image shows a cross-section of a developing sea anemone at the primary polyp stage where fluorescent labels reveal its overall radial symmetry as well as emerging cell types and structural features.