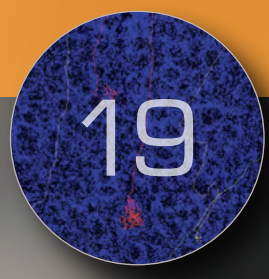
MASTER PLANNED
A CLOSER LOOK AT THE GENES THAT INSTRUCT HOW ANIMAL BODY PLANS DEVELOP

STOWERS REPORT

NEWS AND INSIGHT FROM THE STOWERS INSTITUTE FOR MEDICAL RESEARCH

2019



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In perspective

BY DAVID CHAO, PHD
PRESIDENT AND CEO

In this letter, I am delighted to share more about our upcoming transitions to a new Scientific Director and Dean of the Graduate School. As we announced late last year, Alejandro Sánchez Alvarado will succeed Robb Krumlauf as Scientific Director and Matt Gibson will succeed Scott Hawley as Dean.

Since Robb joined the Institute as its founding Scientific Director almost two decades ago, the Institute has grown and matured from a start-up of a few dozen members to an established institution of five hundred. Robb has played an invaluable role in converting Jim and Virginia Stowers' vision into a world-class basic research institute recognized around the world for its accomplishments. He has made innumerable concrete contributions to the Institute's success, but perhaps his most significant impact has been intangible. Robb's love of science, the Institute and its people has permeated the Institute and become a distinctive part of the Stowers way. After handing over his responsibilities as Scientific Director, Robb will continue to lead his research program on the Hox genes and contribute to the community as a Stowers Investigator.

Alejandro Sánchez Alvarado will succeed Robb in July of this year. Alejandro joined the Institute in 2011, and, from the outset, his exceptional scholarship, scientific acumen and warm laughter have been welcome additions to the community and culture of the Institute. He has led a groundbreaking research program on regeneration that has been recognized by many awards and honors, including his recent election to the National Academy of Sciences. Since 2013, Alejandro has also led an effort critical to the Institute's current and future success - the recruitment of new principal investigators. His work in this role led to the recruitment of four promising junior researchers as new assistant investigators. Driven by the same passion for science and the Institute, Alejandro is eager and ready to build upon the foundation laid by Robb and others and lead the Institute's science to the next level. After adding this new role, Alejandro will continue leading his research program as an investigator of the Stowers Institute and of the Howard Hughes Medical Institute. He will also be assisted by Stowers Investigator Kausik Si in the new role of Associate Scientific Director.

In addition to a new Scientific Director, the Institute will soon have a new Dean for its graduate school. Over a decade ago, Scott Hawley co-authored the original proposal outlining the vision for the graduate school. Soon thereafter, Scott became the founding dean of the newly named Graduate School for the Stowers Institute for Medical Research. Under Scott's leadership, the Graduate School grew from a germ of an idea to a thriving program with almost 50 pre-doctoral researchers in residence. Scott's passion for training, mentoring and teaching has always been a critical driver of the school's meteoric rise. After transferring his responsibilities as Dean, Scott will continue to lead his research program in meiosis as a Stowers Investigator. Scott will be ably succeeded by Investigator Matt Gibson as the new Dean and Assistant Investigator Sarah Zanders in the newly created role of Vice Dean.

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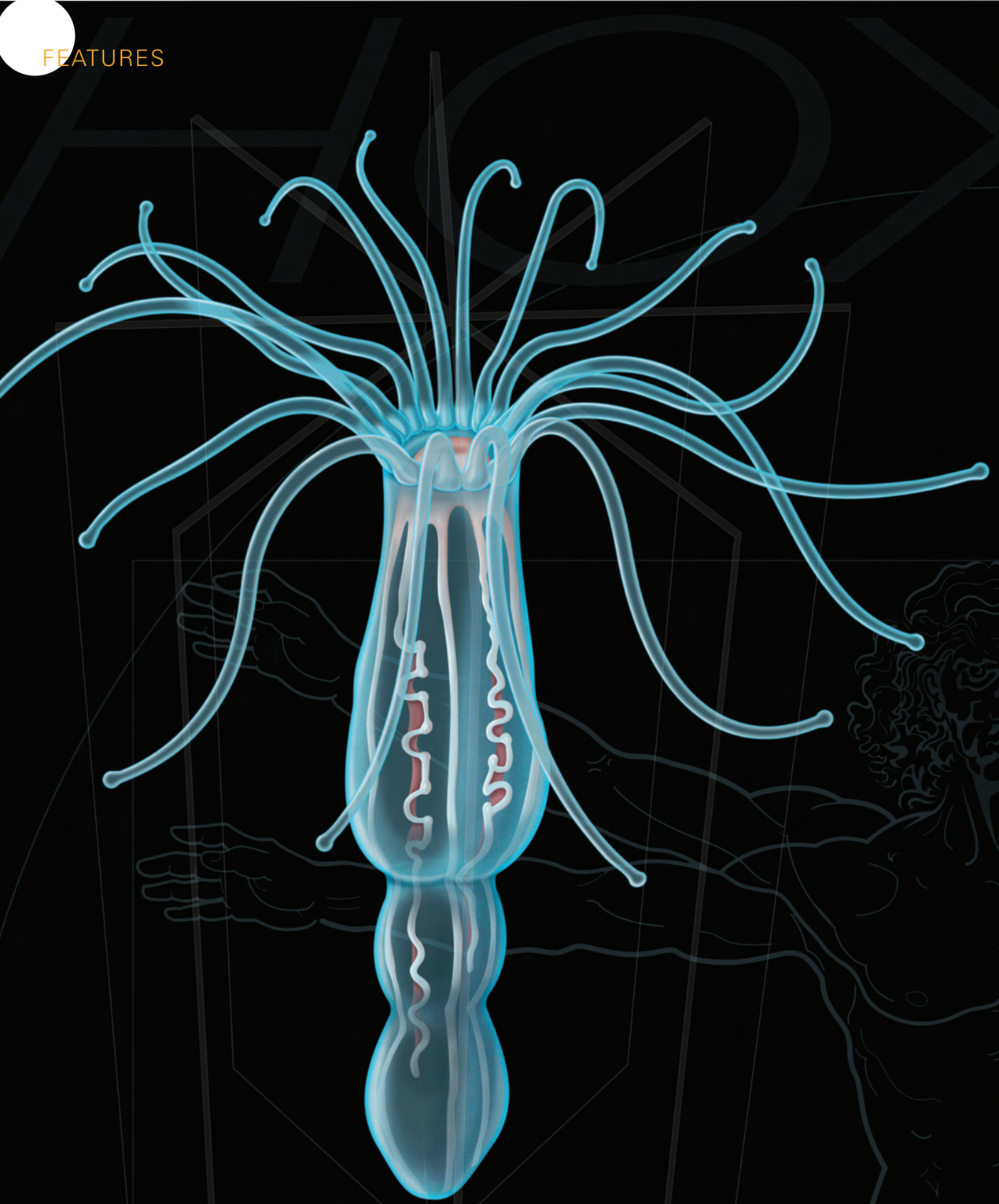


Master Planned

A closer look at the genes that instruct how animal body plans develop

By Anissa Anderson Orr

The leg bone's connected to the knee bone,
The knee bone's connected to the thigh bone,
The thigh bone's connected to the hip bone…

Over the ages, these classic song lyrics have taught countless children how their bodies are knitted together. But have you ever wondered why they fit together that way? Or for that matter, why does any organism develop the way that it does—directed according to some unseen plan?

These questions have puzzled scientists for hundreds of years, and it's only relatively recently, with research into Hox genes, that we are discovering clues to the transformative process that launches an organism's body plan into motion and sets it in stone.

Researchers at the Stowers Institute are helping lead the way in this exciting field, which is providing new insight not only into how bodies come together, but also on how species evolved. New discoveries also hold promise for understanding human health and disease.

Ironically, while Hox genes are master planners, many important findings in this field have arisen when scientists have gone off plan to investigate a promising idea or unexpected observation, conduct research on a little-studied laboratory animal, or collaborate with colleagues from around the world. The support of institutions like Stowers, which encourages taking risks and providing researchers with the cutting-edge scientific tools and stable financial backing they need to succeed, is critical to making this kind of innovative research happen.

"To me, this is a story about how boldness, creativity, and collaboration can lead to interesting outcomes," says Stowers Investigator and Scientific Director Robb Krumlauf, PhD.

UNLOCKING THE SECRETS OF HOX GENES

In 1894 scientists made the first observations that eventually led to the discovery of Hox genes nine decades later in 1984, after noticing bizarre transformations in fruit flies (*Drosophila*) that would be right at home in a horror show. Some had feet where the mouth should be. Others had extra pairs of wings, or legs growing out of their heads instead of antennae. The glitches, called homeotic mutations, were eventually found to be caused by defects in single genes, which the researchers termed homeotic, or Hox, genes.

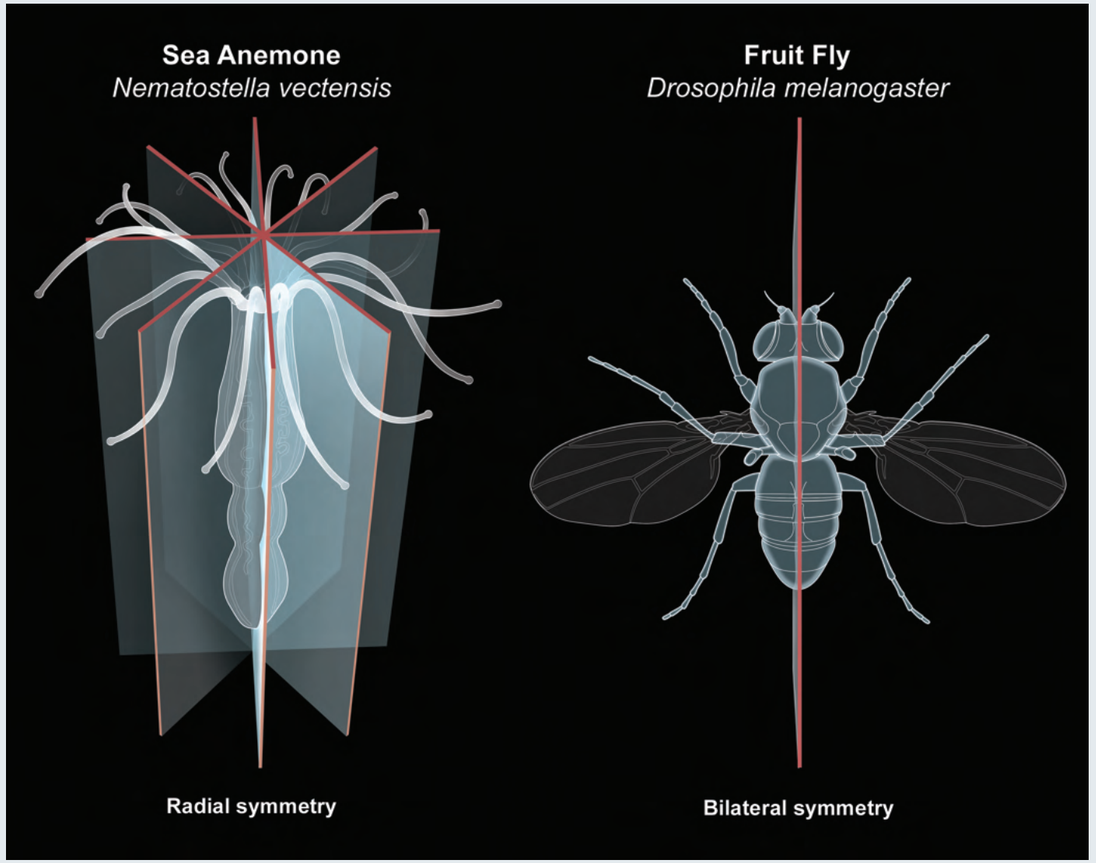
Research over the next several decades revealed details on how Hox genes control the layout of a developing embryo, marking where structures should appear along the body from head to tail, and determined that the DNA sequences of Hox genes in fruit flies all shared a similar stretch of about 180 bases, called the homeobox. This enabled scientists to find related genes with homeoboxes in other species, including other insects, worms, and even mammals. Hox genes are considered to be a key subset of genes in an organism's genome that make up the fundamental toolkit needed to control embryonic development. Almost every animal has homeobox sequences in their DNA, so it's thought that Hox genes emerged early in the evolutionary process.

Krumlauf started investigating Hox genes in the mid-1980s in mice and other vertebrates and has devoted his career to understanding their roles ever since. Amazed by their conserved regulatory powers in so many diverse kinds of animals, Krumlauf says he knew he wanted to spend the rest of his life learning more about these genes and how they serve as master regulatory switches. "As a former chemical engineer, their ability to control biological circuits captivated me. They were part of the instructions for laying down the basic body plan, which I thought was cool."

Considered a pioneer in the field, Krumlauf was elected to the National Academy of Sciences in 2016 for his seminal work on homeobox genes. He has conducted landmark research on Hox genes in a part of the brainstem called the hindbrain, which controls functions like breathing or blood pressure and makes important contributions to head and face development. He's also known for co-discovering collinearity of Hox genes, a phenomenon in which the order of these genes in a cluster along a chromosome is the same order in which they're expressed and function in the animal from head to tail. Over the years, he's been studying the molecular and cellular pathways that regulate Hox genes in patterning the nervous system and head development and how these processes are linked to human diseases. He has also made evolutionary comparisons of how Hox genes are regulated across species as diverse as mice, chicks, and pufferfish.

Recently, his lab has been focusing on Hox genes in the sea lamprey, an eel-like parasitic fish that is part of a lineage of jawless vertebrates that emerged early in the generation of vertebrates about 550 million years ago. The organism is an important model for studying early events in vertebrate evolution. It's also an ideal organism in which to explore the mysteries of common toolkit genes and how they are used, which Krumlauf likens to "a wiring diagram," or an architectural plan used to "put together building blocks and materials to generate very different anatomical structures."

Very different indeed. How can a similar toolkit of genes drive the development of such a wide variety of species—from the humble fruit fly to much more complex mammals?



To find out, Krumlauf's lab is exploiting the advantages of the Stowers-built SIMRbase website, a common framework of genomics tools that can be tailored to a wide variety of model organisms. This platform provides a means to systematically compare Hox genes and other regions of the genome across species. SIMRbase enabled Hugo Parker, PhD, a postdoc in the Krumlauf Lab, to publish the identification of lamprey Hox clusters that control head-to-tail patterning, along with other groundbreaking work reporting the germline sequence of the sea lamprey, in *Nature Genetics* in 2018.

You never know where discoveries will lead. Krumlauf's studies exploring the signals that control how Hox genes themselves are regulated and expressed in development led to a collaboration with Stowers Investigator Linheng Li, PhD, on the roles of Hox genes in blood cells and cancer. The Krumlauf and Li labs coauthored a study published in *Cell Stem Cell* in 2018 in which they found that a key regulatory element called *DERARE* controls the expression of certain Hox genes in blood-forming stem cells. These genes play a critical role in maintaining a healthy balance of blood cells. When they malfunction, they increase the risk for leukemia. Understanding the regulatory mechanisms of Hox genes could help efforts to enhance the function of blood-forming stem cells and find drugs to target certain types of leukemia.

"Hox genes are master regulators. When they go wrong, you may not only end up with abnormal cells or tissues, you could also end up with a disease," Krumlauf explains.

> Why should we restrict ourselves to studying a few books if we have access to an open library from which we can learn how living organisms solve many problems that matter to our health, as well as other aspects of our lives?
>
> *– Aissam Ikmi, PhD*

BREAKTHROUGH FINDINGS IN AN ANCIENT ANIMAL

As much as we've learned about the Hox genes, the origin and evolution of this crucial gene family has remained an unsolved mystery. Where did Hox genes come from, and how did their crucial roles in body patterning arise during ancient evolution? This past fall, more interesting discoveries regarding Hox genes emerged from the Stowers Institute—this time from studies on the sea anemone *Nematostella vectensis* in the lab of Investigator Matt Gibson, PhD.

The role of Hox genes in body patterning had been well-defined in bilaterally symmetric animals like flies, mice, and humans. Surprisingly, these genes are also found in our distant relatives, including simple animals known as Cnidarians (jellyfish, sea anemones and corals). Cnidarians feature radial patterning and lack a head-to-tail axis, raising the question of what Hox genes could be doing. By developing new methods to study developmental gene function in *Nematostella*, the Gibson Lab found that Hox genes also play an unexpected role in controlling the radially symmetric body plan of *Nematostella*.

The breakthrough findings, published in *Science*, were remarkable because Gibson didn't start his lab at Stowers to investigate Hox genes in sea anemones. He has spent most of his career studying epithelia—highly organized layers of cells that line the internal and external surfaces of the body, such as the epidermis, the outermost layer of the skin. That work takes advantage of the fruit fly, the genetic powerhouse where many Hox genes were initially discovered.

Gibson was drawn to *Nematostella* because of its large and complex genome, and because it's flush with epithelial cells. But dedicating part of his research to a much less studied organism was a decidedly risky career move, so Gibson asked for Krumlauf's input first.

"There was a moment where I saw great potential in *Nematostella*, but I wasn't absolutely sure it was a good idea. I asked, 'Should I really jump into a completely new area?' And he said, 'Yes, definitely be bold if that's what you want to explore.'"

Encouraged by Krumlauf's enthusiastic support, Gibson ramped up his lab's focus on the starlet sea anemone. He hired Postdoc Aissam Ikmi, PhD, from the University of Paris, who was willing to take a chance on the new model organism.

"From my perspective, studying different models is like studying different books," Ikmi says. "Why should we restrict ourselves to studying a few books if we have access to an open library from which we can learn how living organisms solve many problems that matter to our health, as well as other aspects of our lives?"

Ikmi went on to play an essential role in establishing the enormous starlet sea anemone colony needed for research, with support from the Stowers Reptile & Aquatics Facility. He also developed tools, based on cutting-edge gene-editing technologies, to manipulate genes in the sea anemone in collaboration with the Stowers Molecular Biology Facility.

A RISK WORTH TAKING

Over the course of a decade, the initial risk Gibson took in studying the starlet sea anemone has paid off, yielding several scientific papers and important discoveries, and laying the foundation for the Hox research recently published in *Science*.

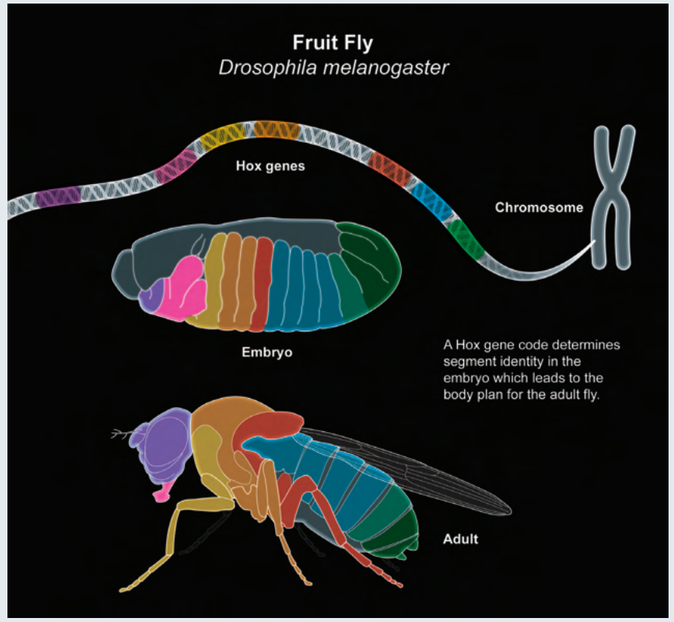
The study's findings were a major step forward in Hox gene research, because understanding the function of Hox genes in the sea anemone helps us understand their roles in our most ancient common ancestor, some 600 million years in the past.

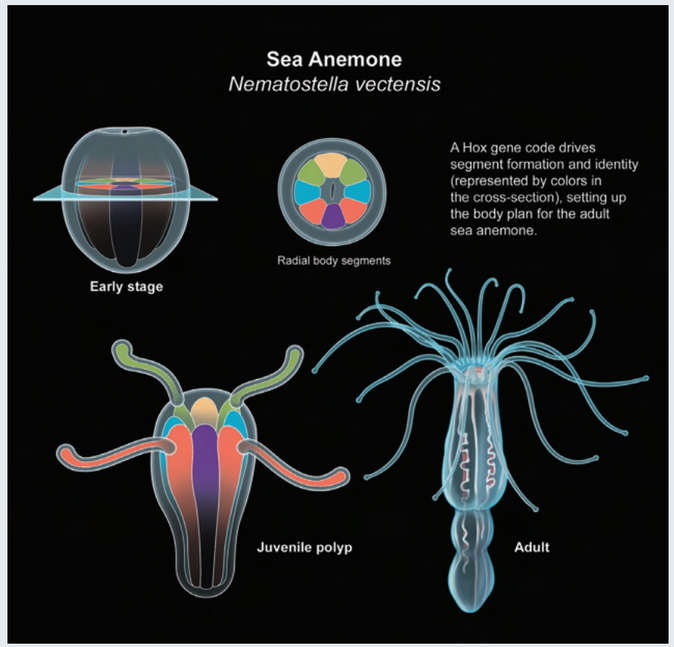
Using gene knockdown technology, researchers in the Gibson Lab disrupted the function of the genes involved in body patterning of the starlet sea anemone through treatment with short hairpin RNAs, which silence gene function. They also used the CRISPR-Cas9 gene editing approach to remove these Hox genes from the genome.

The results were striking, says Gibson.

"Early in development, *Nematostella* have a larval stage where the animals look a bit like a little lemon. There's an outer layer of cells (the rind) covering an inner layer of cells (the fruit). And just like a lemon, when you slice through, *Nematostella* larvae are divided up into eight segments. When we removed the Hox genes, specific segment boundaries were completely lost. It was a really obvious effect and told us right away that Hox genes control radial segmentation in this animal," Gibson says. "Furthermore, these segmentation defects led to even more dramatic disruptions of the tentacles that develop right after the larval state."

In sum, the work shows a key role for Hox genes in radial patterning. The findings were surprising because in bilaterally symmetric animals, Hox genes control the identity of segments along the head-to-tail axis—for example, which part of your spine makes a rib versus a vertebra. In contrast, Hox genes in the sea anemone are responsible for both making and patterning segments.





Shuonan He, Matt Gibson, PhD, Robb Krumlauf, PhD

These functions may have separated over hundreds of millions of years such that Hox genes in present-day bilaterians have lost the role in segment formation and just control segment identity, Gibson says. The finding builds on Krumlauf's earlier discoveries.

"In the mouse, we showed that a couple of Hox genes work also as segmentation genes, making segments, but their primary role was in segmental identity. People thought that (the finding) was just an odd one-off. But what's cool about what Matt and his lab have shown is that it may be an ancient feature of Hox genes in making these integrated segmental structures and also giving them an identity. It's really exciting. It makes everyone reevaluate models on the ancient role of how these systems work," Krumlauf says.

TRAINING THE NEXT GENERATION OF HOX RESEARCHERS

Stowers research trainees have played important roles in advancing Hox gene research.

Ikmi now leads his own lab at the European Molecular Biology Laboratory (EMBL) in Heidelberg, Germany, where he continues to study *Nematostella*, and how the interaction between genetic factors and the environment controls developmental processes.

"One key environmental stress is injury, and we focus on understanding the spectacular ability of sea anemones to regenerate—if you cut them in half, each half will grow into a new sea anemone. They're particularly well-suited for trying to find out why some animals are better at regeneration than others," he says.

Working at Stowers gave him the opportunity to develop new technical skills and mature his research plan to help push his scientific knowledge forward, he adds.

Ikmi's work paved the way for Shuonan He, a predoctoral researcher at the Graduate School of the Stowers Institute for Medical Research and first author of the 2018 *Science* paper. He joined the Graduate School in 2014, after graduating from Peking University with a bachelor's degree in biological science. He says his love of marine biology led him to join Gibson's lab.

"As a mentor, Matt is very open-minded and allows us to develop our own ideas and projects. The freedom to explore is what I enjoy most," He says. "When I first started in the lab, we already had a well-established, daily-spawning *Nematostella* colony, thanks to Aissam and the Reptile and Aquatics team, and the CRISPR-Cas gene editing approach had just been demonstrated in *Nematostella*. I do think it was the perfect opportunity to start my own project on *Nematostella*."

His work has centered on generating mutants for different starlet sea anemone Hox genes. The first two years into his project, he had minimal success despite numerous trials. But after a year of exploration and optimization, he was the first researcher to successfully apply short hairpin RNA, or shRNA, to silence gene expression in the starlet sea anemone. The lab now has a much more efficient shRNA protocol that they have shared with many other Cnidarian labs, as well as a more efficient CRISPR-Cas system they used to generate the Hox mutants in the *Science* paper.

Post publication, He is continuing to focus on the regulatory properties and downstream targets of *Nematostella* Hox genes. He plans to stay in academia after graduation and continue research in the evolutionary developmental biology field.

WHAT'S NEXT?

Scientists at Stowers will continue to dig deeper into Hox gene research, aided by the Institute's unique research environment which provides access to modern laboratory space, advanced equipment, and scientific support services staffed by expert researchers.

But in addition to equipment and resources, Gibson credits the philosophy of the Stowers Institute, which encourages researchers to take substantial risks to pursue the most interesting ideas. He also points to the support and guiding expertise of Krumlauf, a "phenomenal mentor and a phenomenal human being," for spurring him to consider taking a different path—one that coincidentally led to breakthrough discoveries about Hox genes that Krumlauf had studied for most of his career.

"When I first came to Stowers, I had no idea that a big part of my lab would wind up working on *Nematostella*," Gibson says. "Traditionally, if you set up a fruit fly lab, that's what you do for 40 years. The support and environment at Stowers really make it possible for scientists to go in new research directions, and that's a big part of what makes this institution so unique on the world stage."

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– Matt Gibson, PhD

GETTING THE GRANT

How the Stowers Grants Office helps scientists fund research now and prepare for the future

By Jen A. Miller

Amber Garvey, Michelle Lewallen, PhD, Erin Johnson, PhD

The Stowers Institute is distinctive in ways that its founders and leaders envisioned would enable scientific discovery as well as individual researchers. As part of this approach, the Institute is committed to providing innovative opportunities for Stowers scientists to develop skills and knowledge to enhance their research endeavors, both near-term and long-term.

"Part of fulfilling our mission involves developing and preparing tomorrow's leaders in research, and we're continually examining how we can do this more effectively, to propel our science as well as our scientists," says George Satterlee, Executive Vice President of Administration.

"A great example of this process is the evolution of the Stowers Grants Office," says Satterlee. The Grants team offers original resources and comprehensive support for scientists to learn and master the often overwhelming process of finding funding opportunities, writing proposals, submitting applications, and managing awards.

Over the past five years, the Grants Office has leveled up the Institute's ability to assist scientists in this area. And just as important, this progression is recognized as an ongoing process.

Piloting new territory

When Michelle Lewallen, PhD, embarked on a scientific career, she expected to follow a typical academic research path, one that ultimately led to a faculty position. She never expected that she would instead come to lead the Grants Office at the Stowers Institute. Since stepping into that role in 2013, she has helped faculty, predocs, and postdocs apply for and receive millions of dollars in fellowships and grants from dozens of prestigious funding organizations like the National Institutes of Health, American Cancer Society, American Heart Association, March of Dimes, and the Searle Scholars Program.

Our hope is that we can shield the scientists from the tedium and burdens of the application process and free their efforts for the much more important task of developing exciting scientific ideas.

– Michelle Lewallen, PhD

"My science training enables me to relate better with the researchers than someone without that shared experience. It helps me better interpret their needs and develop more effective tools and resources to support their grant-writing endeavors. I can also read their scientific writing and provide feedback, in addition to assisting with administrative aspects," she shares. She doesn't see it as an alternative career path, but a scientific one that combines her scientific knowledge and program development and management skills. She knew that she enjoyed things like writing and getting projects organized—activities that some scientists dread in the same way she dreaded some of the aspects of being a full-time research scientist. "We can still use our scientific training and our love of science, but in a different way to support the scientific enterprise," she explains of scientists like herself who pursue other career tracks.

Scanning the horizon

Lewallen and Amber Garvey, grants development specialist, provide a wide spectrum of support that starts by helping researchers and students identify appropriate funding opportunities. "We're always looking out for what's new," Lewallen says. The Grants team keeps Stowers researchers updated on relevant grant opportunities with a monthly newsletter and posts on the Stowers intranet.

Introducing themselves to researchers happens on day one—the first day researchers arrive on campus. The Grants team gives presentations at new member orientations, which is where Blair Benham-Pyle, PhD, a postdoctoral research associate, first met Lewallen. "During my graduate work, I had been told by several mentors that there was a small list of postdoctoral fellowships offered by foundations to apply for in your first year as a postdoc," she says. "In my very first week at the Stowers Institute, I walked into the Grants Office with a spreadsheet of the fellowship applications I wanted to turn in." Lewallen gave Benham-Pyle deadlines for those fellowships, read proposal drafts, and helped her work through her list. She also made sure Benham-Pyle's applications met the more tedious requirements, like submitting both a digital and hard copy of every document. "Our hope is that we can shield the scientists from the tedium and burdens of the application process and free their efforts for the much more important task of developing exciting scientific ideas." In the end, Benham-Pyle's experience with the Stowers Grants Office was a success, and she and her compelling research proposal were recognized by a prestigious Jane Coffin Childs postdoctoral fellowship.

This support strategy also benefits the principal investigators at the Institute, who are tackling the challenge of writing research grant applications while running their research programs. For a research institution like Stowers, where principal investigators receive base funding from the institution's endowment, applying for grants is still important, says Investigator Julia Zeitlinger, PhD, who received an NIH grant that she applied for with help from the Grants Office.

"If you have additional funding, you can do more. You can expand the research you have," she explains. "This type of increased flexibility in funding also means that when the right person comes along or a new technology opens up, it's easier to manage in terms of budget."

"If you want to have an expansive research program, then you need grant support to do that," added Stowers Investigator Paul Trainor, PhD, who has received funding from the NIH and has served on various grants review panels. "There's just no way around it."

After an award has been won, Lewallen and Garvey pass the baton to Erin Johnson, PhD, grants administration specialist, who helps researchers with aspects of post-award grant management. Johnson assists with periodic financial reports as well as progress updates and final research reports that are required by funding agencies. Johnson, who has a PhD in science, also enjoys the opportunity to utilize some of her scientific training in a professional role that is traditionally highly administrative. "My background allows me to be more efficient in my support role. The advantages range from my ability to better communicate with our scientists to understanding the pressures they are balancing. Being able to read and understand their fascinating scientific ideas is an enjoyable bonus."

Sharpening skills

Stowers Investigators often work with the Grants Office to find grants that are appropriate for them to apply for, and for their trainees, too. Assistant Investigator Sarah Zanders, PhD, came to Stowers with an NIH grant. Lewallen helped her transition the grant from her previous institution and also identify opportunities for her new trainees, who are of different nationalities—something that can matter when applying for grants and fellowships.

"The Grants Office helps us determine good matches, and makes sure that the documents we prepare are actually what the different granting agencies require," says Zanders.

Trainor clarifies that training scientists in grant writing provides important skills for them at many points along their career paths. For students, it gives them practice at what will likely be a crucial part of their professional lives. "If you don't gain experience and practice writing these things from an early stage of your career, then you miss key opportunities to learn how to communicate your science well," he notes. The process can help students accept criticism from reviewers, and rejection, too.

To help researchers at all levels sharpen their skills, the Grants Office frequently hosts grant-related workshops and luncheons with accomplished guest speakers who cover a variety of topics, such as the art of persuasive writing, biosketch and resume writing, and other important skills needed to write successful grants. They invite reviewers from granting agencies to the Institute to discuss what they look for in applications and to network with Stowers scientists.

Anticipating the future

Grants and fellowships also make research trainees more attractive for postdoc or faculty positions. They show how the trainees have already jumped competitive hurdles to obtain research funding. For postdocs getting ready to move to their next position, it can provide money to wrap up their postdoc project and initial funding to start their own lab. It can make a researcher much more competitive in job searches.

"For any scientist, it helps them think through the science," Trainor says.

"When you take the time to sit down and write a research grant, as a trainee or as a faculty member, you have to think carefully about your project. It's a highly detailed road map you're laying out for your research," he explains. "If you don't organize your thoughts and plans by writing a grant or fellowship application, there's a tendency to not think about the work you want to do in as much depth or that far in advance of actually doing it."

Being awarded outside funding is important for the Stowers Institute, too. It reinforces the Institute's position as a premier scientific research center with high-caliber research programs and creates additional channels for sharing Stowers science with the greater scientific community.

"Grant funding can benefit Stowers scientists and the Institute by providing more visibility of the type of research we're working on here. It also enables our investigators to hire more people, expand their programs, bring on additional technology, and ultimately contribute more to scientific discovery," says Lewallen.

"The Grants Office has really hit an effective stride," she adds. "The challenge ahead of us is to continue finding interesting ways to engage our researchers and keep them interested in applying for funding. We're always listening."

A DISCUSSION WITH

ALEJANDRO SÁNCHEZ ALVARADO, PHD

By Jessica Johns Pool

Science, music, art, running, nature, reading: It's hard to find something Alejandro Sánchez Alvarado is not curious about.

By day, the Stowers and Howard Hughes Medical Institute (HHMI) investigator is a pioneering regeneration expert. By night, he's a family man who spends as much time as possible with his wife and two children, while also maintaining a generous schedule dedicated to community outreach.

Sánchez Alvarado is recognized for transforming the planaria flatworm *Schmidtea mediterranea*—famous for its capacity to regrow complete individuals from miniscule body parts—from an unassuming, freshwater-dwelling oddity into a powerful model system for the study of regeneration.

Born and raised in Caracas, Venezuela, Sánchez Alvarado received a BS in molecular biology and chemistry from Vanderbilt University in Nashville, Tennessee, and a PhD in pharmacology and cell biophysics from the University of Cincinnati College of Medicine in Cincinnati, Ohio.

Among his many awards, he was elected a member of the National Academy of Sciences in 2018 and is also a member of the American Academy of Arts and Sciences and the Latin American Academy of Sciences.

Sánchez Alvarado joined the Stowers Institute as an investigator in 2011, with his wife, renowned developmental biologist Tatjana Piotrowski, PhD. Piotrowski also heads her own lab at Stowers, where she uses zebrafish as a model system to study early developmental processes.

HOW DID *SCHMIDTEA MEDITERRANEA* COME INTO YOUR LIFE?

When I was just starting my lab, I really didn't know which organism and what system I was ultimately going to be working on. But my clock was ticking so I began a long, systematic effort to identify a potential organism that would help us interrogate and understand the process of animal regeneration.

I spent a lot of time traveling to some centers of knowledge, usually libraries. It was like searching for treasure.

Google was just beginning to arrive. There was no Google Scholar, and the only way to get to the information I was looking for was to go to libraries and look at the primary texts, or in some cases microfiche, which I also spent a lot of time looking at. When I say microfiche, I still get dizzy. Anyone who is old enough to remember those machines will understand. Microfiche was exhausting.

Eventually, I ended up at an abandoned fountain in Parc de Montjuic in Barcelona, Spain. There was a scientist from Barcelona, Dr. Jaume Baguña, who had written his PhD thesis on *Schmidtea*. He had mentioned to me and others that when it rained, this abandoned fountain filled up with water, and sometimes when it filled with water the animals would come from subterraneous aquifers to the surface to eat, and that we could probably find some there. So that's what we did. I and my then postdoctoral trainee Dr. Phil Newmark waited for the rainy season and then visited Barcelona to collect them.

WHAT WERE SOME OF YOUR FAVORITE LIBRARIES FROM THAT TIME?

I spent time in the Library of Congress in Washington, D.C., poring through all kinds of documents, trying to find examples of animals that regenerated. I also went to the Smithsonian Institution, looking at collections of reprints from Dr. Roman Kenk, who had recently passed away and was a former Director of the Department of Worms, as it was called at the time. Dr. Kenk was completely smitten by planarians, like many other biologists have been in the past, and had amassed the largest collection of reprints in the world of this organism.

They let me go through some of his papers, so I could try to identify the right species. I had already narrowed it down to a specific group of planarians, but I didn't know enough about them because the literature was not really accessible. The papers in Dr. Kenk's reprint collection were of great help in overcoming this difficulty.

I also spent a significant amount of time at the Marine Biological Laboratory in Woods Hole, Massachusetts, where they have a remarkable collection of scientific work that spans centuries. I could walk through the carrels, pull out the volumes that I needed, and then just read.

I spent very long days, and very long nights, which I remember with great warmth, just reading. Getting into the heads of people who were writing those papers, 100, 150, 200 years ago, and appreciating that the questions they were asking were not too dissimilar from the questions that we're asking today, except that they did not have the necessary tools to really delve for a solution like we have today.

WHY IS COMMUNITY OUTREACH SO IMPORTANT TO YOU?

I realized very early on that if we are unable to explain to our fellow citizens what we do, it should be no surprise to us at all that our work is not really appreciated. Many human beings on this planet would like to know where they came from, and that question may take a philosophical bent, a religious bent, a scientific bent. It might even take an agnostic, or a completely nihilistic bent, but it's always there. Hence the success of companies and services providing genealogical information via DNA sequencing. The way I see it is that, irrespective of what our individual drive may be, we are a way by which life can understand itself.

When we can capture and explain the idea that the work we're doing is aimed at understanding basic biological processes that make our lives possible and present it to our fellow citizens, neighbors, and friends, it becomes more of a shared search for answers.

YOU LIKE TO SAY THAT SCIENCE NEEDS THE HUMANITIES. WHY?

Scientists and science cannot operate in a vacuum. The fundamentally shared goals of art and science are to understand and describe the world around us. In fact, the source that brings art and science into life is a shared source. Science and nature influence art, and art can expand the appreciation of science. Art has a really good way of communicating conflicts of emotions, and conflicts of interpretations of the universe. It's always beautiful to see how artists do this.

Scientists are very good at revealing or lifting the veils of the unknown, to see what lies beyond the known, but we are not particularly good at representing that information. So, if you can bring art and science together, and allow the full breadth of our abilities to make sense of and represent that information, it is a much easier thing to appreciate, a much easier thing to understand.

One of the things I am doing right now is bringing practicing artists into my laboratory and sharing with them what we do. They see things that we don't see. And we show them things they have not seen. That helps all of us to see things in a completely different light, and it informs all of our respective thoughts.

HOW DO YOU AND YOUR WIFE BALANCE TWO SCIENTIFIC CAREERS AND FAMILY?

We are still searching. It's like a moving target, but we work in sufficiently different fields that we can still talk about each other's research, and criticize each other's research, without feeling that we are either competing with each other, or have a zero-sum game where one wins and the other loses. We've been lucky in that regard.

It's allowed us to keep our own voice, our own research, and our own identity and way of looking at things. We have very different approaches to science and it constantly reminds me that there is no one way to do great science. That is one of the things I really, really love about having a partner who is also a scientist.

We also invest greatly in family, because no amount of accolades will ever make up for being a bad parent. You can win every prize on the planet, and at the end of the day if you were not a good dad or a good mom to your children, those prizes are meaningless.

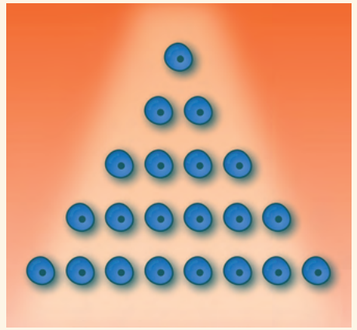
YOU HAVE RECENTLY BEEN NAMED SCIENTIFIC DIRECTOR AT STOWERS. WHAT DOES THAT MEAN TO YOU AND HOW WILL THAT AFFECT YOUR RESEARCH PROGRAMS?

Finding intellectual ecosystems in which the practice of science can be carried out rigorously and with minimal distractions are few and far between. Seven years ago, when my lab members and I moved our families and research programs to Kansas City to join the Stowers Institute, there was a sense that we had finally found a place where we could take a stab at solving difficult, complex, and stubborn problems like, in my case, regeneration. I myself felt rejuvenated.

Today, I espouse the certainty that a place like the Stowers Institute can be a fountainhead of biomedical research innovation, a place where fundamental problems of biology can be systematically and rigorously dissected, a place where scientists can follow ideas of great substance, whether they are fashionable or not. Think about it: What Jim and Virginia Stowers envisioned, and many great leaders have cultivated during the past 19 years, is nothing short of extraordinary. Ours is a veritable engine of discovery: a simultaneous and graceful act of courage and optimism in the ability of our species to vanquish the unknown.

Our Institute is unique in many respects and unlike any other I am aware of. We are relatively young and are collectively building a distinctive and distinguishing culture of excellence and collegiality. I envision the Institute's research efforts to not only grow in depth and complexity, but also extend into novel areas of inquiry where few would dare to go, while creating new models of how to carry out great science. I consider myself fortunate that in my career I will have a chance to contribute to this unique, collective effort to advance human knowledge.

RESEARCH OPENS DOOR TO EXPANDING ADULT STEM CELLS AVAILABLE FOR TRANSPLANTS

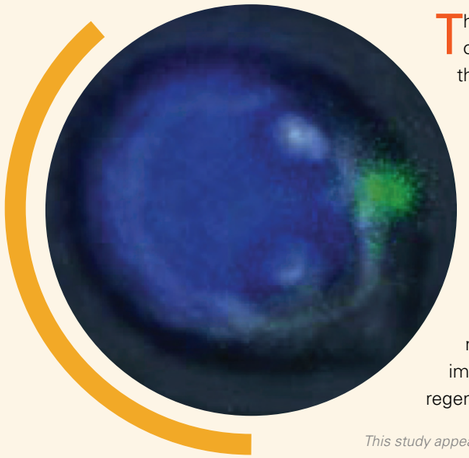


Right now, there's a large gap between the number of patients who need bone marrow and umbilical cord blood adult stem cell transplants and the number of transplant units available for use. This gap is due to the low rate of match between bone marrow donors and possible hosts, and the amount of human umbilical cord adult stem cells needed to treat one adult patient.

Research from the Linheng Li Lab and collaborators has revealed that reducing the function of a protein in human umbilical cord adult blood-forming stem cells allowed those cells to expand. These findings could provide an approach for bridging the adult blood-forming stem cell treatment gap for conditions like leukemia, blood disorders, immune system diseases, and other types of cancers, and may also be more broadly applicable to other types of adult stem cells.

This research was published online July 31, 2018, in Cell Research.

SCIENTISTS HAVE CAPTURED THE ELUSIVE CELL THAT CAN REGENERATE AN ENTIRE FLATWORM

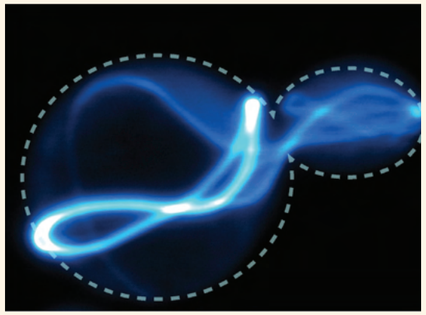


The amazing freshwater flatworm known as planaria is a favorite of scientists who study regeneration in research organisms in the hopes of unlocking this property in humans. Over a century ago, they traced planaria's regenerative powers to a special population of adult stem cells called neoblasts. But until recently, they lacked the tools necessary to home in further on the individual cells truly capable of regeneration.

In a study that combined genomics, single-cell analysis, flow cytometry, and imaging to isolate this elusive cell, scientists in the Sánchez Alvarado Lab and their Stowers collaborators report that a molecule called TSPAN-1 that sits of the surface of cells can be used to purify regenerative neoblasts from similar cell types. These findings have important implications for advancing the study of stem cell biology and regenerative medicine.

This study appears in the June 14, 2018, issue of the journal Cell.

NEW ASSAY REVEALS BIOPHYSICAL PROPERTIES THAT ALLOW CERTAIN PROTEINS TO INFECT OTHERS

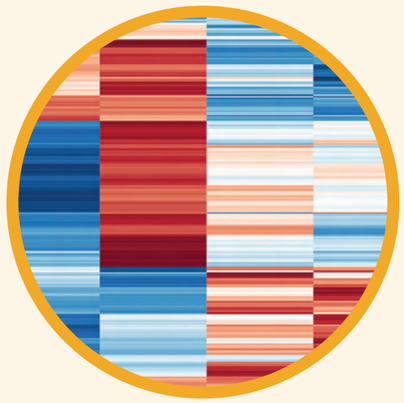


Proteins are essential workhorses of cells and have many roles, from providing structural support to catalyzing almost all of the chemical reactions that must occur for the organism to survive. A protein's function is dictated by its three-dimensional shape. However, a prion protein will sometimes transform itself into a different shape that "infects" other proteins by templating them to adopt the alternate shape. In some cells and tissues, prion accumulations disrupt normal functions and lead to disease. In other cells, however, prion self-assemblies are essential for their normal functions.

How and why do some proteins exhibit prion behavior? Researchers from the Halfmann Lab have identified a physical basis for the transformation. They describe the development of a new technique called Distributed Amphifluoric FRET that measures nucleation—the first step in the transformation—in living cells. The assay can distinguish between proteins that exhibit prion behavior and those that do not. This approach may help researchers understand more about prions associated with diseases as well as prions involved in normal biological processes.

The research was published in the July 5, 2018, issue of Molecular Cell.

NEW MODEL FOR PREDICTING NEUROBLASTOMA OUTCOMES INCORPORATES EARLY DEVELOPMENTAL SIGNALS



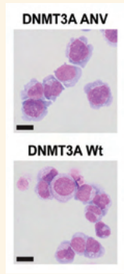
Neuroblastoma, the most deadly cancer for infants and children younger than two years of age, is difficult to diagnose and treat. To improve the chances for survival, scientists have been searching for ways to better understand the cellular mechanics of what causes neuroblastoma and how it progresses.

Using published research on molecular signals important in development and also implicated in neuroblastoma, researchers from the Kulesa Lab and collaborators created a logic-based model that predicted the favorable or unfavorable outcomes of very young neuroblastoma patients with greater accuracy than current methods of predicting outcomes. This work demonstrates the ability of such models to predict disease outcomes and offer a better understanding of molecular network interactions in disease.

This study was published in the July 2018 issue of Biophysical Chemistry.

HOW REGULATION OF A HOX GENE CLUSTER MAINTAINS NORMAL BLOOD-FORMING STEM CELLS AND INHIBITS LEUKEMIA

Hox genes play a critical role in maintaining blood-forming stem cells, and abnormal Hox gene expression creates a risk of forming leukemia. Researchers co-led by Investigators Linheng Li, PhD, and Robb Krumlauf, PhD, found evidence that a key regulatory element called *DERARE* controls Hoxb gene cluster expression in blood-forming stem cells.



"It's like we found a general control that simultaneously turns the lights on and off in many rooms, rather than having a single switch that controls each individual room," says Li. Understanding this regulatory mechanism of the Hoxb cluster provides insight for enhancing blood-forming stem cell function and finding drugs to target acute myeloid leukemia (AML).

This article was published in the May 3, 2018, issue of Cell Stem Cell.

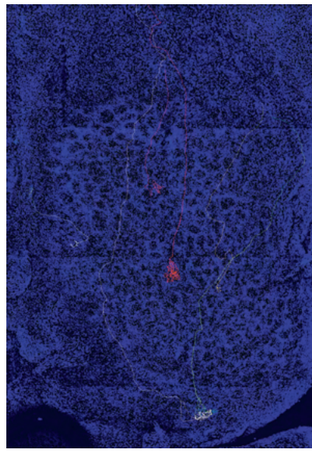
NEW STUDY PROBES THE ANCIENT PAST OF A BODY PLAN CODE

New work from the Gibson Lab has provided a view into the evolutionary history of some of the genes involved in the determination of animal body plans. The findings reveal clues about ancestral functions of Hox genes, which are known to be important regulators of body plan layout for organisms such as spiders, fish, dogs, and humans that have roughly symmetrical right and left sides about a head-to-tail axis.

The researchers studied Hox gene function in the starlet sea anemone, which is a member of a group of radially symmetric animals that also includes jellyfish and corals. Using gene knockdown technology, the researchers report evidence that Hox gene function is important in regulating the sea anemone body plan during development and speculate that a primitive "Hox code" may have been co-opted for use in head-to-tail body patterning by bilaterally symmetrical animals. These findings give researchers a better understanding of the evolution of developmental processes.

These findings were reported in the September 28, 2018, issue of Science.

"NAVIGATOR" NEURONS PLAY CRITICAL ROLE IN SENSE OF SMELL



A newly discovered group of "navigator" neurons may hold the key to understanding the neural circuitry behind our sense of smell. The study builds on a breakthrough 2014 report from the Yu Lab that showed a critical period in olfactory wiring. Glitches in the wiring affect how scents are perceived. Yu and his colleagues found that in mice, there's a brief window to fix problems—about a week after mice are born.

In their follow-up report, the researchers detail the surprise discovery of a group of olfactory sensory neurons, or "navigator" neurons, that play an essential role in establishing the olfactory map, a kind of code book for the scents we encounter. The navigator neurons also correct faulty wiring that can impair the sense of smell. Because navigator neurons look identical and function the same as other neurons, the Stowers researchers creatively employed a variety of approaches and technologies, some they developed themselves, to finally pinpoint them. Learning more about navigator neurons could hold promise for regenerating and repairing olfactory neurons and neurons in other types of neural systems, such as those involved in spinal cord injury.

This report appeared online October 25, 2018, in Neuron.

Stacey Hanlon, PhD

AFTER-HOURS NETWORKING BUILDS CONNECTIONS

By Cathy Yarbrough

Stacey Hanlon, PhD, came to Stowers in October 2014 as a postdoctoral researcher to follow up on intriguing findings from the lab of Stowers Investigator Scott Hawley, PhD, where his team had discovered B chromosomes in a laboratory stock of the fruit fly *Drosophila melanogaster*.

B chromosomes are extra chromosomes that are carried in addition to the normal complement of chromosomes, or A chromosomes, that supply the essential genetic material required for an organism's growth, development, and reproduction. Typically, B chromosomes lack protein-coding genes, are small, and arise from A chromosomes.

First described over a century ago, B chromosomes have since been identified in a wide range of animal and plant species. However, their occurrence in the Hawley lab's stock of *D. melanogaster* provides the first opportunity to investigate these nonessential chromosomes in an established model organism for which a wealth of genetic and molecular tools already is available.

Since joining Hawley's lab from the University of California at San Francisco, where she earned a PhD in biochemistry and molecular biology, Hanlon has subjected *D. melanogaster* B chromosomes to extensive molecular analysis. "We want to know how B chromosomes arise, and what it takes to stabilize and maintain them through multiple generations," she says.

The results of Hanlon's studies may improve scientific understanding of other extra chromosomes, including the small supernumerary chromosomes that have been linked to various human syndromes, intellectual disabilities, and infertility. "The gain of just a small part of a chromosome can negatively impact human health in ways we do not fully understand," she says.

In the December 2018 issue of *Genetics*, Hanlon and her Stowers collaborators reported their research findings thus far. Among the key results is the deep sequencing of the *D. melanogaster* B chromosome, which confirmed that it carries no known protein-coding genes and revealed the presence of a previously uncharacterized unique repetitive sequence. Based on cytological examination of this repetitive sequence, evidence points to chromosome 4 as the origin of the B chromosome.

When not investigating B chromosomes, Hanlon relaxes with other postdocs as well as predocs and research technicians. "I enjoy taking part in the vibrant Kansas City culture with Stowers colleagues who have become good friends," she says. "Whether it's live music or just trying a new place for dinner and drinks, getting to know fellow members in a more casual atmosphere reinforces our professional relationships and makes me more comfortable to discuss new ideas and ask questions when we're together at work."

Hanlon also enjoys local trivia nights and engages in indoor rock climbing because "it helps to clear my mind," she says. "I also like to go to estate sales and look for older biology textbooks. It's really amazing how much we've learned in such a short amount of time!"

In fall 2019, Hanlon will apply for an academic faculty position and will continue to investigate the B chromosomes of *D. melanogaster* in her future independent laboratory. "I have learned firsthand how Dr. Hawley has been able to build and maintain a successful laboratory," she explains. "He puts his lab members first—no exceptions—and is constantly thinking about our success. Specifically, he is always willing to discuss an idea or encourage a risky experiment, and knowing I have his support makes me more confident to explore new directions and push my science forward."

A FEAST OF FUNDING

2018 and early 2019 were especially fruitful for Stowers scientists in training. Four predoctoral researchers in the Graduate School and one postdoctoral researcher in the Gibson Lab were awarded competitive fellowship and grant funding from the National Institutes of Health.

Nicole Nuckolls was awarded a two-year fellowship from the Eunice Kennedy Shriver National Institute of Child Health and Human Development. Her research will examine a class of genes called killer meiotic drivers. This class of genes acquired its name because these genes bias their own transmission to gametes (such as eggs and sperm) by poisoning all gametes but rescuing only the gametes that inherited them during the process of meiosis. Nuckolls's goal is to use yeast to identify the mechanism that enacts the poison-antidote meiotic drive. This research may lead to a better understanding of the origins of infertility.

María Bravo Núñez received her six-year award from the National Cancer Institute. It will support her work focused on identifying mechanisms that cause aneuploidy and infertility. Aneuploidy is a condition in which errors in chromosome segregation generate cells with too many or too few chromosomes. This condition is the leading cause of infertility and congenital birth defects such as Down syndrome.

Specifically, Bravo Núñez will investigate whether genetically parasitic genes contribute to errors in chromosome segregation.

Irina Pushel received a three-year fellowship award from the National Institute of Dental and Craniofacial Research for a project that aims to establish the Hoxa2 gene's activity in craniofacial neural crest cells (cNCC) in a mouse model system. This cell type originates in the brain during early development. From there, cNCCs migrate out and give rise to bones, tissues, and nerves of the head. When there are disruptions in this process, craniofacial defects and disorders can occur. Pushel plans to identify the relationships between certain genes involved in this process so that she can bring greater understanding to the related human process.

Cassandra Kempf also received a three-year award. The award from the National Institute of General Medical Sciences funds her research of the Sin3 complexes. These protein complexes have been linked to cancer and neurological disorders. Kempf aims to identify direct interactions of these proteins, some of which may likely be competing for the same interactions in the same cell, using biochemical and quantitative imaging techniques and then build a model of the protein interaction network whereby direct interactions can be defined in a systematic way.

Eric Hill, PhD, was awarded a two-year fellowship through the National Institute of General Medical Sciences. He received funding for a project that will examine the similarities and differences between the developmental and the regenerative organ formation in the starlet sea anemone, *Nematostella vectensis*. The sea anemone is well-suited for this project because all organs are formed through normal embryonic development but can also fully regenerate following removal in the adult anemone. Better understanding of this function may reveal deep insights into natural mechanisms that underlie whole-organ regeneration.

Maria Bravo Núñez, Irina Pushel, Nicole Nuckolls

Eric Hill, Cassandra Kempf

BRIDGING THE GAP AS A MENTOR

By Cathy Yarbrough

Scheduling time to mentor the graduate students and postdoctoral researchers in her lab at the Indiana University School of Medicine (IU) is a high priority for Amber Mosley, PhD, Associate Professor of Biochemistry and Director of Proteomics at IU.

Mosley joined IU in 2010 after completing her own postdoctoral studies at the Stowers Institute, where she was co-mentored by Michael Washburn, PhD, Director of the Proteomics Center, and Investigator Jerry Workman, PhD. Like Workman, Mosley conducts research related to gene transcription, the copying of a DNA sequence into a messenger RNA (mRNA) molecule. Cellular machinery subsequently translates the mRNA molecule into a specific protein.

"I realize how important mentoring is to a scientist's career because of the excellent mentoring that I received while I was at Stowers," Mosley shares. Workman and Washburn have continued to help Mosley advance her career. "In fact, they recently wrote letters in support of my NIH grant application," she says.

During her almost six years at the Institute, Mosley was based in the institute's Proteomics Center. "I had not worked in proteomics before arriving at Stowers," says Mosley, who received a PhD in biochemistry at the University of Kentucky College of Medicine (UK).

Prior to joining Stowers, Mosley applied molecular biology and biochemical approaches, but not proteomics, to her graduate studies on gene transcription at UK. Proteomics was then an emerging field. During her 2004 interviews for a postdoc position, Washburn introduced Mosley to the center's Multidimensional Protein Identification Technology (MudPIT), a powerful mass spectrometry technique capable of generating a high volume of data about protein-protein interactions.

Recognizing the potential of proteomics to enrich scientific understanding of gene transcription, Mosley asked to be located in the Proteomics Center when Stowers offered her a postdoc position. While a postdoc, Mosley became a proteomics expert, thanks to the training provided by Washburn and Laurence Florens, PhD, head of Proteomics. Mosley's gene transcription research benefitted from her newfound expertise in proteomics. Among her findings was the discovery that the phosphatase enzyme Rtr1 is a regulator of gene transcription.

At IU, Mosley regards the time and effort that she spends in mentoring as "paying it forward." Her schedule includes specific times to meet each graduate student and postdoc in her lab. Mosley also plans to mentor IU junior faculty as part of the university's Independent Investigator Incubator. "It's extremely helpful when more experienced scientists take an active interest in your career," she says.

Mosley's training in the Institute's proteomics team provided not only expertise in the field but also insight about interacting with faculty members who use service centers such as IU's proteomics facility. "At Stowers, I learned the importance of helping faculty members with their experimental design and establishing realistic expectations about what could be achieved and when it could be achieved," Mosley explains.

With a husband, two daughters, two dogs, two cats, and a tortoise at home and a time-demanding career at IU, Mosley said she tries to have realistic expectations about what she can achieve daily. "I have a full but very busy life," muses Mosley.

SEVENTH SET OF SCIENTISTS

The Graduate School of the Stowers Institute for Medical Research launched its seventh year with six predoctoral researchers whose interests in science were sparked in a variety of interesting ways. Get to know this intriguing group better by visiting https://www.stowers.org/gradschool/predocs.

Kaelan Brennan

Purdue University

Kaelan Brennan's earliest curiosity about science-related topics began in a garden, when his mother explained that even though the plants couldn't move or talk, they were still very much alive and growing, just like he was. That sparked many questions and a future interest in biology. In high school, he even took AP Biology twice because he found it was so much fun.

Luciana Castellano

National University of General San Martin

Everything about nature, from planets to individual cells, interested Luciana Castellano when she was a little girl in Buenos Aires, Argentina. But it was her high school biology and genetics classes that solidified her desire to one day pursue a career in scientific research.

Aubrey Kent

William Jewell College

Aubrey Kent says that if anyone told her six years ago she would be working on a PhD, she would have laughed. Home-schooled during high school, Kent wasn't exposed to much science until she decided to pursue higher education in her 20s. That's when she discovered her passion for the biological sciences.

Originally, Kent enrolled at a community college with the aim of becoming a radiology technician. A general biology course got her hooked.

Yue Liang

Wuhan University

While earning her bachelor's degree in biological sciences from Wuhan University in Hubei, China, Yue Liang spent eight months at the Australian National University's John Curtin Medical School. There, she studied DNA double-strand breaks and the role histone proteins play in the correct transfer of genetic information. This experience fueled her desire to pursue basic scientific research as a lifelong career.

Emma Moore

University of Houston

Emma Moore caught the research bug during high school when she interned in a marine biology lab. She had always enjoyed science, but this formative experience made her appreciate the level of discussion and thought required to perform research. After that first lab experience, she continued to find internships that exposed her to different kinds of research.

Sajjita Saha

Indian Institute of Science Education and Research, Kolkata

As an 8-year-old, Sajjita Saha wanted to understand how her pet dog knew she was coming home from school and would be waiting at the door with a toy so they could go out and play. Her mother explained that her dog's sense of smell was more powerful than a human's, but that answer didn't satisfy the curious Saha. Such childhood questions led her to major in science.

Promotion and renewal

The Stowers Institute relies on the Scientific Advisory Board for guidance in matters of importance to the Institute's achievement of scientific excellence. It pursues this through evaluation of current research underway at the Institute, discussion of future research initiatives and new technologies to be developed at the Institute, review of candidates for appointment and reappointment who have passed through the screening and evaluation process, and ratification of those candidates who meet the high standards of the Institute for appointment or reappointment as independent scientists.

In 2018, the SAB recommended renewal of Investigator Paul Trainor, PhD, for another seven-year term. They also recommended the promotion of Associate Investigator Julia Zeitlinger, PhD, to full Investigator.

Trainor's research focuses on understanding the normal course of vertebrate head and face development and identifying genes that when mutated result in birth defects.

Zeitlinger's research aims to identify predictive rules by which gene expression programs are established in an organism and apply them to human disease.

Rohner research rewarded

Assistant Investigator Nicolas Rohner, PhD, became the first Stowers scientist to receive a Mallinckrodt grant. He was awarded $60,000 per year for three years. The award will partially fund Rohner's research on the freshwater fish, *Astyanax mexicanus*, an emerging metabolic and genetic model system for studying metabolism.

The Edward Mallinckrodt, Jr. Foundation is a private foundation that funds basic biomedical research. Based in St. Louis, the Foundation's mission is to support early-stage investigators engaged in biomedical research that has the potential to significantly advance the understanding, diagnosis, or treatment of disease.

Rohner and his lab will compare genomes of two distinct populations of *Astyanax mexicanus*: a surface-feeding form with ample food supply and a cave-dwelling, dark-adapted form with limited and seasonal food supply. The researchers seek to identify the genetic changes the cavefish have acquired that allow them to be starvation-resistant and to circumvent the negative health consequences usually associated with such extreme metabolic conditions. This research has the potential to yield information that may provide a better biological basis for therapeutic interventions for diabetes.

Rohner's research on cavefish has also garnered him a generous grant from the Juvenile Diabetes Research Foundation. The nearly $300,000 two-year grant will further fund his research programs that seek to find answers and possible treatments for diabetes and associated auto-immune reactions.

Top science award goes to Sánchez Alvarado

Spring 2018 arrived at the Stowers Institute with the announcement that Alejandro Sánchez Alvarado, PhD, a Stowers and Howard Hughes Medical Institute (HHMI) investigator, had been elected a member of the prestigious National Academy of Sciences (NAS).

Membership in the NAS is considered one of the highest honors given to a scientist in the United States. The Stowers investigator was inducted into the NAS at its 156th annual meeting in 2019 in Washington, D.C.

A pioneering regeneration expert, Sánchez Alvarado transformed the flatworm *Schmidtea mediterranea*—famous for its capacity to regrow complete individuals from miniscule body parts—from an unassuming, freshwater-dwelling oddity into a powerful model system for the study of regeneration.

"The Stowers Institute is proud of Alejandro's pioneering work in establishing the flatworm as a model system and building an international community devoted to its study," says David Chao, PhD, president and CEO of the Stowers Institute. "We are delighted and privileged to count such an innovative and inspirational scientist as a colleague and friend."

Zeitlinger lands a zinger with NIH grant

Investigator Julia Zeitlinger, PhD, was awarded a four-year, approximately $2.3 million grant from the NIH's National Human Genome Research Institute. This marks the first grant awarded to a Stowers scientist by this NIH institute.

Zeitlinger's research focuses on how DNA sequence information in the genome controls gene regulation. The Zeitlinger Lab aims to develop breakthrough genomic techniques that will allow for the collection of "cis-regulatory" information. A cis-regulatory module is a stretch of DNA where a number of transcription factors can bind and regulate expression of nearby genes and regulate their transcription rates. However, scientists have encountered challenges with collecting and mapping cis-sequence information due to insensitive and sparse data.

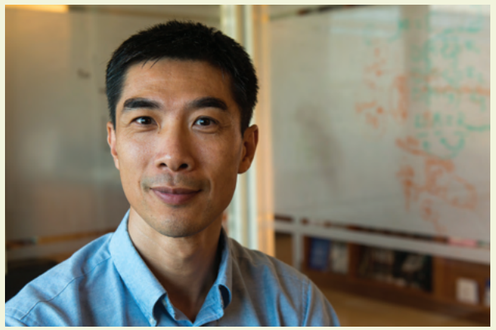
National Human Genome Research Institute

Zeitlinger and her lab have developed a technique that will allow for improved data collection with smaller samples, eventually even as small as a single cell, yet with greater resolution and sensitivity. With better sampling technique and data collection, Zeitlinger hopes to improve the ability to study mammalian embryogenesis which may improve our understanding of development, evolution, and disease.

Two Stowers investigators secure pilot project grants from KU

Investigators Jennifer Gerton, PhD, and Kausik Si, PhD, both received one-year pilot project grant funding through the University of Kansas (KU). Si is using his funds from the KU Alzheimer's Disease Center to examine the role of a neuronal RNA binding protein and its role as a biochemical substrate of long-term memory. Gerton received funds from the KU Cancer Center Biology Research Program. She is using her grant funding to investigate whether centromere sequence instability in cancers could result in aneuploidy.

Yu scores five-year funding for olfactory system research



Investigator Ron Yu, PhD, has received a five-year, $2.3 million grant from the NIH's National Institute on Deafness and Other Communicative Disorders to fund research on the molecular mechanisms that control the critical period—a time when neurons and their circuits are particularly sensitive to influence from the environment—in olfactory system development.

In the mammalian brain, olfactory sensory neurons (OSNs) regenerate continuously, so it has been thought that the olfactory system does not exhibit a critical period during development. Yu's team discovered that, in fact, there is a critical period in the first postnatal week during which OSN connections can be modified. New studies from the team indicate two separate developmental events occurring before and after the critical period, accompanied by significant changes in gene expression.

Yu and his lab plan to probe these genetic switches to gain a greater understanding of adult neurogenesis and how developmental and aging processes affect olfactory functions. Olfactory deficiency is often the earliest sign of neural degenerative diseases such as Alzheimer's and Parkinson's. A mechanistic understanding of the developmental processes may provide insights into neurodegeneration.

Baumann recognized with the George R. Collins Education and Training Award

Diana Baumann, head of the Stowers Reptile & Aquatics Facility, was selected as the 2018 recipient of the American Association for Laboratory Animal Science (AALAS) George R. Collins Education and Training Award for her outstanding contributions to the field of laboratory animal training and education over the course of her career.

AALAS is a membership association of professionals employed around the world in academia, government, and private industry who are dedicated to the humane care and treatment of laboratory animals, as well as the quality research that leads to scientific gains that benefit people and animals.

Baumann was presented the award during a ceremony at the organization's annual meeting in October 2018.

Zanders lands not one, but two major awards

Assistant Investigator Sarah Zanders, PhD, received two highly competitive and prestigious awards in 2018. In July, she received notification that she had been selected as the 2018 National Institutes of Health (NIH) Director's New Innovator Award recipient. This nearly $2.5 million award is part of the High-Risk, High-Reward Research program and is intended to support exceptionally creative early-career investigators who propose innovative and high-impact projects.

Zanders was also named a 2018 Searle Scholar. This highly competitive award is presented to only 15 individuals each year. Each $300,000 award funds the independent research of outstanding early-career scientists who have recently been appointed as assistant investigators.

Zanders' research focuses on selfish genes in gametogenesis.

Zanders explains, "Genomes contain 'good genes' that promote the health of an organism and 'bad genes' that promote their own survival at the expense of their host. Parasitic bad genes can affect crucial cellular processes. This is especially true of gametogenesis, the process that generates eggs and sperm. Meiotic drivers are one type of bad gene. These DNA parasites exploit gametogenesis to bias their own transmission. Instead of being transmitted to 50% of gametes (such as sperm) like regular alleles, meiotic drive alleles can be transmitted to up to 100% of functional gametes."

By studying the *wtf* family of meiotic drive genes in the fission yeast *Schizosaccharomyces pombe*, Zanders and her lab aim to uncover the strategies used by *wtf* genes and explore how they have affected genome evolution.

Sharing BIG IDEAS @ScienceStowers

> "Our Institute's great convening power attracts the very best scientists. What better way to share the excitement and importance of science in our lives than to have our visitors share their creative and daring scientific ideas in an engaging and accessible way with the greater Kansas City community?"
>
> *– Alejandro Sánchez Alvarado, PhD*


Manu Prakash, PhD

In 2018, the Stowers Institute launched a new lecture series, BIG IDEAS @ScienceStowers, with talks by two dynamic and creative scientists. The lecture series was developed to meet the greater Kansas City community's increasing curiosity and interest in science by presenting cutting-edge and provocative scientific ideas in an engaging and accessible way.

Like excited concert-goers, guests streamed into the Stowers auditorium as vivid scientific images and the faces of researchers panned across the stage screen. As the lights dimmed and the spotlights brightened, voices hushed. Guests were greeted by Stowers Investigator Alejandro Sánchez Alvarado, PhD. Sánchez Alvarado exuded his own excitement as he described the launch of the lecture series that is designed to inspire a thirst for scientific knowledge and illustrate the roles that scientific discovery plays in both our lives and our communities.

"Our Institute's great convening power attracts the very best scientists. What better way to share the excitement and importance of science in our lives than to have our visitors share their creative and daring scientific ideas in an engaging and accessible way with the greater Kansas City community?"

The Institute's inaugural guest was Manu Prakash, PhD. With a bachelor's degree in computer science and engineering and a PhD from MIT, Prakash leads a curiosity-driven research group in the department of bioengineering at Stanford University. Prakash is an inventor at heart and designs and builds tools that address unmet needs in global health. One of those tools is a low-cost field microscope that allows communities around the world to observe the microcosmos. Prakash shared the process of identifying challenges, designing solutions, and deploying these


Ahna Skop, PhD

tools to enable open-ended scientific curiosity and inquiries in communities around the world.

By connecting the dots between science education, biodiversity mapping, environmental monitoring, and global health, Prakash explained the role of "simple" tools in advancing access to science and better human health in a resource-limited world.

The second event featured Ahna Skop, PhD, an artist and professor in the Department of Genetics at the University of Wisconsin-Madison. There, she runs a lab that investigates the molecules and mechanisms that control how cells divide during embryonic development. Recognizing that scientists' curiosity often originates in observing the beauty of nature, Skop curates art exhibits that promote the beauty of science.

Throughout her lecture, Skop illustrated how creativity is a driving force in art as well as science and recounted how she is empowering creativity in the classroom to the benefit of students, particularly those who struggle with standard approaches to learning.

More BIG IDEAS @ScienceStowers lectures are planned for 2019.

POMP AND CIRCUMSTANCE

In 2018, two predoctoral researchers were awarded the degree of PhD by the Graduate School of the Stowers Institute for Medical Research. Wanqing Shao, PhD, and Cori Cahoon, PhD, were hooded and received their diplomas in a ceremony attended by their colleagues, mentors, friends, and family.

Shao's thesis work in the Zeitlinger Lab focused on Pol II, which is a well-established regulator of the timing, rate, and possibly the magnitude of transcriptional responses. Transcription, which is the first step in gene expression, involves copying a gene's DNA sequence to make an RNA molecule, and regulation of Pol II pausing allows fine-tuning of gene expression. Shao's research examined the relationship between two of Pol II's regulatory roles—transcription initiation and pausing—as well as the role of promoter sequences in Pol II pausing. Shao's thesis study provides valuable insights into transcriptional response regulation and constructs a framework for analyzing the interplay between transcription initiation, Pol II pausing, and core promoter sequences in vivo.

Cahoon completed her thesis work in the lab of Investigator Scott Hawley, PhD. Her research focused on understanding the role of the synaptonemal complex in the segregation of chromosomes during gamete formation. Errors in meiotic chromosome segregation are the leading cause of miscarriages and birth defects in humans. Chromosome segregation errors can result in conditions such as trisomy 21 (Down syndrome), trisomy 18 (Edwards syndrome), and monosomy X (Turner syndrome).

ADVANCING INTERNAL DIALOGUE

In what has become an annual event, Stowers members converged on the Kauffman Foundation Conference Center for two days in September. The 12th Young Investigators Science Retreat (YISR) provided young scientists an opportunity for growth by sharing their work. An Institute-wide event, YISR also promotes internal collaboration through scientific dialogue and fosters a wider sense of community.

YISR features short talks and poster presentations primarily by predoctoral and postdoctoral researchers and staff scientists. These opportunities allow trainees and other scientists to gain confidence in their presentation strengths and provide important feedback from fellow researchers and mentors through questions and answers, and poster discussions.

The event was highlighted by keynote speaker Jesper Svejstrup, PhD, who delivered the Jim Stowers Memorial Lecture titled "Transcription and the Response to DNA Damage." Dr. Svejstrup is a group leader at the Francis Crick Institute in London, where his lab studies the molecular mechanisms of transcription and how transcription interacts with processes such as DNA repair, replication, and recombination.

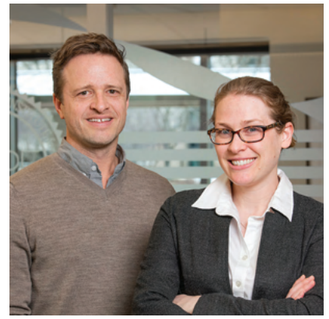
YISR is sponsored by the Crossroads Committee which is comprised of students, postdoctoral researchers, and core and staff scientists. The committee also organizes professional development workshops throughout the year.

These opportunities allow trainees and other scientists to gain confidence in their presentation strengths and provide important feedback from fellow researchers and mentors through questions and answers, and poster discussions.

TRANSITIONS AT THE HELM

As one year was ending and another was just on the horizon, Stowers Institute and Graduate School leadership announced a series of significant transitions that will play out in full in 2019.

SCIENTIFIC DIRECTOR. On July 1, 2019, Stowers and Howard Hughes Medical Institute Investigator Alejandro Sánchez Alvarado, PhD, will become the Institute's new Scientific Director, replacing Robb Krumlauf, PhD, who has served as Scientific Director since the Institute began operations. Investigator Kausik Si, PhD, will take the new position of Associate Scientific Director. Krumlauf will continue to serve as Scientific Director until July 1. Afterward, he will remain at the Institute as an active investigator and Scientific Director Emeritus.



DEAN OF THE GRADUATE SCHOOL. At the same time, Investigator Matt Gibson, PhD, will become the Graduate School's new Dean while Assistant Investigator Sarah Zanders, PhD, will take the new position of Vice Dean. Gibson will replace Investigator Scott Hawley, PhD, who was instrumental in developing and launching the graduate program. Hawley will remain at the Institute as an active investigator and Dean Emeritus.

President and CEO Dave Chao reflects, "Robb and Scott have been with the Institute from its earliest days and have played integral parts in its success. Over almost two decades of service, their exceptional leadership, scientific acumen, scholarship, and collegiality have helped make the Institute and its graduate school a tremendous success. We all look forward to the Institute's continued success under the dynamic and capable leadership of Alejandro, Kausik, Matt, and Sarah."

In perspective

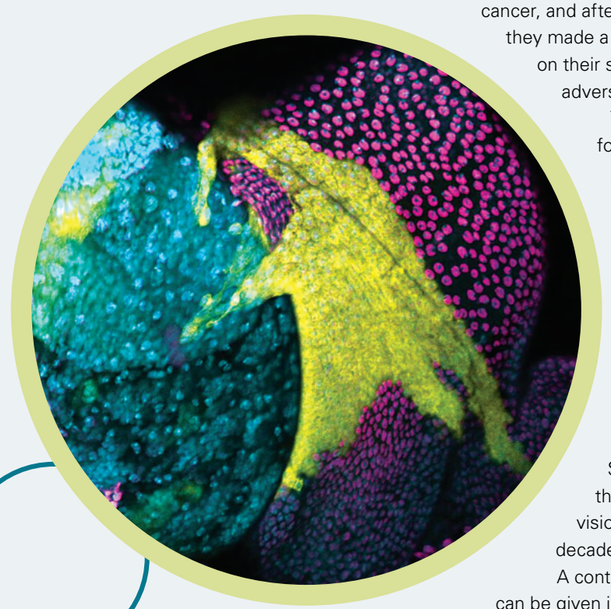
▸ continued from page 1

As the Institute welcomes its next generation of leaders, I am as struck as much by their differences as by their similarities. Our scientific leaders, past and present, come from dramatically different backgrounds, work on dramatically different areas of biology and have effective, but dramatically different, leadership styles. There is strength in the diversity of our leaders, and there is even more strength in what our leaders have in common—a love for science, the Institute and its members. As they prepare to build upon the accomplishments of our founding generation of scientific leaders, I am impressed by our new leaders' confidence, passion and commitment. Perhaps the greatest gift that the Institute has received from its founders is a vision and set of values that have inspired our leaders and members to build a special institution where collaboration, creativity and an enterprising approach all combine to make magic happen.

As you read the latest examples of the Institute's accomplishments and initiatives in these pages, I hope you share my pride in what the Institute has achieved, my excitement about our new leaders, and my confidence in Jim and Virginia Stowers' credo that "The Best is Yet to Be."

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®.

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Stephen Garcia
John Geli
Jennifer Gerton
Mark and Rhonda Gilstrap
Michael Gomez
Stephen and Patricia Gound
Robert Guillocheau
Bernard Hamblin
John Hartley
Yutaka Itabashi
Wesley Kabance in Memory of Nancy Kabance
James Kais
Steven and Joyce Klein in Memory of James E Stowers Jr.
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Labconco Corporation
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Barbara Marshall
James McCarthy
David McLeod
Kara Miller
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John and Karen Thiel
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William Yoerger
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Up to $999

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Alex and Beth Arnz in Memory of Nancy Kabance
Michael and Rhonda Banks in Memory of Kathleen Dvergsten
Audrey Barstad in Memory of Kathleen Dvergsten
Robert Bilo
Richard Boeth
Shirley Bousman
Harold Boxberger
The Branciforte Family in Memory of Nancy Kabance
Janice Burch and Michael Platner in Memory of Anna Elizabeth Ross
Judith Bustamante Beard
Eden Butler in Memory of Nancy Kabance
Laura and Wesley Cameron in Memory of Kathleen Dvergsten
Stephen Campbell
Christina Carpenter
Patricia Carson in Memory of Richard Arthur Hultquist
Cleo Chang
Nathan Chaudoin
Harriet Church in Memory of Nancy Kabance
Mike and Brenda Costigan in Memory of Edward Costigan
Fred III and Carolyn Coulson in Memory of Frederick Coulson Jr. and Mary Coulson
Jody Craven
Sridhar Dhandamudy in Memory of Nancy Kabance
James and Cheryl Doig in Memory of Kathleen Dvergsten
Julie Dowling in Memory of Nancy Kabance
Ruby and Kelly Dunn in Memory of Kathleen Dvergsten
Richard Eagar
Mark Elliott
John Estes in Memory of Nancy Kabance
Charles and Joni Etherington
Arthur Frankel in Memory of Nancy Kabance
Travis Gavinski
Vince Gianatasio
Matthew Gibson
Jerry Giovinazzo
Katy Graham, *including In Memory of Kathleen Dvergsten In Memory of Thelma Nadine James*
Great-West Financial
Jeanne Greenwald in Memory of Martin Greenwald and James E Stowers Jr.
Edward Jr. and Jody Griffin
Sara Gude
Ted Halpern in Memory of Nancy Kabance
Heather Hassett
Norene Hedrick, *including In Memory of Nancy Kabance*
Brian Heinke
Melissa Hemann
Jason Hoffman
Joseph Hogan
Lori and James Houghtaling in Memory of Kathleen Dvergsten
Bettina and Dennis Hoye in Memory of Kathleen Dvergsten
John and Connie Hoye in Memory of Kathleen Dvergsten
Carol Ann Huseby
Hy-Vee Inc
Douglas Igel
IMA Foundation
Michael Jackson
Catherine Jaquette in Memory of Nancy Kabance
Gayle Job in Memory of Nancy Kabance
Shubha Johnson on behalf of Oakton HS Boys Basketball Program in Memory of Nancy Kabance
Jane Johnston in Memory of Anna Elizabeth Ross
Galen Kabance in Memory of Nancy Kabance
Kansas City Young Matrons
Kristina and Bill Keck
Kelly Kerr
Phillip and Christina Kline in Memory of Kathleen Dvergsten
Frances and Jim Kurtenbach, *including In Memory of Kathleen Dvergsten In Memory of Margie Jeroma Yarbrough*
Brian and Teri Kurtz in Memory of Nancy Kabance
Paula Kurtz, Kim Kurtz Burzinski and Joe, Kris Kurtz, Kelly Kurtz in Memory of Nancy Kabance
Barbara Lewis
Christopher Luongo
Nancy Maritato in Memory of Nancy Kabance
Markel Corporation
Patti Mathews in Memory of Nancy Kabance
Kathy McMillen in Memory of Nancy Kabance
Jack and Betty Miller in Memory of Kathleen Dvergsten
Steven Miyao
Jim and Susie Morris
Vincent Morris
Shari Mount
Brian Munn
Cynthia Neath
Margaret Nelson in Memory of Nancy Kabance
Paula Ness in Memory of Kathleen Dvergsten
Pamela and Keats Nicoll in Memory of Nancy Kabance
Richard O'Donnell in Memory of Nancy Kabance
Frank Leo O'Gara
Audra Olson
James and Josephine Olson
Kirsty and Matt Peev in Memory of Nancy Kabance
Brian Pendland
Carol and Loyola Puckett in Memory of Nancy Kabance
Tanya Ratliff
Alexander Reed
Chris and Lisa Reitz in Memory of Nancy Kabance
Retirement Benefits Group
Gary Reznik
Martha Rocha
Edward Rosenberg
Route 66 RV Network
Stanley Sanborn
Jamie Scheibach
Michelle Schmader
Danielle Scholes
Marilyn Schuetz in Memory of Kathleen Dvergsten
James and Susan Seidel in Memory of Nancy Kabance
Paul Shahrokhi
Tom and Amy Shelton
Pat and Lynette Smith in Memory of Nancy Smith Kabance
Erin Spivak
Claire Storey
Michael Suess
Brian and Kristen Sweeney
Stephen Thune
Karyn Walden-Forrest
Diane Walgamuth in Memory of Kathleen Dvergsten
Matthew Watson
Lila Weinstein
Carl J Westring
Kathleen Whitelock in Memory of Nancy Kabance
Daniel Wilcox
Renn and Michele Williams in Honor of Jennifer Marbutt
Kerry Woods
Lorna Wright
Ting Xie
Christopher Zinzi in Memory of Nancy Kabance

BACKSTAGE PASS

The Cube is a high-tech supermarket of sorts for a plethora of commonly used scientific supplies. With dedicated space, knowledgeable personnel, and time-saving technology, it is part stockroom, part convenience store, and part showroom. Researchers enjoy the convenience of on-site shopping and the opportunity to view new products before deciding to purchase. Lab space is freed up as well by eliminating the need to store large supplies of frequently used items like pipettes and gloves. And the Cube's technology makes the process of shopping simple. Each item is labeled with an RFID tag that is automatically scanned when placed on the checkout table and billed to the corresponding lab after a quick biometric scan of the shopper's fingertip.

THE CUBE BY THE NUMBERS

$6,003,494.69
Total of purchases

3,669,700
Number of gloves purchased

128,863
Total items sold

35,001
Media Prep Facility items purchased through the Cube

27,510
Number of items delivered to labs since 2013

18,246
Number of deliveries to labs since 2013

5,830
Purchase orders issued for Cube items

777
Number of users since 2013 with access to checkout

$0
Total freight charged by suppliers for items in the Cube

(Based on 2018 Numbers)

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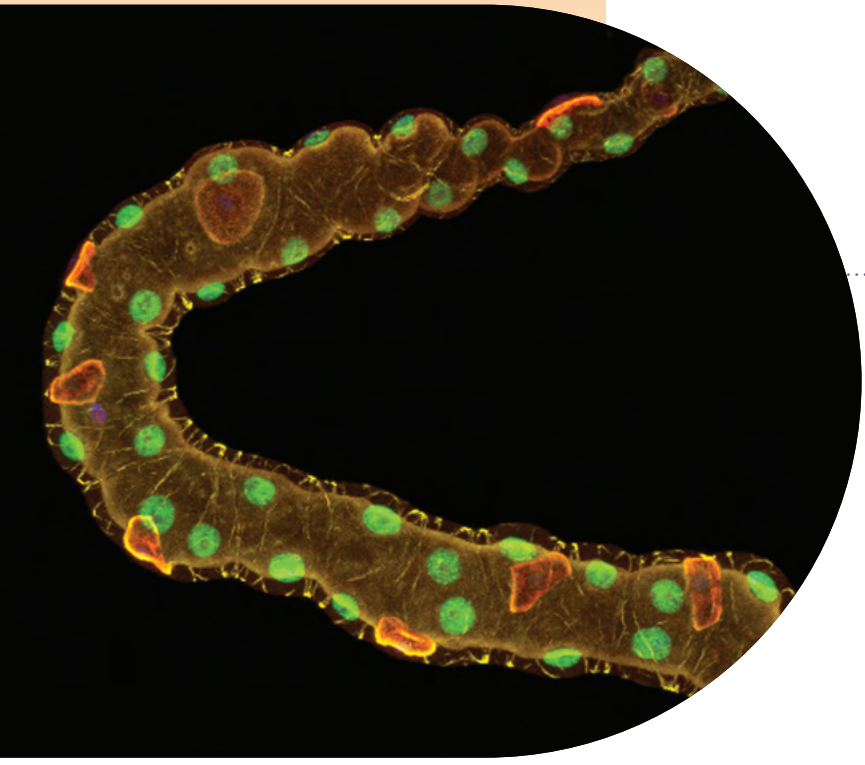
TO MAKE A SIGNIFICANT CONTRIBUTION TO HUMANITY THROUGH MEDICAL RESEARCH BY EXPANDING OUR UNDERSTANDING OF THE SECRETS OF LIFE AND BY IMPROVING LIFE'S QUALITY THROUGH INNOVATIVE APPROACHES TO THE CAUSES, TREATMENT, AND PREVENTION OF DISEASES.



Fruit fly malpighian tubules, stained here for actin and DNA, fulfill a similar role as the vertebrate kidney. Gibson Lab researchers identified a novel gene that regulates the functioning of this essential structure.