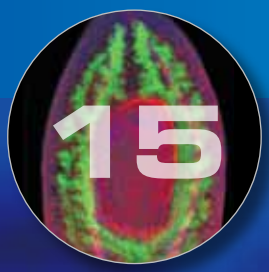
THE POWER OF COLLABORATION

A DEEPLY INGRAINED CULTURE OF COLLABORATION AND TEAMWORK DRIVES RESEARCH AT THE STOWERS INSTITUTE.

STOWERS REPORT

NEWS AND INSIGHT FROM THE STOWERS INSTITUTE FOR MEDICAL RESEARCH

SPRING 2012



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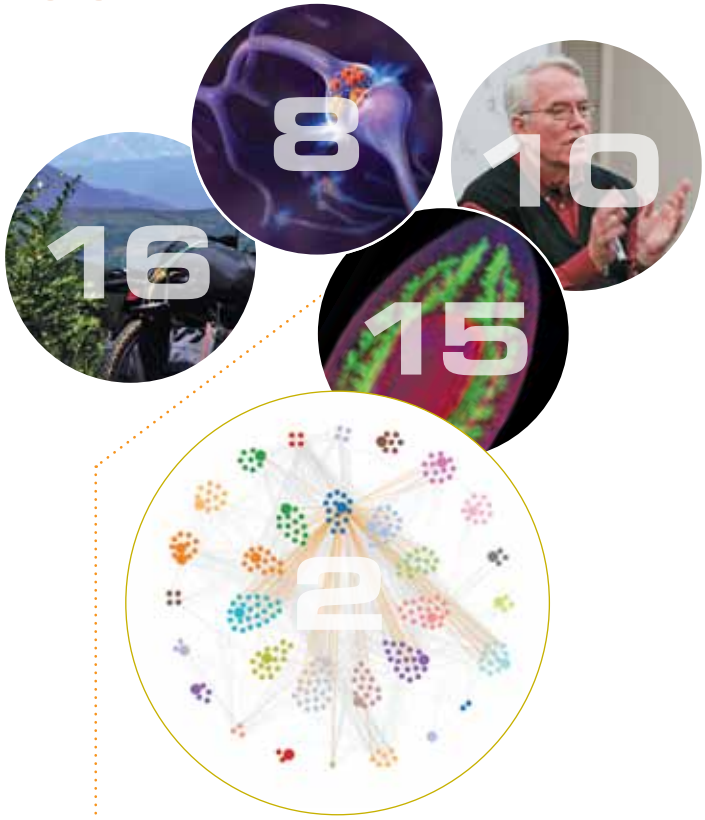

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In perspective

BY DAVID CHAO, PHD,
PRESIDENT AND CEO

One of the most pervasive stereotypes perpetuated in books and movies is the romantic image of the lone scientist: A solitary genius—brilliant, driven, and maybe a bit strange—making a revolutionary scientific discovery while experimenting in the basement.

Solo authors may indeed have had the upper hand in the past. Take Johann Gregor Mendel, whose work in the mid-eighteen hundreds led to the concept of heredity units, now known as genes. He ran a one-man lab in the Moravian monastery where he spent his days as a monk, painstakingly counting the seeds produced by at least 28,000 pea plants. Today, he would be hopelessly outgunned.

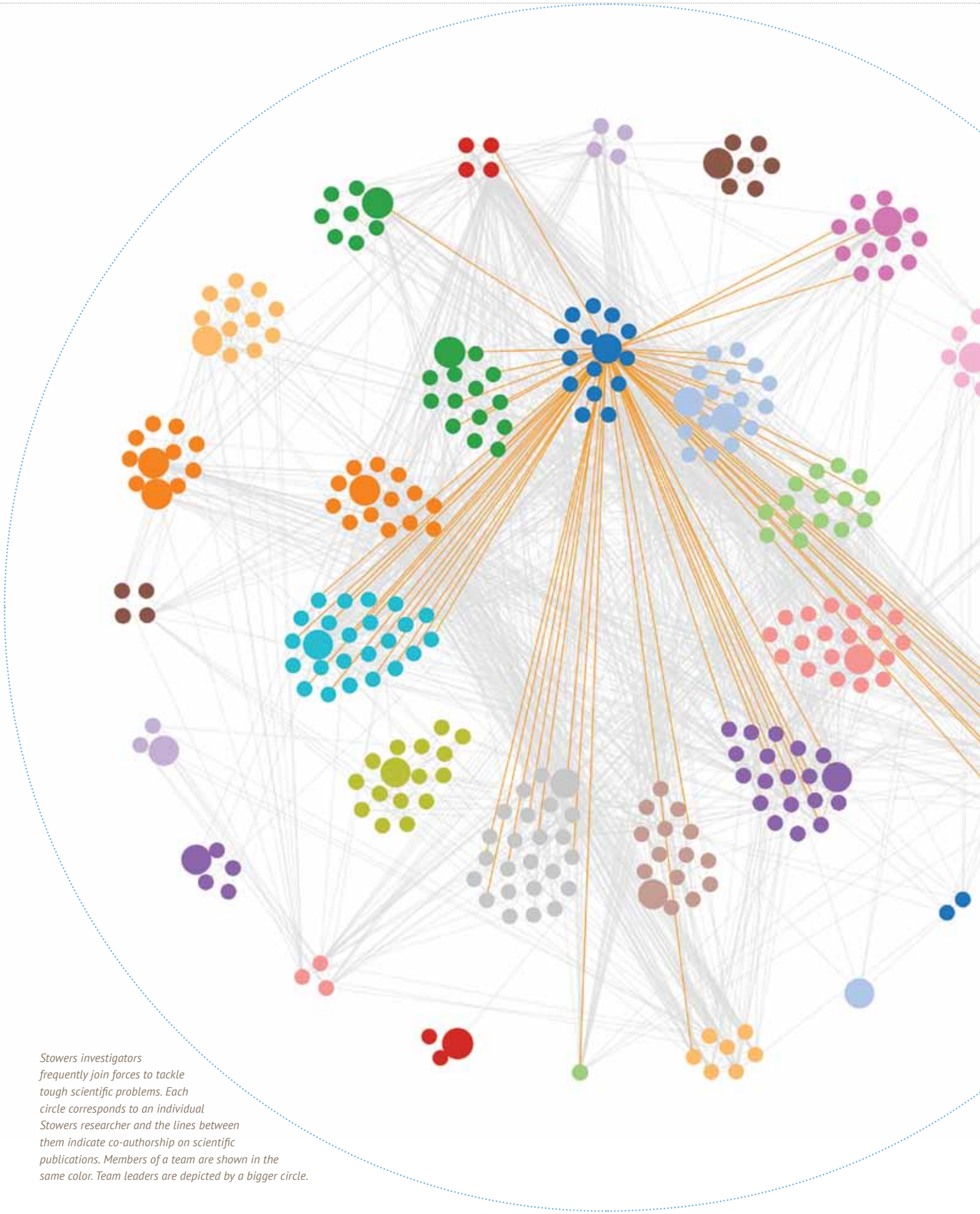
Science in the twenty-first century is all about collaboration and teamwork. A wide-ranging study by three professors at Northwestern University demonstrates that teams dominate the modern-day production of scientific knowledge. The authors analyzed 19.9 million scientific papers published over five decades and 2.1 million patents filed, and found that both team size and the contributions of teams to science had increased dramatically over the last several decades.

The shift toward collaborative research raises the question of whether teams actually produce better results. Individual team members may bring specialized skills and knowledge to the table, but coordinating a large group has its cost. In the words of F. Scott Fitzgerald: "No grand idea was ever born in a conference."

One way to measure the impact and influence of a research study is to determine how often it has been cited by other publications. More influential papers are cited more often, and the number of citations directly correlates with research quality. During the study period, teams consistently published papers with higher impact compared to the work of individuals. What's more, collaborative efforts were also more likely to produce papers that were singularly influential, triggering the kind of radical innovation long thought to be the sole province of highly creative individuals.

Jim and Virginia Stowers recognized the power of "group genius" and made collaboration an important founding principle of the Stowers Institute. They envisioned a highly collaborative, intellectually stimulating environment where scientists would freely share their ideas and create the kind of creative synergy that spurs great discoveries. A little more than a decade since its doors opened, Stowers investigators have published more than 830 scientific articles and garnered more than 25,000 citations, which serve as tangible proof of the wisdom of the Stowers' founding principles.

This issue's cover story digs deeper into one particularly impressive and successful collaboration involving no fewer than seventeen contributors, and illustrates our researchers' enthusiasm for teaming up beyond the walls of the institute with colleagues all over the world. This, I believe, is one reason for their productivity and high level of success. I hope you will enjoy reading about the power of collaboration and get a taste of what it means to be a scientist in an era when teamwork trumps solitary endeavors.



Stowers investigators frequently join forces to tackle tough scientific problems. Each circle corresponds to an individual Stowers researcher and the lines between them indicate co-authorship on scientific publications. Members of a team are shown in the same color. Team leaders are depicted by a bigger circle.

By Elise Lamar, PhD

THE POWER OF COLLABORATION

With modern science splintering into ever more specialties, collaborations across disciplines have taken the place of Renaissance men who could do it all. Today, it takes a team of highly specialized experts to succeed.

Both textbooks and Hollywood often link discovery with out-sized personalities. Students and movie-goers alike learn that Darwin "discovered" where we all came from after a long sea voyage and that Pasteur proved bacteria do not materialize out of nothing by experimenting with beef broth. These stories reassure us that if you give a lone genius time for contemplation and a few simple tools, great insights are sure to follow.

But discovery in the era of post-genomic biology doesn't happen that way. In the nineteenth century Mendel may have deduced the laws of inheritance while gardening, but in 2001 decoding the human genome took not one, but two, fiercely competitive camps with a collective population of about six hundred contributors. Today's advances in bioscience are more likely when investigators with diverse talents — and access to highly sophisticated equipment — join forces to tackle a problem, and a recent groundbreaking study by Conaway & Co. is a case in point.

Deconstructing Mediator

The star of the study, which graced the cover of a recent issue of the prestigious journal *Cell*, was a group of proteins collectively known as Mediator. The Mediator machinery provides a much-needed boost to RNA polymerase (pol II), the enzyme that copies a gene's DNA into the RNA intermediaries necessary to construct proteins. In addition to facilitating the assembly of pol II at the start site, Mediator shifts the enzyme into high gear, accelerating the synthesis of those RNA transcripts.

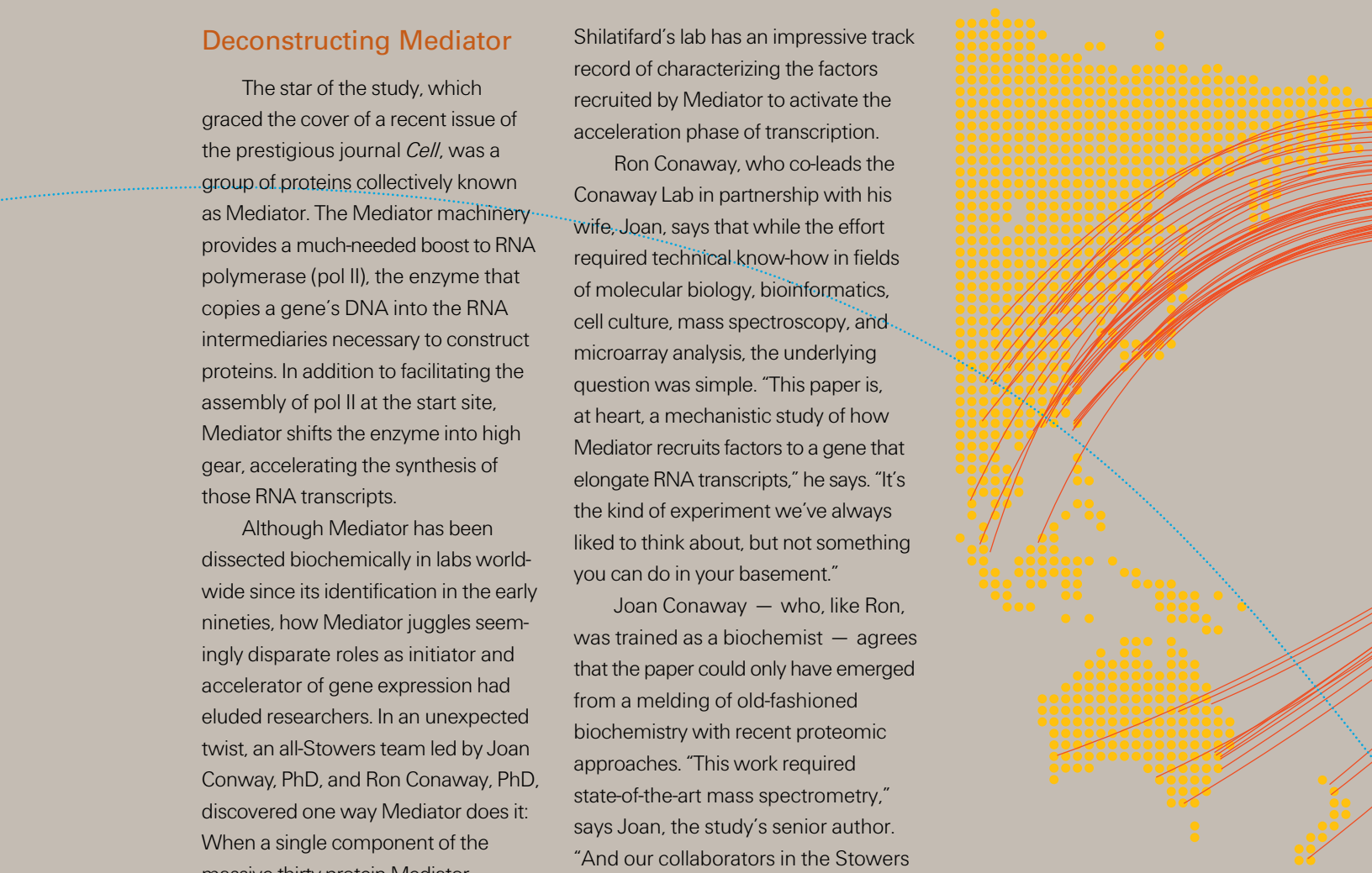
Although Mediator has been dissected biochemically in labs worldwide since its identification in the early nineties, how Mediator juggles seemingly disparate roles as initiator and accelerator of gene expression had eluded researchers. In an unexpected twist, an all-Stowers team led by Joan Conway, PhD, and Ron Conaway, PhD, discovered one way Mediator does it: When a single component of the massive thirty-protein Mediator machine switches allegiances, pol II shifts from a static state to an active, gene-expressing mode.

The discovery sheds new light on life's most fundamental process, namely, how information encoded in our genome is transcribed into a blueprint for proteins. Identifying the linchpin involved the coordinated effort of no fewer than seventeen Stowers researchers: the Conaways plus seven members of their lab, including the study's first author Hidehisa Takahashi, PhD; Investigator Ali Shilatifard, PhD, and two members of his lab; four researchers in the institute's Proteomics Center; and an in-house research advisor.

Each contributor applied unique skills to the project. The Conaways brought two decades of molecular analysis of both pol II and Mediator. Shilatifard's lab has an impressive track record of characterizing the factors recruited by Mediator to activate the acceleration phase of transcription.

Ron Conaway, who co-leads the Conaway Lab in partnership with his wife, Joan, says that while the effort required technical know-how in fields of molecular biology, bioinformatics, cell culture, mass spectroscopy, and microarray analysis, the underlying question was simple. "This paper is, at heart, a mechanistic study of how Mediator recruits factors to a gene that elongate RNA transcripts," he says. "It's the kind of experiment we've always liked to think about, but not something you can do in your basement."

Joan Conaway — who, like Ron, was trained as a biochemist — agrees that the paper could only have emerged from a melding of old-fashioned biochemistry with recent proteomic approaches. "This work required state-of-the-art mass spectrometry," says Joan, the study's senior author. "And our collaborators in the Stowers proteomics core are among the developers of these techniques."



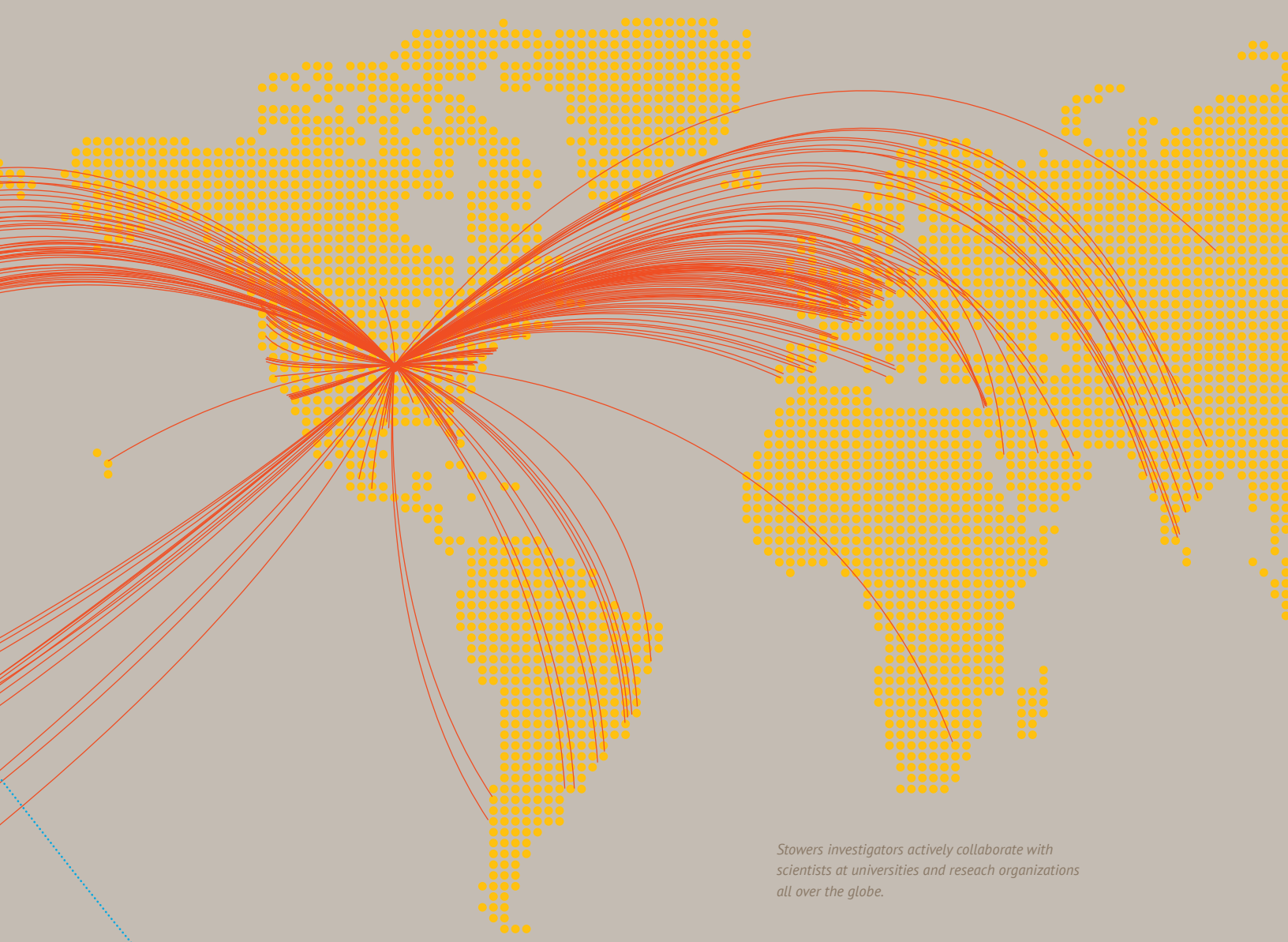
Mediator meets MudPIT

Most Stowers faculty members say that the excellence of the core centers — facilities that provide technical and intellectual support — is a major attraction of the institute. Currently, Stowers investigators can consult with twelve core groups, which offer not only state-of-the-art equipment, but a highly trained scientific staff skilled in areas as diverse as cell culture, electron microscopy, and reptile husbandry.

For the Mediator study, no core was more critical than the Proteomics Center, whose expertise is in assessing interactions between a cell's protein components — that is, the state of its "proteome."

The paper reported how a short segment of Mediator subunit #26 recruited mutually exclusive protein partners — one tethering pol II to a gene's start site and the other freeing it to catalyze RNA synthesis. The ability to rapidly identify interactors in small samples of cellular soup and then figure out what part of subunit #26 they stuck to required a mass spectroscopy method called MudPIT, for multidimensional protein identification technology.

MudPIT was developed in part by the Proteomics Center's director, Michael Washburn, PhD, when he was a postdoc with proteomics pioneer John Yates at the Scripps Research Institute in La Jolla, California. Both Washburn and Laurence Florens, PhD,



Stowers investigators actively collaborate with scientists at universities and reseach organizations all over the globe.

who heads the Proteomics Core and also hails from the Yates Lab, were authors on the Mediator paper as were two other members of their team.

Washburn and Florens' association with the Conaway Lab is a deep one: They began analyzing protein interactions in samples for the *Cell* study soon after they came to Stowers in 2003, and have since used MudPIT to analyze approximately fourteen hundred protein samples from the Conaway Labs for this and other studies. Those collaborations have produced twenty peer-reviewed publications, including the July 2011 paper and a pivotal 2004 paper published in *Molecular Cell* that ended controversy as to what subunits Mediator actually comprises.

Although undoubtedly successful, collaborations might seem like the polar opposite from those deeply satisfying eureka moments, where, in a sudden flash of insight, a new idea is born.

But Washburn rejects the notion that a team approach takes the excitement out of discovery. "It's the drive for dollars that's taken the romance out of science," he says. "Stowers has actually helped bring the collaborative spirit back into science by providing resources that enable people to do great work together."

Joan Conaway agrees, saying that Stowers' investment in technology is one of the things that make it such an exciting place to work. "More important, Stowers has recruited the very people who helped develop these approaches," she says. "Here, investigators aren't limited by technology. If you can think of a good experiment, you will find people here with the expertise and enthusiasm to help you do it."

Collaborare

People flummoxed by electronic gadgets can take comfort knowing that scientists often feel exactly the same way. Ron Conaway notes that even when highly trained PhDs gain access to state-of-the-art equipment like mass spectrometers or DNA sequencing machines, they can have difficulty making sense of the mathematical output.

"But this is where Stowers does it right," he says. "They provide money

not only for hardware but for salaries of experts who act as an interface between you and the technology." One of those interfaces on the Mediator paper was Stowers Research Advisor Chris Seidel, PhD.

Seidel champions collaboration, so much that his e-mail signature reads, "Latin: collaborare — to labor together." Since his recruitment to Stowers in 2002, Seidel has acted as a personal data analysis trainer for any faculty member seeking help. His expertise is in microarray technology — the analysis of genome-wide changes in gene expression — which he gained building microarray robots in graduate school at the University of California, Berkeley, and for Children's Hospital Oakland Research Institute.

"The advent of genomics has changed biology," says Seidel. "Most biologists don't have experience interpreting genomic data or know how to effectively harness bioinformatics and computer programming languages."

To address such needs, a few years back Stowers President and CEO David Chao, PhD, and Scientific Director Robb Krumlauf, PhD, created an intermediate layer of professional scientists called research advisors who work in an in-house freelance capacity. In addition to Seidel, three other advisors help scientists strategize about microscopy and bioinformatics.

"We serve as consultants. We may design experiments, analyze data, or develop technology," says Seidel, who for the *Cell* paper helped design and interpret microarray experiments testing whether gene expression patterns changed after Mediator subunit #26 was manipulated. "We approach a project at any level and act as a collaborator to bring groups together."

Proximity matters

Like most scientists, Stowers investigators interact closely with colleagues worldwide. But the Mediator paper embodies one of Jim and Virginia Stowers' founding principles when they created the institute. They were convinced that talented people do their very best when working under the same roof.

Although the Stowers Foundation began as a consortium of labs distributed across the nation, Jim Stowers' overriding goal — based in part on his business success at American Century — always was to create a research environment where people see and talk to each other every day. That goal was realized when the Stowers Institute opened its doors in Kansas City in 2000.

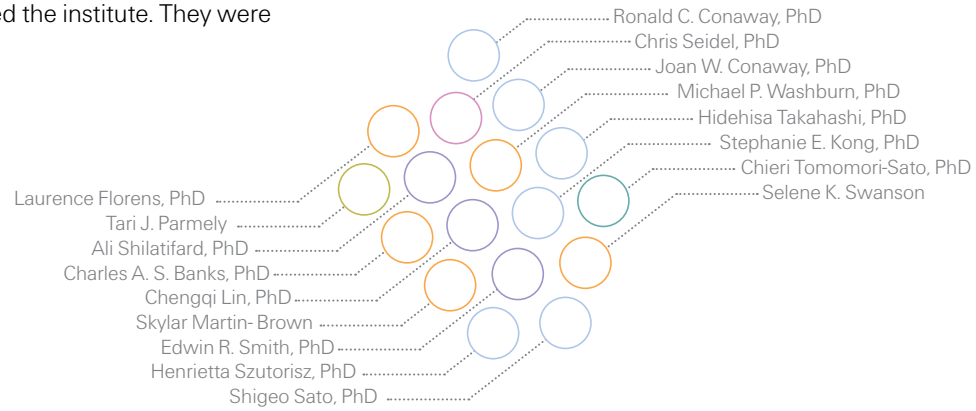
"We don't think (the consortium approach) is the most efficient way of doing science," Jim Stowers said in a 2007 interview. "Virginia and I think that science should be done in one place so scientists can help each other."

Krumlauf attributes the institute's rapid success to the authenticity of this principle. "What is unusual here is the number of extensive collaborations within the institute. Collaboration is just ingrained in our culture," he says. "That means that science moves faster, and synergy between investigators can stimulate ideas that might not occur to one person working in isolation."

Seidel also thinks the idea of the lone discoverer is overrated. "Amelia Earhart had a navigator," he says. "I don't think anyone thinks less of her because she wasn't solo."

Shilatifard agrees. "The days of Mitchell are over," he declares, referring to British biochemist Peter Mitchell, who left academia to conduct research at his estate into how mitochondria produce cellular energy — work that (full disclosure) earned him a Nobel Prize in chemistry in 1978.

"Science is collaborative now: you aren't going to make a big discovery in your garage," Shilatifard says. "There are too many things to understand — biochemistry, genetics, drug discovery, mouse work, bioinformatics — no one person can do it all. Now investigators must be humble enough to ask for help and then be lucky enough to have great colleagues to provide it." SJ



WEB SPECIAL:
Visit **stowers.org/stowersreport/maps** to explore all collaborations of Stowers investigators through interactive collaboration maps.

MAKING MEMO

A PROTEIN WITH PRION-LIKE PROPERTIES MAY PLAY A KEY ROLE IN TRANSFORMING SHORT-TERM MEMORY INTO LONG-TERM MEMORY, ENABLING US TO RECALL EVENTS FROM OUR DISTANT PAST.

As we form memories the connections between neurons in our brain undergo subtle changes. But how these connections, or specialized contact points called synapses, stay strong and keep memories alive for decades has remained elusive. Associate Investigator Kausik Si, PhD, and his team discovered a major clue in the tiny brains of fruit flies: The ability of the synaptic protein Orb2 to form hardy, self-copying protein clusters known as oligomers may be what makes memories stick.

The finding supports a surprising new theory about memory, and may have a profound impact on explaining other oligomer-linked functions and diseases in the brain, including Alzheimer's disease and prion diseases. "The idea that prion-like molecules could have a normal physiological function has challenged our perception about prions and proteins as a heritable factor," says Si.

Prions first made headlines when they were identified as the cause of bovine spongiform encephalopathy, which later became known as "mad cow disease." During a prion infection, the infectious form of the prion protein converts the normal version of the protein into a toxic form that clumps together, triggering an out-of-control chain reaction that wreaks havoc on brain cells. Despite their similarities, Orb2 and prions differ in important ways.

"Unlike prions, Orb2 doesn't convert spontaneously but instead oligomerizes in a controlled fashion in response to a physiological signal," Si explains. And unlike other known prion-like aggregates, oligomeric Orb2 doesn't kill nerve cells. Instead it regulates the synthesis of proteins necessary to maintain increased synaptic strength. What's more, once activated, oligomeric Orb2 can replenish itself without any further input making it a perfect "molecular flag" to designate a synapse for a sustained increase in its efficiency.

Si's investigations in this area began nearly a decade ago during his doctoral research in the Columbia University laboratory of Nobel-winning neuroscientist Eric Kandel, PhD, in the sea slug *Aplysia californica*, which has long been favored by neuroscientists for memory experiments because of its large, easily studied neurons. He found that in *Aplysia*, a protein known as CPEB that maintains an increase in synaptic efficacy, has an unexpected property.

A portion of the structure is self-complementary and — much like empty egg cartons — can easily stack up with copies of itself. CPEB thus exists in neurons partly in the form of oligomers, which increase in number when neuronal synapses strengthen.

CPEB-like proteins exist in all animals, and in brain cells they play a key role in maintaining the production of other synapse-strengthening proteins. Studies by Si and others in the past few years have hinted that CPEB's tendency to oligomerize is not merely incidental, but is indeed essential to its ability to stabilize longer-term memory. "What we've lacked till now are

Illustration credit: Nicolle Rager-Fuller Sayo-Art

RIES LAST

experiments showing this conclusively," Si says.

The key was to show that the disruption of Orb2 oligomerization on its own impairs fruit flies' ability to form long-term memories. Yes, fruit flies can learn. They can be trained to associate a chemical odor with a sugary reward. Hungry flies will rely on these odor memories to guide their behavior for several days after training. In a different memory test known as male courtship conditioning, male flies are exposed to an unreceptive female. Lured by the female, male test flies will initiate courtship, but their advances are inevitably rejected by the unreceptive female. After being scorned multiple times over several hours, the fly learns not to make advances when they encounter an unreceptive female again at a later time.

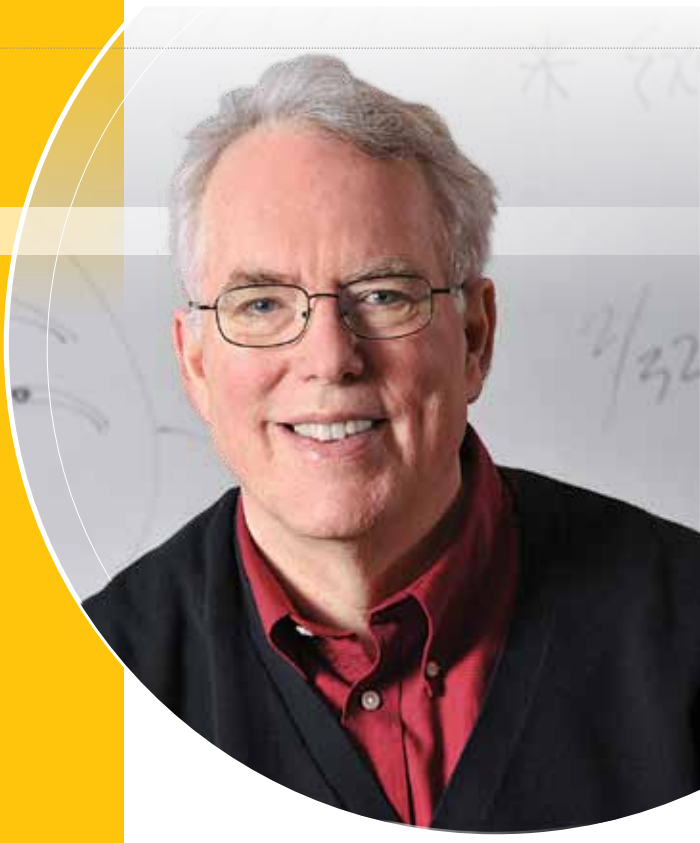
When the researchers interrupted Orb2's ability to stack up, the genetically modified fruit flies flunked their long-term memory tests. "For the first twenty-four hours after a memory-forming stimulus, the memory was there, but by forty-eight hours it was gone, whereas in flies with normal Orb2 the memory persisted," recalls Amitabha Majumdar, PhD, a postdoctoral researcher in Si's lab who performed most of the fly experiments.

Si and his team are now following up with experiments to determine how long Orb2 oligomers are needed to keep a memory alive. "We suspect that they need to be continuously present, because they are self-sustaining in a way that Orb2 monomers are not," says Si.

By Crystal Gammon

A DISCUSSION WITH

R. SCOTT HAWLEY



R. Scott Hawley, PhD, began his career in genetics research a bit unintentionally. As a high school student, he planned to become a lawyer and advocate for people with developmental disabilities. But his plans quickly changed when he took his first college course in genetics and was captivated by the field.

Now, as a Stowers investigator, Hawley spends each day working to understand the intricacies of meiosis in *Drosophila*, and how we might use these clues to understand and prevent developmental disabilities in our own species. An avid educator and award-winning textbook author, Hawley recently took on the role of dean of The Graduate School of the Stowers Institute for Medical Research, which will welcome its first class in the fall of 2012.

This month, Hawley was inducted into the National Academy of Sciences, joining an elite cadre of the nation's most accomplished scientists.

WHAT IS THE MOST INTERESTING QUESTION IN YOUR FIELD OF RESEARCH?

There's an observation that makes no sense to me as a biologist: If someone who's 23 is going to have a baby, the probability that the child will have Down syndrome is only one in a few thousand. But if she's a little older, say 34 or 35, then the risks start to go up into the range of one percent. And if she's in her early- to mid-40s, the risks are much higher.

Why is the ability to carry out meiosis (see right sidebar) properly so sensitive to age? If we understood those processes at a molecular level, maybe we could begin to ask why a woman's age makes a difference. We might be able to ask more informed questions about a number of human birth defects.

WHAT TIES TOGETHER THE MANY PROCESSES YOUR LAB STUDIES?

I like to think of meiosis as a ballet with many dancers. Many different events — processes affecting the nuclear envelope, the chromosomes within the nucleus, as well as the cytoplasm surrounding the nucleus in the oocyte — all must follow the same choreography to occur correctly and at exactly the same time.

IN THE NEXT DECADE OR SO, HOW WILL RESEARCH LIKE THIS CONTRIBUTE TO MEDICAL SCIENCE IN GENERAL?

Someday I hope we're able to understand what predisposes a given meiosis to make mistakes, or have a means of identifying an oocyte that has already made mistakes. Ultimately, a better understanding of what's happening biologically will allow people — doctors, patients, and parents — to better understand the reproductive process.

HOW DID YOU END UP IN THE FIELD OF MEIOTIC RESEARCH?

When I was in high school, I had a couple of epileptic seizures. The only consequence, as far as I was concerned, was that I ended up in a PE class with a lot of kids with developmental disabilities. This was in the late sixties, and there was about every kind of political movement for equality you could imagine, but I noticed no one was fighting for the rights of people with birth defects. So I went off to college intending to be a lawyer. By accident, the undergraduate advisor assigned to me was a geneticist named Crellin Pauling, whose father, Linus, won a couple of Nobel Prizes. Crellin said, "Look, if you want to do something about birth defects figure out what causes them and try to do something about it." He recommended that I should at least take a genetics course. I did, and I fell in love with the elegance and beauty of genetics.

WHAT MAKES THE STOWERS INSTITUTE A GREAT PLACE TO LEARN ABOUT SCIENCE?

We are making an immense investment in the medical scientific community of the next generation by providing students with opportunities to do real science. I think you simply cannot learn science from Betty Crocker labs. If you want to follow a recipe, go into your kitchen and bake cupcakes. The fun stuff is when you get answers you don't expect and learn from those experiences. One of the things I wish the community realized is just how many UMKC, KU-Edwards, Rockhurst University, and KU-Lawrence students we have in our labs — people who are going to go on to graduate school, medical school, and MD/PhD programs.

ARE YOU EXCITED TO START THE NEW GRADUATE PROGRAM HERE AT STOWERS?

Unbelievably so. It is such an incredible new opportunity. I feel sometimes we're not only creating a graduate school, but in some ways we're reinventing graduate education. To me, this is an incredible challenge. And I love it.

HOW WILL THE STOWERS GRADUATE SCHOOL BE DIFFERENT?

We're looking for people who want to do science, who have already been successful in labs and know that's what they want. We are not making decisions based on GPAs and GREs because numbers don't define any of us. Instead we

MEIOSIS

Meiosis is a special type of cell division that occurs during the formation of egg and sperm cells. It reduces the number of chromosomes carried by an individual's regular cells by half and thus allows the genes of two parents to be combined without increasing the total number of chromosomes. Any misstep during meiosis can lead to miscarriage, birth defects, and contribute to infertility.

ask students to tell us about the research they've done. We want to know how well they can describe it, and it gives us a chance to assess their critical thinking skills.

LOOKING TWENTY YEARS DOWN THE ROAD, WHAT DO YOU HOPE THE INAUGURAL CLASS OF STOWERS INSTITUTE GRADUATES WILL HAVE DONE FOR MEDICAL RESEARCH?

My hope is that twenty years from now we will be looking at scientists who have made transformative advances in terms of biology. They'll be researchers who have completed a PhD here, gone on to become postdocs at really good places, started their own labs, and are out there doing really exciting, important science.

HOW DO YOU VIEW YOUR ROLE AS A MEMBER OF THE NATIONAL ACADEMY OF SCIENCES?

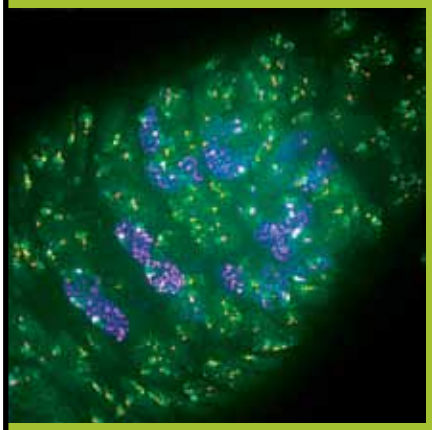
It is a tremendous honor — literally one of the most amazing events in my life — and I think there is a responsibility that comes along with it. The academy plays an important role in issuing reports on the status of American science, especially how specific scientific issues are taught and how they impact the general public. I really look forward to participating in that process.

WHAT ARE SOME OF YOUR INTERESTS OUTSIDE THE LAB? DO YOU SEE THEM AS SEPARATE CREATIVE OUTLETS, OR DO THEY COMPLEMENT YOUR WORK?

I can't separate any of it. I've been working on a novel for a really long time, and I write a lot of poetry. Writing is an opportunity for me to try to realize how words are connected to thought. It's really incredibly valuable, and it's similar to what I get from art, literature, and even bird-watching. My wife and I have taken up bird-watching recently, and observing living systems is phenomenal to me.

WHAT KEEPS GETTING YOU OUT OF BED EVERY MORNING?

The coolness of experiments. It's an amazing thing to actually have the resources and tools at your disposal to come up with ideas and test them. To be able to go into the lab and say, "You know, it would be really interesting to look and see if..." This job gets better every day. I'm more excited about doing science now than I've ever been.



PAIRING UP: HOW CHROMOSOMES FIND EACH OTHER

Meiosis — a special type of cell division — cuts in half the number of chromosomes carried by an individual's regular body cells. It allocates precisely one copy of each chromosome to each egg or sperm cell, thus ensuring that the proper number of chromosomes is passed from parent to offspring. And because chromosomes come in pairs — twenty-three sets in humans — the chromosomes must be properly matched before they can be divvied up.

In a recent study, Stowers researchers shed light on how fruit fly chromosomes line up to prepare for meiosis. First, they gather their centromeres, the anchor points that control the separation of chromosomes when cells divide, in one corner of the nucleus. Once chromosomes have paired up — chromosome 1 handed down from the mother with chromosome 1 handed down from the father and so forth — they initiate the formation of the synaptonemal complex, a "protein-zipper" that runs the entire length of each pair of chromosomes.

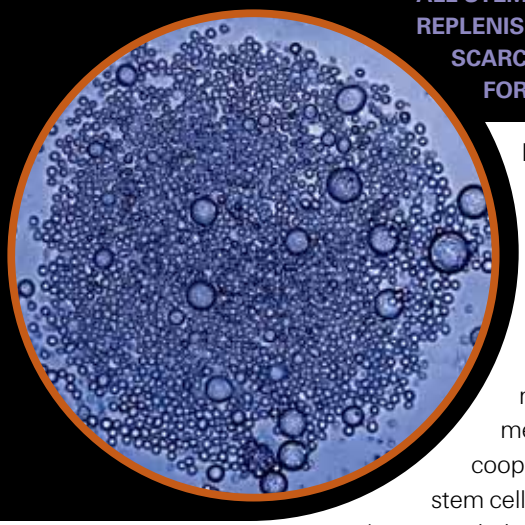
"Understanding this and other mechanisms involved in meiosis is important because of the crucial role meiosis plays in normal reproduction — and the dire consequences of meiosis gone awry," says Stowers Investigator R. Scott Hawley, PhD. "Failure of the meiotic division is probably the most common cause of spontaneous abortion and causes a number of birth defects such as Down syndrome."

WEB SPECIAL: Watch an animation of chromosomes pairing up as they prepare for meiosis. stowers.org/stowers.org/meiosis-video

The study appeared in the November 8, 2011, issue of *Current Biology*

ADULT STEM CELLS FLOURISH IN THE LAB

ALL STEM CELLS–REGARDLESS OF THEIR SOURCE—SHARE THE REMARKABLE CAPABILITY TO REPLENISH THEMSELVES BY UNDERGOING SELF-RENEWAL. YET, SO FAR, EFFORTS TO GROW SCARCE HEMATOPOIETIC (OR BLOOD-FORMING) STEM CELLS IN SUFFICIENT NUMBERS FOR USE IN THERAPY HAVE BEEN MET WITH LIMITED SUCCESS.



In their latest study, Stowers Investigator Linheng Li, PhD, and his team identified three distinct molecular mechanisms that cooperatively drive stem cell renewal in hematopoietic stem cells.

Applying their insight to stem cells isolated from mouse bone marrow, the researchers successfully expanded hematopoietic stem cells a hundredfold in the lab.

The transplantation of human hematopoietic stem cells isolated from bone marrow is used in the treatment of anemia, immune deficiencies, and other diseases, including cancer. However, since bone marrow transplants require a suitable donor-recipient tissue match, close to one in three patients who could benefit from stem cell transplant —and as many as ninety-five percent of nonwhite patients—never find a suitable match.

Hematopoietic stem cells isolated from umbilical cord blood could be a good alternative source. Readily available and immunologically immature, they allow the donor-recipient match to be less than perfect without the risk of immune rejection by the transplantee. Unfortunately, their therapeutic use is limited since umbilical cord blood contains only about one-tenth of the stem cells found in bone marrow.

"Being able to tap into stem cells' inherent potential for self-renewal could turn limited sources of hematopoietic stem cells such as umbilical cord blood into a readily available stem source with significant clinical impact," says Li, while cautioning that his team's findings have yet to be replicated in human cells.

The study was published in the September 15, 2011, edition of *Genes & Development*.

ON CUE

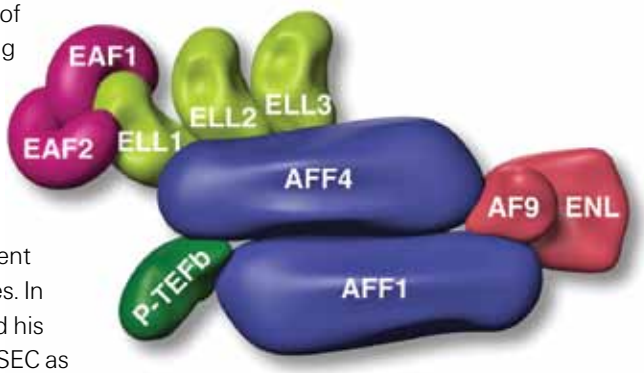
JUST LIKE ORCHESTRA MUSICIANS WAITING FOR THEIR CUE, RNA POLYMERASE II MOLECULES ARE POISED AT THE START SITE OF MANY DEVELOPMENTALLY CONTROLLED GENES, WAITING FOR THE SIGNAL TO PLAY THEIR PART IN THE GENOMIC SYMPHONY.

An assembly of transcription elongation factors, known as the Super Elongation Complex, or SEC, assists in triggering the paused RNA polymerases to start transcribing the gene ahead, found Stowers Investigator Ali Shilatifard's team and their collaborators in Robb Krumlauf's lab.

Transcriptional control by RNA polymerase II (pol II) is a tightly orchestrated, multi-step process that requires the concerted action of a large number of players to successfully transcribe the full length of genes. For many years, the initiation of transcription—the assembly of the basal transcription machinery at the start site—was considered the rate-limiting step. "We know now that the elongation step is a major node for the regulation of gene expression," says Shilatifard, PhD. "In fact, we have shown that mislocated elongation factors are involved in the pathogenesis of infant acute lymphoblastic and mixed lineage leukemia."

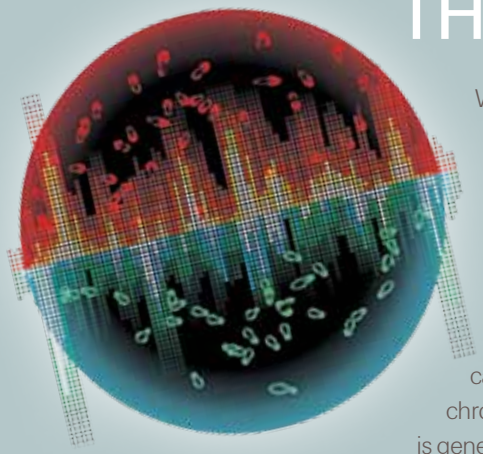
Mixed lineage leukemia is caused by a chromosomal translocation of the gene named MLL, resulting in its fusion to a seemingly random collection of other genes. Although the translocation partners don't share any obvious similarities, they all create potent leukemia-causing hybrid genes. In an earlier study, Shilatifard and his colleagues had identified the SEC as the common denominator shared by all MLL-fusion proteins, explaining how the accidental activation of developmentally regulated genes as a result of these MLL translocations could lead to leukemia.

The study appeared in the July 15, 2011, issue of *Genes & Development*.



The Super Elongation Complex (SEC)

REBALANCING THE GENOME



When the going gets tough, yeast cells can loosen the reins on their genome, discovered Stowers Investigator Rong Li, PhD, and her team, readily acquiring or losing whole chromosomes to enable rapid adaptation.

CELLS TRYING TO KEEP PACE WITH A CONSTANTLY CHANGING ENVIRONMENT MUST STRIKE A FINE BALANCE BETWEEN MAINTAINING THEIR GENOMIC INTEGRITY AND ALLOWING ENOUGH GENETIC FLEXIBILITY TO ADAPT TO NEW CONDITIONS.

Most often associated with cancer and developmental defects, chromosome instability, or aneuploidy, is generally detrimental to the integrity of a multicellular organism. Yet, from a single cell's perspective, an abnormal number of chromosomes is not necessarily a bad thing. Many wild yeast strains and their commercial cousins, used to make bread or brew beer, have adapted to their living environs by rejiggering the number of chromosomes they carry.

"Cells with a regular set of chromosomes are optimized to thrive under 'normal' conditions," says Li. "In stressful environments, additional or missing chromosomes can confer a distinct advantage on cells when it comes to finding creative solutions to roadblocks they encounter in the environment."

Known as adaptive genetic change, the concept of stress-induced genetic variation first emerged in bacteria and departs from a long-held basic tenet of evolutionary theory, which holds that genetic diversity — evolution's raw material from which natural selection picks the best choice under any given circumstance — arises independently of hostile environmental conditions.

The observation of stress-induced aneuploidy in yeast cells casts the molecular mechanisms driving cellular evolution into a new perspective and may help explain how cancer cells elude the body's natural defense mechanisms or the toxic effects of chemotherapy drugs.

The study was published in the January 29, 2012, online issue of *Nature*.

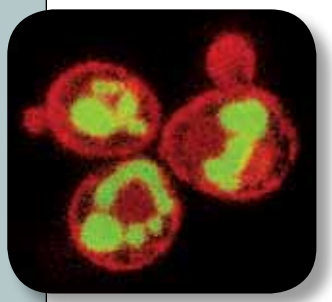
One for you, one for me

Each time a cell divides — and it takes millions of cell divisions to create a fully grown human body from a single fertilized cell — its chromosomes have to be accurately divided between both daughter cells. Assistant Investigator Sue Jaspersen, PhD, and her collaborators used, ironically enough, the single-celled organism *Saccharomyces cerevisiae* — commonly known as baker's yeast — to gain new insight into the process by which chromosomes are physically segregated during cell division.

The Stowers researchers found that a protein known as Mps3 not only ensures that cells have two functional spindle pole bodies, which generate the mitotic spindle apparatus that helps pull the chromosomes apart, but also that both spindle pole bodies are properly anchored in the nuclear membrane.

"When you enter mitosis, you need to have two spindle pole bodies on which you can pull the chromosomes. If you don't, the probability of errors in chromosome segregation increases exponentially," explains Jaspersen. "Even small mistakes can lead to birth defects, genetic instability, and cancer."

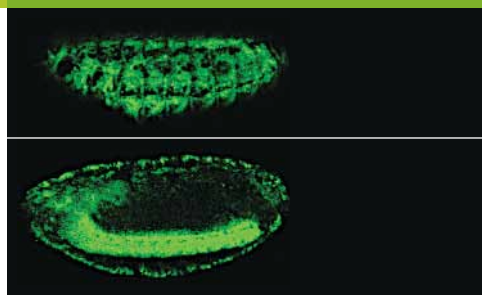
Unlike DNA molecules, which serve as templates for the production of identical copies, the spindle pole body is a large protein structure composed of soluble proteins and so-called integral membrane proteins, which are anchored in the nuclear envelope. When the researchers introduced a specific Mps3 mutation into yeast cells, they found that, although their DNA had been duplicated, these cells had multiple duplication defects, including blocking insertion of the spindle pole body into the nuclear envelope.



What was most striking, however, was that nearly every cell examined had nuclear membranes that were, essentially, overgrown — with two to eight layers of nuclear envelope, and multiple lobes and extensions — instead of a simple spherical structure, suggesting the Mps3 was remodeling the nuclear membrane to accommodate the spindle pole body.

The study was published in the November 17, 2011, issue of *PLoS Genetics*.

THE UNFOLDING SAGA OF TRANSCRIPTIONAL CO-ACTIVATORS



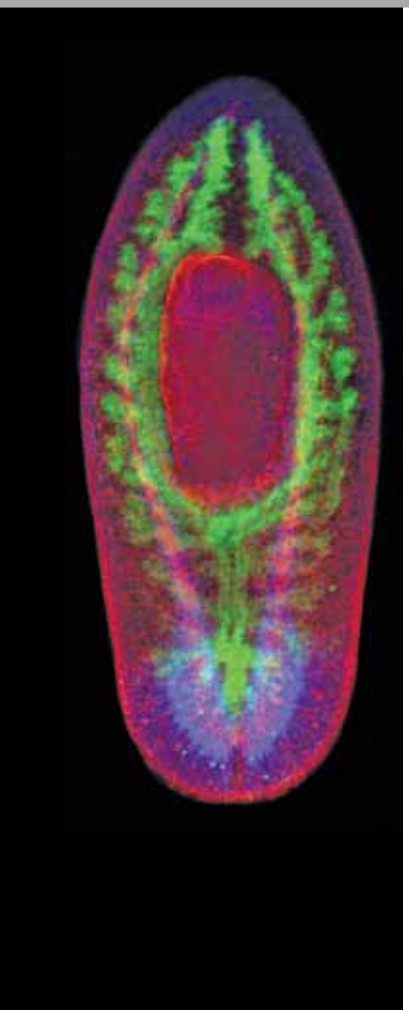
Successful gene expression requires the concerted action of a horde of gene regulatory factors. Long overshadowed by bonafide transcription factors, co-activators—the hangers-on that facilitate transcription by docking onto transcription factors or modifying DNA packaging—have recently come to the fore. The highly conserved co-activator SAGA, short for Spt-Ada-Gcn5-Acetyl transferase, is one of them.

Best known for lending a helping hand during the early steps of transcriptional initiation in yeast, a collaboration between Stowers researchers Susan Abmayr, PhD, and Jerry Workman, PhD, uncovered that SAGA also plays an important role in tissue-specific gene expression in fruit flies. When Senior Research Associate Vikki Weake, PhD, who led the study, determined the composition and localization of the SAGA complex in muscle and neuronal cells of late stage embryos of the fruit fly *Drosophila*, she found that SAGA was associated with considerably more transcription factors in muscle compared to neurons.

In an unexpected twist, the team detected SAGA together with polymerase as the promoters of genes that appear not to be transcribed and that therefore may contain a paused, or stalled, polymerase. Paused RNA polymerase II, preloaded at the transcription start site and ready to go at a moment's notice, is often found on developmentally regulated genes.

"Pausing is not as prevalent in yeast as it is in multi-cellular organisms," explains Workman. "It allows genes to be synchronously and uniformly induced. The presence of SAGA with polymerase that has initiated transcription but is paused prior to elongation suggests a prominent function for SAGA in orchestrating tissue-specific gene expression."

The study was published in the July 15, 2011, issue of *Genes & Development*.



FROM WORM TO MAN

OUR BODIES ARE PERFECTLY CAPABLE OF RENEWING BILLIONS OF CELLS EVERY DAY, BUT FAIL MISERABLY WHEN IT COMES TO REPLACING DAMAGED ORGANS SUCH AS KIDNEYS.

Using the flatworm *Schmidtea mediterranea* — famous for its capacity to regrow complete animals from minuscule flecks of tissue — as an eloquent example, research conducted in the laboratory of Howard Hughes Medical Institute Investigator Alejandro Sánchez Alvarado, PhD, revealed how our distant evolutionary cousins regenerate their excretory systems from scratch.

Planarian protonephridia, which are distributed throughout a flatworm's body, combine pressure filtration with filtrate modification similar to mammalian nephrons, the basic functional unit of kidneys. To study protonephridia's development the researchers simply cut the animals' heads off and watched how they regrew the missing body part, including excretory tubules, within a week. They found that protonephridial tubules originated from a precursor structure, which undergoes extensive branching morphogenesis, the same process that also shapes vertebrate organs such as lung, kidneys, or mammary glands.

"We take it for granted that we go to bed with two sets of fully functional kidneys and that we wake up with them the next morning, but we don't understand the fundamental processes that give rise to this very well choreographed maintenance of an organism's form and function," says Sánchez Alvarado. "We can now start to use planaria as a model to begin to understand how adult animals maintain their form and function over a very long time."

The study was published in the August 2011 issue of *Development*.

GUANGBO CHEN
The power of observation

Photo credit: Guangbo Chen

Graduate students are budding scientists in training acquiring the skills to become independent thinkers and successful researchers. But they are also an integral part of the hands-on workforce, bringing enthusiasm, talent, and fresh perspective to the bench.

When Guangbo Chen talks about his research, eyes sparkle, hands fly, and the unexpected growth patterns of his research subjects — millions and millions of yeast cells — quickly turn into "a situation." In vivid detail, the graduate student training with Stowers Investigator Rong Li, PhD, describes visual observations that made him stop and think. In fact, it was a puzzling detail in the appearance of yeast cells he was growing in the lab that directly led him to the last piece of evidence for the *Nature* paper he just published. (For more detail, see page 14).

Chen trained his visual sense early on. While growing up in China, he took regular art classes and was thrilled when one of his paintings was chosen to be included in a group exhibition in Japan. But it was his mother, a practicing internist, who regularly brought her young son with her to the clinic, who drove home the importance of careful observations. "She was very good at looking at patients and data to figure out what was going on inside them," says Chen.

Chen's father, an engineering professor whose life was derailed by the Cultural Revolution when he was banished to the countryside for more than a decade, emphasized the importance of hard facts and actions versus ideology. "A lot of dinner table conversations focused on the value of doing science versus talking ideology," remembers Chen, which reinforced his decision to pursue a career in research. "Science is the most powerful way to change the world."

After graduating with a biology major from Fudan University in Shanghai, Chen enrolled in the Interdisciplinary Graduate Program at the University of Kansas Medical Center in 2007. But before traveling to the United States, he indulged his adventurous streak and embarked on a solitary bike ride through Shangri-La, a primarily Tibetan county in southwest China that was renamed in 2001 in honor of the fictional land of Shangri-La in the 1933 James Hilton novel *Lost Horizon*.

"For me, long distance bike rides are a great way to explore the world," says Chen. "It gives you time to take in the vistas, to see the mountains, the rivers and the people." These days, he's no longer satisfied with looking at mountains. Instead, he prefers to summit them. Two years ago, he climbed to the top of Handies Peak, an awe-inspiring fourteener in the Rocky Mountains, where he proposed marriage to his girlfriend.

The same intrepid attitude serves Chen well in the lab, where he isn't afraid of asking the big questions. "When I joined Rong's lab, I wanted to study how whole genomes respond to their environment," he says.

After three years of chipping away at the project, Chen's keen eye sealed the deal. When he grew some of his stress-adapted yeast cells under favorable conditions, he noticed their irregular surface. Baffled by what he saw, he launched a large-scale investigation assisted by the Stowers' famously supportive core facilities and research advisors.

"The cooperation not only improved the efficiency by combining different expertise," says Chen, "but it was also an important learning process for me. When Chris Seidel helped us analyze the microarray data, I began to appreciate the power of computation in biology, and decided to take his course on genomics."

Before long, Chen was able to show that under stressful conditions yeast cells' genomes become unstable, readily acquiring or losing whole chromosomes to enable rapid adaption. "From an evolutionary standpoint, it is a very interesting finding," explains Chen. "It shows how stress itself can help cells adapt to stress by inducing chromosomal instability. Meanwhile, it may also help us to understand the root of genomic instability in other circumstances, such as cancer."

After his successful scientific premiere, the scientist-in-the-making is ready for more. "I really enjoy the investigative process," says Chen. "The high stakes of resolving 'why' in biomedical research makes it an exhilarating adventure. I love adventure."

Photo credit: Guangbo Chen

Global reach

THE GRADUATE SCHOOL OF THE STOWERS INSTITUTE FOR MEDICAL RESEARCH IS PREPARING TO WELCOME ITS FIRST CLASS OF STUDENTS TO ITS PHD PROGRAM IN BIOLOGY IN THE FALL OF 2012.

"We are actively recruiting promising students from around the world to pursue innovative and creative research in the biological sciences," says Ana Pedraza, PhD, head of student affairs for The Graduate School. "In addition to scientific maturity and demonstrated research experience, we look for curiosity and a strong enthusiasm for science that can carry prospective students through for the duration of their graduate studies."

The first semester of the program will be comprised of intense modular courses that emphasize critical reading and writing while exposing students to a wide range of techniques to solve basic biological problems. The second semester will consist of three rotations through Stowers laboratories, which broadens students' knowledge of research conducted at the Stowers Institute and enables each student to choose a dissertation laboratory.

Thereafter, students will pursue their doctoral research in a dynamic and prestigious Stowers laboratory, while continuing to receive extensive support from a mentoring faculty member and The Graduate School office. The program strives for degree completion within five years from matriculation.

"The Graduate School of the Stowers Institute for Medical Research will offer its students a unique education that will prepare them to be strong, creative, and independent researchers," says R. Scott Hawley, PhD, dean of The Graduate School.

RESEARCH EXCELLENCE rewarded with three prestigious fellowships

Excellence in research does not happen in isolation. It is clear that cooperation and collaboration of researchers worldwide now drives the search for answers to scientific questions, which in turn drives the competition for highly prestigious external fellowship funding. Three young Stowers researchers were the 2011 recipients of just such awards.

Jamie Dyer, PhD, a postdoctoral research associate in the lab of Stowers Investigator Jerry Workman, PhD, received a Ruth L. Kirschstein National Research Service Award. The three-year fellowship supports Dyer's research into the function of myeloid leukemia factor (MLF), which is mutated in myelodysplastic syndrome and acute myeloid leukemia. As little is known about how mutated MLF proteins drive the formation of cancer, Dyer's research aims to determine the role of MLF in normal and cancerous cells.

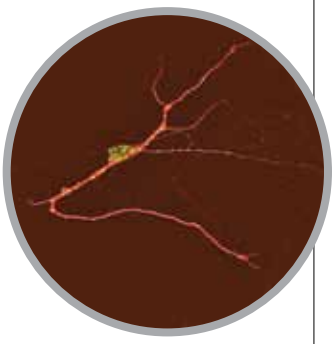
Predoctoral researcher Ram Kannan, a member of the Baumann Lab, was awarded a two-year American Heart Association fellowship to identify factors that promote the processing of the RNA component of telomerase using the fission yeast *S. pombe* as a model system. Telomerase helps maintain the ends of chromosomes, which shorten with every cell division. Understanding telomerase biogenesis and why shorter telomeres are strongly correlated with various cardiovascular disorders (CVD) may improve CVD diagnosis and treatment.

A senior research associate in the Ron Yu Lab, Sachiko Haga-Yamanaka, PhD, received a two-year fellowship from the Japan Society for the Promotion of Science, which is awarded to Japanese postdoctoral scientists conducting research at foreign institutions. The award supports Yamanaka's research into the neural mechanism underlying innate and learned social behaviors guided by the mouse vomeronasal system, a small sensory organ found in the noses of all terrestrial vertebrates except higher primates. Although, as a species, human beings no longer rely on pheromones in social communications, dissecting the neural circuitry behind these important functions of the brain may lead to a better understanding of how the brain works and to possible treatments for neurological diseases.

From left to right: Sachiko Haga-Yamanaka, Ram Kannan, and Jamie Dyer.

JOINT PROJECT BY STOWERS RESEARCHERS BLANCHETTE AND SI WINS 2011 WILLIAM B. NEAVES AWARD

Marco Blanchette, PhD



The 2011 William B. Neaves Award was presented to Assistant Investigator Marco Blanchette, PhD, and Associate Investigator Kausik Si, PhD, who teamed up to explore how the internal state of an organism impacts the memory storage machinery at the molecular level.

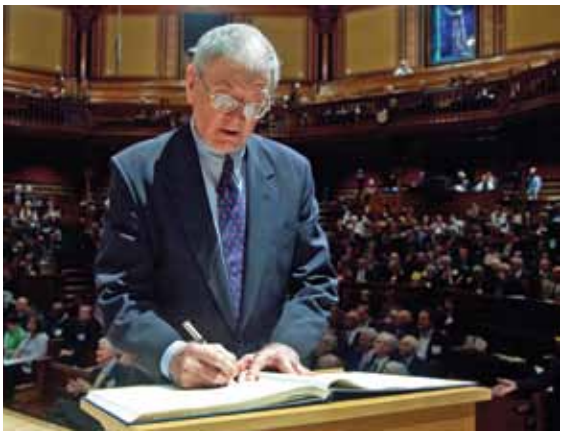
Memories are formed when a series of biochemical events induce changes in the connection points or synapses between neurons (see also page 8). Which experiences are singled out to be stored as long-lasting memories depends on the value attached to the experience as well as the motivational state of the organism.

"But how the external experience and the internal state interact at the molecular level to convert some experiences into long-lasting memories is still largely unknown," explains Si, a neurobiologist, who uses fruit flies to study the molecular basis of long-term memory.

Preliminary findings led Si to suspect that a process known as alternative splicing may play a crucial role in determining which short-term memories are transformed into stable long-term memories. Alternative splicing — a carefully regulated adaptation of a routine RNA-editing step — enables a single gene to code for multiple proteins by snipping out long stretches from transcribed messenger RNA. To explore his hypothesis further, Si turned to Stowers colleague Blanchette, an expert in RNA processing. Together they will take a closer look at the role of alternative splicing in long-term memory.

Established in honor of William B. Neaves, PhD, president emeritus of the Stowers Institute for Medical Research, the award was designed to encourage and support Stowers researchers who wish to pursue innovative, high-risk research projects with the potential for broad impact.

WILLIAM B. NEAVES INDUCTED INTO THE AMERICAN ACADEMY OF ARTS AND SCIENCES



Bill Neaves, PhD, president emeritus of the Stowers Institute and newly elected member of the American Academy of Arts and Sciences, adds his name to a rarefied list of some of the world's most accomplished leaders from academia, business, public affairs, the humanities, and the arts.

Founded in 1780 by President John Adams, James Bowdoin, John Hancock, and other scholar-patriots, the American Academy of Arts and Sciences is one of the nation's most prestigious honorary societies.

2011 HUDSON PRIZE AWARDED TO MATTHEW GIBSON

Associate Investigator and developmental biologist Matthew C. Gibson, PhD, has been named the recipient of the 2011 Hudson Prize by the M.R. and Evelyn Hudson Foundation. Through the Hudson Prize, the Texas-based foundation recognizes and supports the work of outstanding early career scientists at the Stowers Institute for Medical Research.

Gibson, whose research focuses on early embryonic development, received a one-time grant of $50,000 to expand his research into the control of cell division in epithelial cell layers. Epithelia are closely packed and highly organized tissue layers that cover all internal and surface areas of the body.

Throughout his scientific career, Gibson has been particularly interested in understanding animal development through the lens of epithelial architecture. How are polarized cell layers constructed and maintained, for example, and how do they influence developmental processes? As a postdoctoral fellow, he discovered an unexpected role for the signaling molecule BMP in controlling the shape and fate of epithelial cells that form fruit fly wings.

From there he turned his attention to a very different venture: to define mathematical principles governing how polygon-shaped cells pack into rapidly proliferating epithelial sheets. Surprisingly, no single set of genes regulates this process. Instead, Gibson's work shows that simple mathematical rules govern the shape and sidedness of dividing epithelial cells.

At the Stowers Institute, Gibson's lab has continued to focus on epithelial biology, recently demonstrating the mechanism underlying nuclear movements during epithelial cell division. Separate lines of inquiry have explored the control of epithelial growth, and have also demonstrated that polygonal cell packing can influence the spatial orientation of cell division in tissues as different as fruit fly larvae and cucumber epidermis.

STOWERS INTERN ANDREI KUCHARAVY WINS GRAND PRIX DE STAGE DE RECHERCHE DE L'ECOLE POLYTECHNIQUE

Andrei Kucharavy, a bioinformatics student at the prestigious L'Ecole Polytechnique in Paris, has been selected to receive the Grand Prix de Stage de Recherche de l'Ecole Polytechnique for the work he performed during his three-month summer internship at the Stowers Institute. The honorary award is given annually to six students who perform exceptional interdisciplinary work during their research internships.

During his time at Stowers, Kucharavy worked closely with Arcady Mushegian, PhD, head of bioinformatics research, to probe the genomes of close relatives of *Mycoplasma genitalium*, the microbe that Mushegian had used as the starting point to determine the smallest set of genes an organism needs to survive in an experimental environment.

"Ecole Polytechnique students are known for their excellent training in science and mathematics, but Andrei exceeded all expectations," said Mushegian. "I am sure we will hear more about his successes in the near future."

Kucharavy also worked with research advisors Jay Unruh, PhD, and Boris Rubinstein, PhD, on developing a simulation of cell division mechanisms in budding yeast in collaboration with members of Rong Li's lab.

"The team spirit at Stowers was really great. Never before have I seen a place where the collaboration among scientists was so easy and where ideas circulated so rapidly and easily," says Kucharavy, who also fondly recalls the daily sustenance provided by the Stowers cafeteria's breakfast burritos.

Photo credit: © Ecole Polytechnique, J. Barande

STOWERS INSTITUTE RECEIVES *CEO CANCER GOLD STANDARD*™ ACCREDITATION

The Stowers Institute's commitment to the health of its employees and their families has been officially recognized with a *CEO Cancer Gold Standard*™ accreditation.

"As an organization dedicated to improving human health through basic research, the Stowers Institute for Medical Research is proud to have received CEO Cancer Gold Standard accreditation," says David Chao, PhD, president and chief executive officer of the Stowers Institute. "We believe our efforts to improve human health begin with extending our mission to our employees by creating an environment that encourages a healthy lifestyle."

The Stowers Institute was founded by James "Jim" E. Stowers Jr. and Virginia G. Stowers. Inspired by their personal experiences with cancer, the couple made it their mission to improve people's lives through innovative approaches to the causes, treatment, and prevention of diseases, including cancer. The CEO Gold Standard accreditation proves that the Stowers' commitment to eradicating disease is an internal, as well as external, commitment to health.

ANNIVERSARY CELEBRATION WITH MENORAH MEDICAL CENTER: PAST MEETS PRESENT

The Stowers Institute commemorated its tenth anniversary and its historic ties to Menorah Medical Center with a reception on October 4, 2011. The celebration opened with a presentation by Stowers President and CEO Dave Chao, PhD, who highlighted some of the institute's remarkable scientific successes since its inauguration. Speakers Dick Brown, chairman of the Stowers Institute Board of Directors, and event co-organizer Gina Kaiser, president of the Menorah Legacy Foundation Board, reflected on the tradition of commitment to community embodied both by Menorah and Stowers.

Guests of honor included current and former leaders of the Menorah Medical Center board; Menorah medical staff and employees; representatives of the Menorah Medical Center Women's Auxiliary and members of the board of the Jewish Hospital Foundation and the Menorah Legacy Foundation.

The Institute owes its spectacular location to the vision of its founders Jim and Virginia Stowers, but also to the relationship with Menorah Medical Center. In 1995, Stowers purchased Menorah's former home and began converting the property into the cutting-edge research facility it is today.

Recognizing the hospital was a symbol of hope for many generations, the Stowers family wanted to carry on that legacy by incorporating the main hospital building into the design of the Stowers Institute. They wanted it to become a symbol of hope for future generations.

But these two institutions share more than just a physical location. During her remarks that evening, Kaiser described the synergy between Menorah and Stowers via the Judaic concept of "tikkun olam," or "healing the world." Menorah's efforts to heal the sick, she pointed out, have been mirrored by Stowers' efforts to find lifesaving cures for debilitating diseases.

From left to right: Linda Sims, Arnold Brown, Gerre Minkin and Rodney Minkin.

MATTHEW C. GIBSON AND KAUSIK SI PROMOTED TO ASSOCIATE INVESTIGATORS, RONG LI RENEWED AS INVESTIGATOR

MATTHEW C. GIBSON, PhD, is particularly interested in the genetic and physical processes that control the architecture of epithelia, which are highly organized layers of tissue that cover all body surfaces with an uninterrupted sheet of cells. Gibson started his scientific career defining the role of extracellular signals in regulating the growth and patterning of *Drosophila* imaginal discs, or flattened epithelial sacs that develop into different organs and appendages, such as eyes and wings, in adult fruit flies.

Since joining the Stowers Institute in 2006, Gibson extended his studies to exploring the integration between processes of cell proliferation and morphogenesis (the elaboration of shape) in epithelia as diverse as fly wings and sea anemone tentacles. Most recently, he defined the mechanism underlying nuclear movements during epithelial cell division, and showed that geometrical interactions between neighboring cells can determine the spatial orientation of cell division.

KAUSIK SI, PhD, who moved to the Stowers Institute in 2005, uses fruit flies to study the biochemical basis of long-term memory. He was the first to suggest that a protein with prion-like properties may be at the center of a series of biochemical changes at the connection points between brain cells that form the basis for memory persistence.

Working with the mollusc *Aplysia*, a popular model system to study learning and memory, Si and his colleagues later demonstrated that neuronal activity generates prion-like CPEB aggregates and, rather than poisoning a neuron like a real prion would, the transformed CPEB protein stabilizes connections between neurons. The latest study from his lab shows that, like *Aplysia* CPEB, an activated fruit fly version called Orb2 undergoes prion-like conformational changes, which are necessary to establish a persistent "memory trace."

RONG LI, PhD, whose multifaceted research program, relies heavily on high-end imaging coupled with computational modeling, explores how cells — bundles of bustling matter, in Li's words — impose order on seemingly loosely interacting and fluctuating components to accurately carry out complex tasks and specialized functions, time after time.

Li's findings cover a lot of ground and frequently force scientists to rethink long-held assumptions. For example, most recently she demonstrated that aging yeast cells don't require an active transport system to keep age-related "junk" out of daughter cells, but instead rely on cell geometry and slow diffusion rates to ensure daughters' youthful state. She's also found that mammalian oocytes rely on a powerful intracellular stream — instead of the more customary structural tethers — to position chromosomes far off-center to prepare for a highly asymmetrical cell division.

STOWERS INSTITUTE WELCOMES TWO NEW FACULTY MEMBERS

Alejandro Sánchez Alvarado

Tatjana Piotrowski

Renowned developmental biologist Tatjana Piotrowski, PhD, and pioneering regeneration expert Alejandro Sánchez Alvarado, PhD, joined the Stowers Institute for Medical Research last year.

Associate Investigator Piotrowski hails from the University of Utah's School of Medicine, where she was an associate professor in the Department of Neurobiology and Anatomy. She uses zebrafish as a model system to study early developmental processes such as collective cell migration, cell type specification, and stem cell biology.

Piotrowski is particularly interested in the development of hair cells, which detect water movement along the lateral line in fish. These hair cells are arrayed along the animal's trunk and form the lateral line sensory system unique to aquatic vertebrates. Deflection of those hair cells, which resemble the hair cells responsible for hearing in the human inner ear, enables fish to orient themselves and detect other organisms in the water.

Her research uncovered a previously unappreciated role for glia — the nervous system's support crew — in the regulation of hair cell precursor proliferation and functional maturation. Piotrowski also identified several genes required for the coordinated migration of groups of cells, a process that is still poorly understood.

At Stowers, Piotrowski will continue to use zebrafish to dissect the molecular programs governing the migration and differentiation of hair cell precursors. Since fish hair cells — in contrast to hair cells in the inner ear of vertebrates — regenerate readily following hair cell death, she will use the same model system to gain a better understanding of the molecular and cellular basis of hair cell regeneration.

"I am truly excited about being at the Stowers Institute," says Piotrowski. "My research on the mechanisms underlying sensory organ development and regeneration will benefit tremendously from the cutting-edge technology and unique resources available at the Institute."

Piotrowski's husband, Howard Hughes Medical Institute Investigator Alejandro Sánchez Alvarado, also hails from the University of Utah, where he held the H.A. & Edna Benning Professorship of Neurobiology and Anatomy. One of the world's leading authorities on regeneration, Investigator Sánchez Alvarado transformed the flatworm *Schmidtea mediterranea* — famous for its capacity to regrow complete individuals from minuscule body parts — from an unassuming, freshwater-dwelling oddity into a powerful new model system for the study of regeneration.

Sánchez Alvarado identified and characterized dozens of genes and genetic programs that drive regeneration and ensure the anatomical and functional integration of newly made parts into older, pre-existing tissues. He showed that adult somatic stem cells are the only proliferating cell type participating in regeneration and generate the approximately forty different cell types found in an adult flatworm.

"I am thrilled to be here," says Sánchez Alvarado. "Scientifically, there's no better place to be. This is not only an outstanding opportunity to advance my laboratory's planarian research program in particular, but also regeneration biology as a whole. I am planning to take full advantage of the unique environment the Institute has to offer."

Piotrowski received her master's degree from the University of Tübingen, Germany, and her doctorate from the Max Planck Institute for Developmental Biology in Tübingen.

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.

To learn more about Tatjana Piotrowski's and Alejandro Sánchez Alvarado's work:
http://www.stowers.org/faculty/piotrowski-lab
http://www.stowers.org/faculty/sánchez-lab

The Stowers Institute's scientific effort is made possible by the proceeds we receive from our Hope Shares Endowment. The Institute welcomes contributions to the Endowment in any amount. Individual or cumulative contributions of $1,000 or more establish a Hope Shares account, which can be opened in your name or in memory or honor of someone you love.

LIFETIME CONTRIBUTIONS

The information listed below represents contributions from, in memory of, or in honor of the following as of December 31, 2011.

$10 Million+

Pamela Stowers

$1 Million+

American Century Investments Foundation
From Pamela Stowers In Memory of Laura Stowers

$500,000+

Dunn Family Foundation
Barnett and Shirley Helzberg
Margaret Lichtenauer Estate

$100,000+

American Century Investments Employees
Cerner Corporation (in kind)
Country Club Bank
The Richard H. Driehaus Charitable Lead Trust
Frederick and Louise Hartwig Family Fund
Felix and Helen Juda Foundation
Tom and Nancy Juda Foundation
James Kemper Jr.
David and Wendy Welte
Hank Young (*Gameface* book proceeds)

$50,000+

Richard and Jeanette Brown
William and Priscilla Neaves
Polsinelli Shughart PC
James Stowers III
Roderick and Linda Sturgeon

$25,000+

Mildred E. Coats Trust

JE Dunn Construction Company (in kind)

Irving Kuraner

Labconco Corporation

Menorah Medical Center Inc. (in kind)

Rubin Postaer and Associates

From Marilyn Prewitt Trust in Memory of Marilyn Prewitt

In Memory of Robert Ruisch Jr.

Jonathan and Cyndi Thomas

John and Shirley Wagner

From Bruce and Laurie Wimberly in Memory of Virginia Wimberly

$10,000+

Enrique Chang and Catherine Farley

David Chao and Julia Zeitlinger

Cisco Systems Inc.

In Memory of James and Eleanor Drake

Webb Gilmore

Gilmore and Bell

Ruth C. Hill Trust

Allan and Margot Huber

IBM

Brian Jeter

In Memory of Carlo Jonathan

Jack and Rena Jonathan

From Jim and Virginia Stowers in Memory of Felix Juda

David and Susan Keefer

In Memory of Helen Kirby

From Bo Kreiling in Memory of Helen Jayne Kreiling

In Memory of Helen Lebens

Bill and Peggy Lyons

Barbara Marshall

Mark and Martha Miller

Mistler Family Foundation

Amy Noelker

Tom and Jeanne Olofson

The J.B. Reynolds Foundation

Landon Rowland, Kansas City Impact Fund

Sanders Morris Harris

In Memory of Richard Smith, Wendell Smith, and Laura Stowers

Rick and Betsey Solberg

Kathleen Stowers-Potter

David and Jeannine Strandjord

Bryon Thompson

In Memory of Vernon Voorhees II

Michael and Louise Zolezzi

$5,000+

Clay Blair Family Foundation

Mary Breed Brink

Cancer Golf Association

David and Nancy Dilley

From Drs. James Griffin III and Margo Denke in Memory of James Griffin Jr.

Irv and Ellen Hockaday

Thomas Kmak Family

Dawn Lind

Lucent Technologies (in kind)

Catherine Netherland

From John and Susan McMeel in Memory of John O'Day

In Memory of Albert Otten and William Ellis

Robert and Jan Peterson

Don and George-Ann Pratt

Austin and Laura Wilson

$1,000+

Herbert and Estelle Adler

Alexander Family Foundation

Don and Christine Alexander

From Rob Aneweer in Memory of Dave and Jim Aneweer

Elmer and Verna Armbruster

Malcolm and Kathy Aslin

Donald and Margaret Austin

From Michael and Dana Schaadt in Memory of Carol Barry and Herbert Schaadt

Paul Jr. and Joan Bartlett

Jonathan Bauman

Janice Beatty

From Bert and Joan Berkley in Memory of Kitty Berkowitz and Janice McInrath

From Jim and Virginia Stowers in Memory of Arthur Brand

Gregory Broome

In Memory of Carol Ann Brown

Mary Jo Browne

In Memory of Evelyn "Lovey" Byrer

Michael and Gretchen Carter

Shirley Christian

In Memory of Alice "Penny" Cohn

Gilbert and Lois Cole

From Lauren and Ryan Contillo and Kathleen Stowers-Potter in Memory of Lawrence Joseph Contillo

From Cathryn and Jay Linney in Memory of William Cordes

From Frederick Coulson III in Memory of Frederick Coulson Jr.

Jody Craven

Alan Critchell

Phillip Davidson

In Memory of Walter Day

From Jim and Virginia Stowers in Memory of Walter Day

Marshall and Jill Dean

In Memory of Carol Denicole

In Memory of Mark Dover

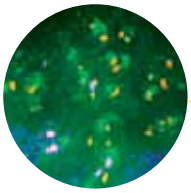
Terrence and Peggy Dunn

In Memory of Dana Eckles

In Memory of William Edwards

Ron and June Estabrook

Joseph Fairfax



Jill Farrell

Banning Flynn

From David Ford In Memory of Theresa Ford

From Brett Hart In Memory of Theresa Ford

From Stephen Thune In Memory of Theresa Ford

Jody Anne Frederickson

Abby Freeman

William and Laura Frick Foundation Fund

Stephen Garcia

The William George Family Charitable Trust

Marsha and Jules Goldman

Samuel Goller

Samuel Goller and Melody Goller

Stephen and Patricia Gound

Laura Greenbaum

Mary Louise Greene

Edward Jr. and Jody Griffin

Richard and Andrea Hall

Bernard Hamblin

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Henson Trust Fund

From Betty Henson in Memory of Paul Henson

From Jim and Virginia Stowers in Memory of Paul Henson

John and Connie Hoye

In Memory of Estelline Huey

Robert and Lynette Jackson

Harrison Jedel

Jeff Johnson

Leroy Larsh Johnson

Sandra Kasahara

Otto and Margarete Katke Charitable Foundation

Kelly Kerr

Mark Killen

In Memory of Gary Kostuke

Bob and Myrna Krohn

Kuhn and Wittenborn Advertising

From Kathie Nelkin In Memory of Edward Lane

The Linney Family Foundation

From Jim and Virginia Stowers in Memory of Jane Lundgaard

Linsley and Jane Lundgaard

Patricia Mansker

Mary Kay McPhee

From Thomas and Janet Ink in Memory of Hazel Meany

Robert and Shirley Meneilly

Brendan Murray

Kathleen Nelson

Jeannette Nichols

Jennifer Noland

Stephen Novak

In Memory of Caryn Lisnek O'Connell

Frank Leo O'Gara

James Olson

Parris Dobbs Spirit of The Heart Fund

Robert Pearson

From Jim and Alex Potter, Lauren and Ryan Contillo, and Kathleen Stowers-Potter in Memory of James William Potter

From Michael Green In Memory of Mary Lee Pricco

Michael J. Rainen Family Foundation

Katherine Richardson

Isabelle Berry Reed Revocable Living Trust

Craig and Maryanne Roepke

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Norma Schank

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From Jack Searcy in Memory of Barbara Searcy

Gino and Paetra Serra

Daniel Shiffman

In Memory of Elanor Smith

Darrell and Marjorie Spaedy

In Memory of Paul Stoffel and Aimee Stoffel

Robert and Kathleen Stout

From Sierra Aviation in Honor of Jim and Virginia Stowers

Michele Stowers

From Merriman Foundation In Memory of Pam Stowers

Mark A. Susz Revocable Trust

Ten Ten Foundation

In Memory of Honorable Elwood Thomas

Harold and Ruthie Tivol

Robert and Roselle Tomsovic

Charles and Carol Diane Tritschler

David Tucker

John and Ollie Urie

Margaret Van Wagoner

Howard and Frances Vaughan Charitable Foundation

Dennis and Sally Von Waaden

Jean Weitzmann

John Whitten

Jon Zindel

2011 CONTRIBUTIONS

In 2011, contributions were received from, in memory of, or in honor of the following:

$10 Million+

Pamela Stowers

$10,000+

American Century Investments Foundation
Richard and Jeanette Brown
David Chao and Julia Zeitlinger
James Kemper Jr.
Mistler Family Foundation
Rubin Postaer and Associates
Roderick and Linda Sturgeon
David and Wendy Welte

$5,000+

Enrique Chang and Catherine Farley
David and Susan Keefer
William and Priscilla Neaves
Catherine Netherland
James Stowers III

$1,000+

Jonathan Bauman
Janice Beatty
Alan Critchell
Phillip Davidson
Stephen and Patricia Gound
Irv and Ellen Hockaday
Allan and Margot Huber
John and Connie Hoye
William Kreiling
Labconco Corporation
Linney Family Foundation
Barbara Marshall
Amy Noelker
Parris Dobbs Spirit of the Heart Fund
Robert and Jan Peterson
Don and George-Ann Pratt
Marilyn Prewitt Trust
David and Jeannine Strandjord
David and Eden Thorne
Jean Weitzmann
John Whitten

Up to $999

Anonymous
Michele Barbeck
Larry Bingham
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Lewis and Mildred Chadderdon
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Nadine Dean
Dorothy Denny
Doan Duong
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Susan McCune
John and Susan McMeel
Frances Madelyn Meany
Debra Morris
From Kurt and Barbara Johnson in Memory of Lindsey Morris-Elwood
From The Fabulous Book Club Babes in Memory of Lindsey Morris-Elwood
Jennifer Noland
Frank O'Gara
Michael Raddie
Katherine Richardson
Barbara Roach
Vivien Schlozman
Larry Schmidt
Daniel Shiffman
William Shilling
Bruce and Celia Solomon
Spahr Family
Kevin Stone
Robert and Kathleen Stout
Association for Corporate Growth in Honor of Jonathan Thomas
Jonathan and Cyndi Thomas
Stephen Thune
From Herbert and Estelle Adler in Honor of Mr. and Mrs. Alan Weinberger
Bob Weisensee
Robert and Diana Williams
Jessica Witt
William Wong
Lorna Wright

Every attempt has been made to ensure the accuracy of the above list. In case of error or omission, the Stowers Institute wishes to be advised.

For more information on how to establish a Hope Shares account, please visit www.stowers.org/support or call (816) 926-4065.

BACKSTAGE PASS

Zebrafish, rather unassuming one-and-a-half-inch-long striped creatures, take center stage in the labs of many Stowers investigators. Researchers prize zebrafish for their transparent embryos that enable them to follow the development of tissue and organs in microscopic detail, but also as a valuable model system to study the development of human disease. Behind the scenes, a team of specially trained aquatics experts cares for the fish in a state-of-the-art facility, raising them on a homegrown diet of single-celled paramecia and brine shrimp.

ZEBRAFISH BY THE NUMBERS

260,000
gallons of water filtered and re-circulated each day

25,000
size of the current zebrafish population

14,000
number of breedings set up in 2011

8,000
number of manual water quality tests performed annually

2,086
number of tanks holding fish

228
number of zebrafish strains housed in the aquatics facility

200
average number of eggs per clutch

150
gallons of paramecia grown for food annually

108
pounds of brine shrimp eggs hatched for fish food

37
pounds of processed dry food fed to fish

2.5
average lifespan in years

STOWERS INSTITUTE®
FOR MEDICAL RESEARCH

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Fax: (816) 926-2000
www.stowers.org

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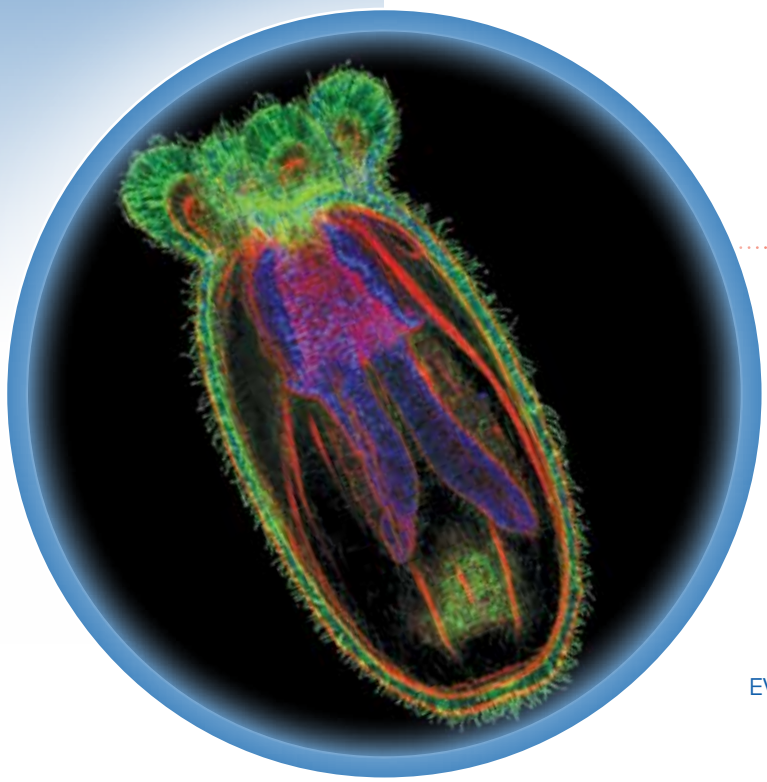
OUR MISSION:

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.



ALTHOUGH THE TINY STARLET SEA ANEMONE NEMATOSTELLA VECTENSIS OCCUPIES ONE OF THE LOWER BRANCHES ON THE TREE OF LIFE, ITS GENOME IS SURPRISINGLY SIMILAR TO OUR OWN. ASSOCIATE INVESTIGATOR MATTHEW GIBSON, PHD, TAKES ADVANTAGE OF NEMATOSTELLA'S SURPRISING DEGREE OF GENOMIC COMPLEXITY TO STUDY THE EVOLUTIONARY HISTORY OF GROWTH CONTROL.