STOWERS INSTITUTE
FOR MEDICAL RESEARCH

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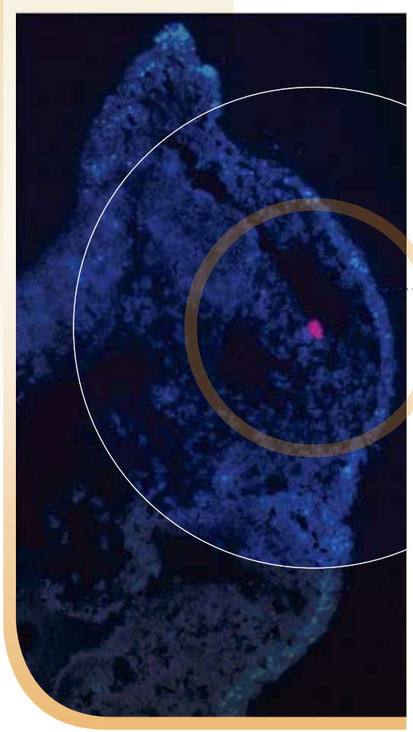
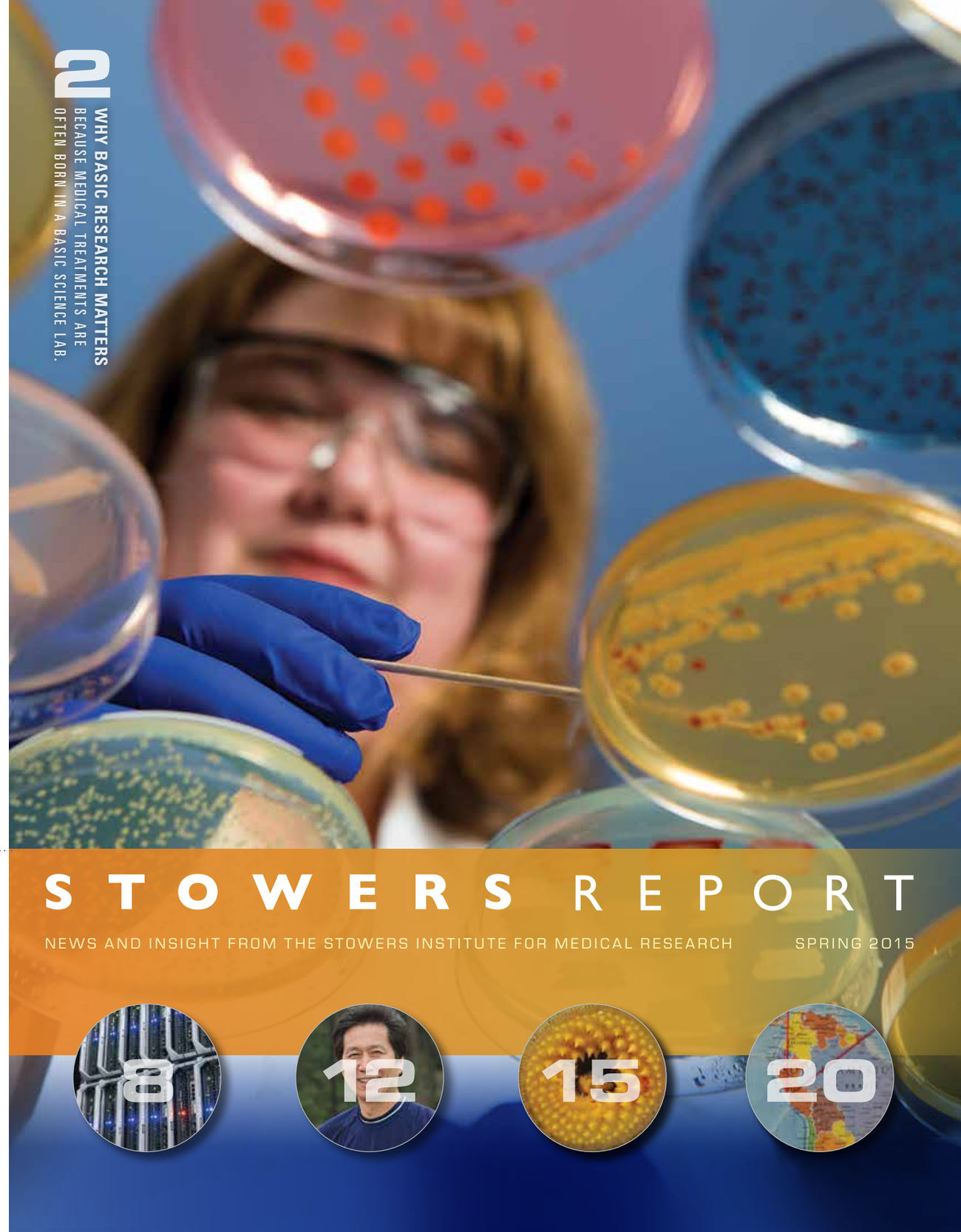
OUR MISSION:

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.



SPECTRAL IMAGING OF A SINGLE PHOTO-CONVERTED CHICK NEURAL CREST CELL (RED) ALONG ITS MIGRATORY ROUTE THROUGH SURROUNDING TISSUE.

Image courtesy of Cathy McKinney and Jason Morrison, Imaging/Kulesa Lab.



WHY BASIC RESEARCH MATTERS
BECAUSE MEDICAL TREATMENTS ARE OFTEN BORN IN A BASIC SCIENCE LAB.

STOWERS REPORT

NEWS AND INSIGHT FROM THE STOWERS INSTITUTE FOR MEDICAL RESEARCH SPRING 2015

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In perspective

BY DAVID CHAO, PHD
PRESIDENT AND CEO

Basic biomedical researchers seek answers to fundamental questions about how living organisms develop and function. In addition to increasing our fundamental understanding, some of these discoveries become starting points for developing new medical applications, often in unexpected ways.

"In many cases, understanding a disease requires first understanding the details and principles underlying a normal biological process. With this understanding, scientists can more readily determine what cellular and molecular changes lead to disease. This broader intellectual foundation enables the rational pursuit of new approaches to identify abnormalities, fix them or even prevent them from occurring in the first place.

This issue of the Stowers Report focuses on how basic biomedical research is essential to the development of new and better approaches for improving human health. The cover story highlights several Stowers research programs that have particular relevance to cancer, a disease afflicting millions of patients around the world.

Cancer is a group of diseases characterized by uncontrolled cell growth and the potential to spread to other locations within the body. Using model organisms, Stowers researchers investigate biological processes frequently affected in cancer, such as cell division, differentiation, and migration. Clarifying how genes and molecular pathways contribute to these normal processes helps researchers determine what is abnormal about them in cancer and ultimately provides the intellectual foundation for diagnostic, therapeutic, and preventative strategies.

History has shown that scientists' desire to understand how cells and molecules work at the most basic level has accelerated the development of new therapies in undeniable and unpredictable ways. For instance, in the 1980's, studies of mating in baker's yeast identified a molecular pathway that is now the target for drugs to treat human melanoma, including one under development by BVD. Likewise, the study of infected wounds in the 1920's led to the isolation of a strain of bacteria that is now the basis for BVD's experimental therapy to treat solid tumors.

Several decades ago, Jim and Virginia Stowers each had personal experiences with cancer that gave them first-hand exposure to the medical technologies and treatments available at the time. Although they emerged as cancer survivors, both had gained a deeper understanding of the difficulties faced by cancer patients and contemplated the best approach to fight the disease.

Mr. and Mrs. Stowers were confident in their belief that a long-term investment in basic research would ultimately have a significant impact on the fight against cancer and other diseases. To ensure the sustainable pursuit of their vision, they created a group of interlinked organizations in American Century Investments, the Stowers Institute for Medical Research, and BioMed Valley Discoveries, Inc. Their philanthropy has resulted in connectivity at an exceptional and unprecedented scale. Since the year 2000, the Institute's ownership stake in American Century has yielded over $1 billion in dividends that support research at the Institute and BVD. Mr. and Mrs. Stowers created and bonded together a set of organizations that ultimately connect the lives of millions – from those who invest at American Century, to those who work at the three organizations, and ultimately to those who might someday benefit from the work.

I hope you enjoy the articles that follow as another installment in the ongoing story of our work to achieve Jim and Virginia's magnificent vision.

By Elise Lamar, PhD

The Case for Curiosity: WHY BASIC RESEARCH MATTERS

Unless you've had cancer or supported someone who has, you may not be aware of the Herculean efforts often required to battle the disease. But if you are a cancer survivor, you've likely thanked an oncologist, possibly even the nurses and technicians at your cancer hospital. Equally worthy of gratitude are the donors whose names are on the building and the fundraisers whose cancer awareness events raise research dollars. Then there are the drug company researchers who turn molecules into cancer therapies as well as the volunteers who undergo clinical trials to optimize these products. All work to fight this insidious disease.

And there are still more people who may have had a hand in a positive outcome. Yet, you probably didn't meet them at the hospital, in your oncologist's office, or at a fundraiser, as they're almost always working, preferring to avoid the limelight. But these driven individuals may have played a big part in your recovery.

THEY ARE BASIC RESEARCH SCIENTISTS.

Shannon Burns and Sue Jaspersen, PhD

A matter of intent

Associate Investigator Sue Jaspersen, PhD, personifies the curiosity-driven mindset of basic scientists at the Stowers Institute for Medical Research. For almost two decades she has studied the biochemical nuts and bolts of cell division in yeast. Her goal? "To understand how cells make decisions about how to grow, divide, make copies of their DNA, and distribute it to daughter cells so that they are healthy and happy and have everything they need to make healthy and happy children of their own!"

Missing from Jaspersen's list is the *intention* to cure a disease or develop a pharmaceutical. Jaspersen, also an associate professor in the Department of Molecular and Integrative Physiology at the University of Kansas School of Medicine, simply wants to know how cells divide, and thinks yeast is the best organism for studying this process. Even without a direct, cure-related purpose, the American Cancer Society awarded her a grant in 2011 to study proteins that sit on the inner face of a yeast cell nuclear membrane: "because that area interacts with chromosomes, and knowing how proteins get to this space might tell us how chromosomes stay organized."

Keeping chromosomes organized is critical. A cancer's signature is chromosomal chaos, or what biologists call genomic instability. Marked by damage such as mutations in DNA strands or abnormal numbers of chromosomes, this genomic instability causes uncontrolled cell division, the trait all cancers share.

Jaspersen's research does not directly address how to avert genomic disaster, but it has unmistakable relevance to cancer, as does any biochemical analysis of cell division. "Understanding how cells do something right will eventually lead to knowing how to treat cancers or inherited diseases in which normal cell division is subverted," says Jaspersen.

One of her current interests is how multiprotein complexes called spindle pole bodies (SPBs) in yeast duplicate themselves one time in preparation for cell division. That event kicks off construction of a gigantic molecular scaffold called the mitotic spindle anchored at each end by SPBs. In a process Jaspersen likens to tugging on a wishbone, replicated chromosomes then get dragged in opposite directions by the spindle into those healthy and happy (if the wishbone is perfectly bisected) daughter cells.

Jaspersen's lab wants to identify molecules that orchestrate this event. For example, in a 2014 collaborative study published in *PLoS Genetics*, Jaspersen and colleagues showed how one protein in the crowd of SPB proteins controlled whether the entire complex duplicated. This work has potential applications to human health, as cancer cells often contain more than one SPB (called centrosomes in mammals), a mistake that might be linked to genomic breakdown.

She says obtaining funding to conduct pure research like this can be challenging because many donors want to see a near-term impact of their philanthropy. "But what is not always clear," she says, "is that funding basic research is a proven route to new and better ways of treating disease."

"You're the scientist."

The idea is not controversial at the Institute. In fact, it is why Jim and Virginia Stowers created the Institute. As an illustration, Associate Investigator Tatjana Piotrowski, PhD, recalls a conversation she had with Jim Stowers in 2010. When asked what he might like her to work on, Mr. Stowers said, "Well, you're the scientist. *You* should know what is important."

Tatjana Piotrowski, PhD

What Piotrowoski deemed important was understanding how cells move. So she built her laboratory around zebrafish as a model organism and decided to study development of sensory hairs that fish use to detect water movement. This sense organ, called the lateral line, forms as a procession of immature precursor cells march collectively from the head to the tail of a fish and mature in a line as they go. But since only aquatic vertebrates have a lateral line, why should a mammal care?

For numerous reasons, not the least being that injured lateral line cells regenerate. Figuring out how they do that, and why analogous hair cells in the human inner ear cannot, might suggest ways to reverse some forms of hearing loss in humans. But embryonic lateral line cells also share the second worst attribute of cancer cells - they migrate in a manner reminiscent of metastatic cancer cells that travel in packs. "If we want to study collective cell migration in a living animal, we must use model organisms, like fish," says Piotrowski. "It is not an exaggeration that a migrating fish cell likely uses cues similar to those used by migrating human cells."

Findings from the Piotrowski lab published this year in *Cell Reports* drive that point home. To define signals that guide lateral line precursors, the researchers first employed genetic techniques to delete a large protein displayed on the membrane of those cells called heparan sulfate proteoglycan (HSPG) and then tracked the cells' progress. HSPG loss caused cells to tumble chaotically rather than move forward in a disciplined fashion. Antennae-like HSPGs are often decorated with complex sugars, or glycans. The work suggests that environmental cues transduced by these glycosylated membrane proteins keep cells marching in line.

Interestingly, HSPGs also extend from certain human cancer cells, among them metastatic breast cancers and melanoma, and clinicians correlate changes in their structure with unfavorable prognosis. Drugs that control HSPG synthesis, called heparanase inhibitors, are being evaluated as anticancer drugs in clinical trials. Whether metastatic human tumor cells use the same signals employed by fish lateral line precursors remains unknown. But if they do, Piotrowski suggests that candidate antimetastatic drugs could be developed using knowledge gained from studying the fish.

Not something a cancer cell invented

Developmental biologist Paul Kulesa, PhD, who directs the Institute's Imaging Center, also studies migration of motile embryonic cells - in his case, neural crest cells in a chick embryo model system. In vertebrates, neural crest cells fan out from the head and embryonic spinal cord to form diverse structures such as facial features, smooth muscle, pigmented cells, and the peripheral nervous system. Like Piotrowski's zebrafish, chick embryos are an ideal system because you can follow a single cell in a living animal.

Jennifer Kasemeier-Kulesa, a research specialist II in the lab, notes that invasiveness is not a sinister attribute but rather

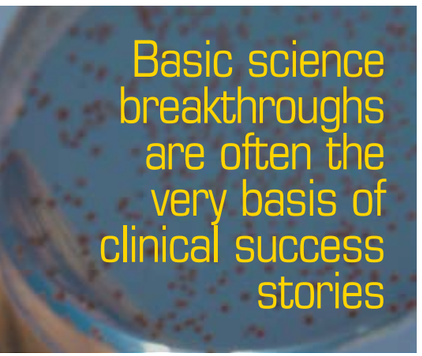
Jennifer Kasemeier-Kulesa, PhD and Paul Kulesa, PhD

a necessity for many well-behaved cells in a developing embryo. "Getting from one point to another in an organism is not something a cancer cell invented," she says. "Cancer cells migrate by pre-empting signals used by normal cells."

Proof for that comes from the lab's ongoing analysis of two neural crest-derived cancers: melanoma, a cancer of pigmented cells, and neuroblastoma, a malignancy of sympathetic nervous system precursors. In a study published in *Pigment Cell & Melanoma Research* in 2012, Kulesa and colleagues reported that human melanoma cells apparently "remember" that they were once neural crest cells, because they migrate along neural crest pathways when placed in a chick embryo. This may mean that tumor cells retain the

molecular detection gear—analogous to Piotrowski's HSPG proteins—required to pick up guidance signals emitted in their ancestral neighborhood.

The Kulesa lab recently received a grant from the National Institutes of Health (NIH) to determine if human neuroblastoma cells behave similarly; they're optimistic, based on their recent discovery of a signaling pathway that controls migration of normal sympathetic nervous system precursors.



Neuroblastoma is the most common cancer of infants. Children born with the disease exhibit tumors along the spine or in the adrenal glands. "In neuroblastoma, neural crest cells never reach their destination and instead remain undifferentiated precursors, forming tumors along the way," says Kulesa. "If human neuroblastoma cells respond to an embryonic chick microenvironment, researchers might be able to use this information to reprogram metastatic cells to become less invasive."

The secrets of life

It may seem surprising for an institute populated by a curiosity-driven faculty and without a single clinical researcher among them to have the words "Medical Research" included in the name. If so, note that Jim Stowers went to medical school, Virginia Stowers went to nursing school, and both battled cancer. For them, the need for better cancer treatment was not an abstract concept. Both were firm in their belief that *medical* treatments are often born in a basic science lab.

Take the top three cancer drugs of 2014: based on sales, they were rituximab (targeting lymphoma and leukemia), bevacizumab (which cuts off a tumor's blood supply), and trastuzumab (the anti-breast cancer drug known commonly by its brand name Herceptin). All three drugs are monoclonal antibodies ("mabs") developed and sold by pharmaceutical companies whose names are household words.

But the fundamental principles underlying each—that man-made antibodies can be engineered to latch onto and kill a cell with great specificity, or that blocking an overactive cell surface receptor can halt tumor growth—were discovered by basic researchers unknown to most people, at least prior to their recognition as Nobel laureates.

In 1984, basic scientists César Milstein, Georges Köhler, and Niels Jerne won the Nobel Prize in Physiology or Medicine for discovering the principle for the production of monoclonal antibodies. Five years later, basic scientists Michael Bishop and Harold Varmus won the same prize for showing how mutant growth factor receptors act as oncogenes.

Where breakthroughs come from

Quite different from basic science on the intent scale is translational or "bench-to-bedside" research. Translational researchers apply basic science discoveries to the diagnosis, treatment, or prevention of a disease, often with the goal of moving a potential therapy toward a clinical trial.

Like all his Stowers colleagues, Investigator Linheng Li, PhD, is firmly anchored at the bench. Nonetheless, his research has direct medical implications. Li investigates adult blood stem cells (called hematopoietic stem cells or HSCs), which can mature into every type of blood cell and construct an entire immune system from a single cell. Using mouse models, Li and his colleagues have determined where HSCs live (in bone marrow niches) and that HSCs are not all alike (they can be active or dormant).

More recently, he discovered that their children take care of them. In a 2014 *Nature Medicine* paper, Li and Postdoctoral Research Associate Meng Zhao, PhD, reported that HSCs are protected in the niche by mature blood cells called megakaryocytes, which emit signals that hold their cellular parents in a quiescent state, ready to jump into action in an emergency, as when an organism loses a lot of blood.

These studies have applications on two bedside fronts, one more obvious than the other. First, bone marrow transplants are basically HSC infusions into patients who have lost blood cells due to disease (anemia) or chemotherapy (cancer). The more we know about HSC biology, the more successful that procedure is likely to be.

Less obvious is a cancer connection that emerged about five years ago. Then, cancer researchers discovered that many tumors harbored small subpopulations of dormant cells that could rebuild an entire tumor from a single cell. Even worse, these tumor-*initiating* cells—sometimes called cancer stem cells—are generally more resistant to chemotherapy than garden-variety tumor cells.

The very existence of tumor-initiating cells is one explanation for why chemotherapy sometimes becomes less effective over time. "At first, you're killing active, proliferating cells, but then dormant ones wake up and undergo expansion," says Li. "To treat cancer effectively, we need to find ways of killing both."

Guided by this new insight, translational researchers have recently brushed up on the biology of normal adult stem cells like HSCs. The signals these cells use to replenish their kind could be hijacked by tumor-initiating cells. In fact, Li lab researcher John Perry, PhD, received a postdoctoral fellowship in 2011 from the Leukemia and Lymphoma Society to address this very possibility. While those studies are ongoing, Perry and Senior Research Specialist Xi (CiCi) He, MD, have obtained evidence from leukemia and adenoma models that quiescent stem cells exhibit resistance to drug treatment. Perry and He are working on a novel strategy to target these drug-resistant cancer cells.

Li says he always keeps applications of his work in the back of his mind, but he has little intention of straying far from the bench. "That's where you work on problems that are fundamental," Li says. "It's where breakthroughs come from."

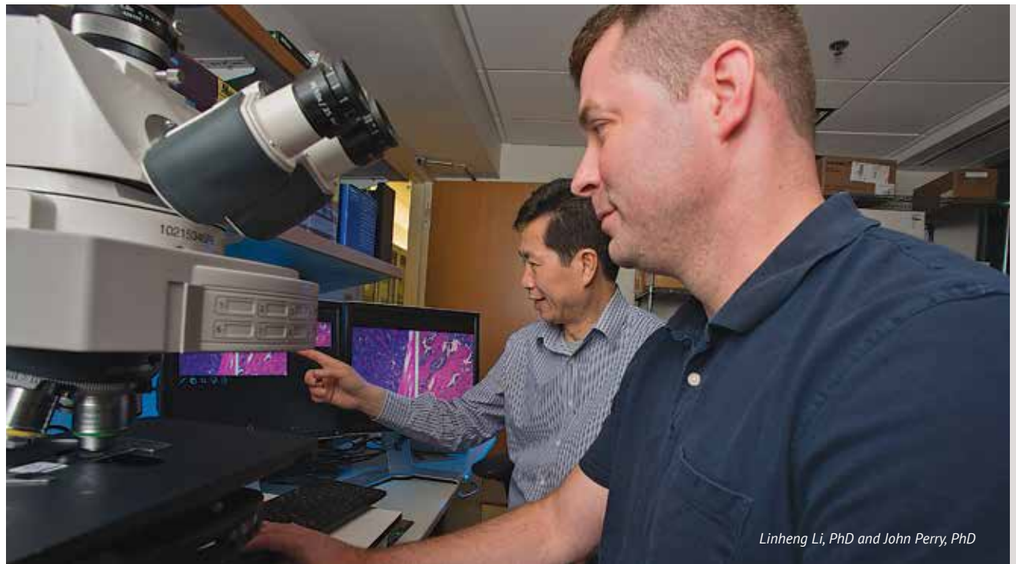
Know your history

Thus, basic science breakthroughs are often the very basis of clinical success stories, a connection Piotrowski is concerned may be unclear to even some biology students. "I worry that developmental biology could fall out of favor, as many students seem to want to work on cancer-related topics," she says. "Many don't realize that the same signaling pathways misregulated in cancer were first identified in developmental studies of the fruit fly *Drosophila*."

Indeed, in 1995, three developmental biologists using the *Drosophila* model system—Ed Lewis, Christiane Nüsslein-Volhard, and Eric Wieschaus—won the Nobel Prize in Physiology or Medicine for their accomplishments in determining genetic and molecular mechanisms of embryogenesis.

The good news is that many researchers like those at the Institute aren't jumping the basic science ship. They are happy to let others apply their findings to potential treatments, in part because they cannot forgo the chance to discover something unsought. According to Kasemeier-Kulesa, "If you focus solely on getting a particular answer, you may not notice something that doesn't pertain to your question. You could miss out on a lot."

No doubt the Nobel laureates would agree.


Linheng Li, PhD and John Perry, PhD

By Anissa Orr

HIGH-TECH TOOLS HELP STOWERS SCIENTISTS FOCUS ON DISCOVERY

The software behind the science

Jenny McGee and Samuel Burns

JUST EIGHT YEARS AGO, ANALYZING RESEARCH DATA WAS A MORE PRIMITIVE AFFAIR, REMEMBERS HUA LI, PHD, A BIOSTATISTICIAN IN THE COMPUTATIONAL BIOLOGY CORE GROUP AT THE STOWERS INSTITUTE. AT THAT TIME, RESEARCH SCIENTISTS COULD STILL CRUNCH NUMBERS FROM MOST EXPERIMENTS ON PERSONAL COMPUTERS AND USE TRADITIONAL CHARTS AND GRAPHS TO HIGHLIGHT FINDINGS. BUT TECHNOLOGICAL ADVANCES YIELDING VAST AMOUNTS OF BIOLOGICAL DATA HAVE FOREVER CHANGED THE WAY RESEARCH IS CONDUCTED, REPORTED, AND SHARED.

"Now it is often impossible to analyze all that data on your own workstation," Li says. "You need to have a room full of servers and good IT [information technology] support. Data storage and computational skills have become essential for biomedical research."

That's especially true for scientists at the Stowers Institute who deal heavily in genomics research that allows studying an organism's complete set of DNA (genome). An estimated 80 percent of data processed by the Computational Biology Core involves sequenced genomic data. Sequencing—figuring out the order of DNA bases in a genome: the As, Cs, Gs, and Ts that make up an organism's genetic code—has become more affordable and accessible for scientists, thanks to high-throughput next-generation sequencing. These technologies also provide scientists with other important forms of genetic information.

To make sense of all that data, Stowers scientists increasingly rely on sophisticated computing technologies. The Institute backs their efforts by devoting a substantial portion of the scientific operating budget to providing and supporting computing resources.

The result is a culture that embraces creativity and technological innovation. In particular, new advances in scientific software programs and computing techniques and tools are boosting productivity and making it easier for researchers to focus on important scientific questions. Here's a closer look at how Stowers researchers are using tech to drive discovery.

Always adapting in IT

Meeting the technology needs of scientists is a constant challenge in an age when new technologies emerge daily and hardware and software quickly become obsolete, says Mike Newhouse, head of Information Management at the Institute.

"The days of stagnant IT are gone," he says. "Today's approach to information management demands a continual fluid change of programs, hardware, and storage. Our job is to adapt and handle those changes as they come up."

Newhouse joined the Institute in 1997 when he was hired by co-founder James E. Stowers Jr. Stowers had pioneered the application of computing power to investment management at American Century Investments—Stowers' renowned investment management firm—and sought to do the same with the Institute's basic research. Newhouse joined as the Institute's sixth staff member and helped build the IT team from the ground up.

Since then, Stowers' information management has grown tremendously—from its humble beginnings in a double-wide trailer with two team members and two computer servers, to its current state-of-the-art offices and data center, housing seventeen team members and more than 250 servers. The rise in storage capacity alone astounds, soaring from just 40 gigabytes to 2.3 petabytes (one petabyte is one quadrillion bytes)—an increase of nearly 60,000 - fold.

"Much of our growth is clearly based around the sequencing data and imaging data we collect now," Newhouse says. "The data our researchers are creating in core groups like Molecular Biology (next-generation sequencing) and Microscopy is massive. The growth is increasing exponentially because of the technologies behind it."

To keep up, Newhouse maintains a strong IT infrastructure that supports new technologies and provides investigators with up-to-date tools, including more than 350 software packages. "Giving scientists what they need is a challenge at many scientific institutions stymied by bureaucracy," he says.

"Here there is an attitude of 'Let's get investigators what they need to do science. And let's get it now,'" Newhouse explains.

Visualizing data from all angles

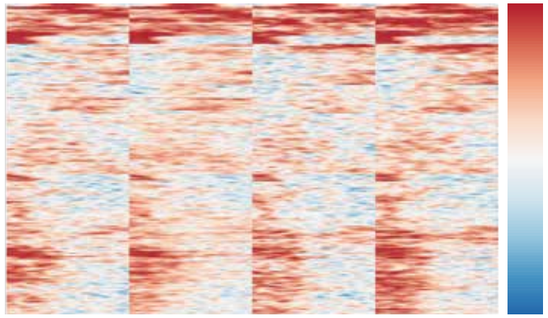
While the Information Management team keeps technology running at the Institute, an array of programmers and analysts helps researchers process, analyze, and visualize data. Many of these adept data handlers can be found in the Institute's Computational Biology Core group, which provides computational support to labs on projects lasting from days to years.

"Piles and piles of sequences don't mean much, and tables of numbers are really hard to look at and interpret," says Programmer Analyst Madelaine Gogol. "But seeing data distilled into a plot or figure will allow you to pull meaning from it much easier. Patterns emerge and help you understand what is going on. Like the saying says, 'A picture is worth a thousand words.'" Gogol and her Computational Biology colleagues create pictures that precisely illustrate complex data, using a variety of software and programming tools and their own custom scripts. The information revealed can be insightful or surprising, and may lead to more questions begging to be explored.

Madelaine Gogol and Arnob Dutta, PhD

Gogol recently completed a year-long project with Arnob Dutta, PhD, a postdoctoral research associate in the laboratory of Jerry Workman, PhD. He studied how the SWI/SNF chromatin remodeling complex, a group of proteins that work together to change the way DNA is packaged, regulates gene transcription. Gene transcription is the first step of the process by which information encoded in a gene directs the assembly of a protein molecule. Recent studies have found that 20 percent of all cancers have mutations in the SWI/SNF complex, and have led scientists, like Dutta, to investigate the complex in more detail.

To help Dutta visualize his results, Gogol used programming packages created in R, an open source computing language used for data analysis, to map individual sequence reads to their position in the genome. She then sliced out the



regions around the genes, retaining only the desired genetic area. Next, she clustered the genes by comparing the patterns in each row to one another and placing the two closest rows together. Finally, she represented the numerical values with a color gradient to form a graphical image called a heat map.

The final visualized data pops in red and blue. The image gives an immediate global view of gene profiles across different experimental conditions as well as how genes cluster into groups with similar profiles. Dutta used the heat map to understand how a particular component of the chromatin remodeling complex associates with genes under different conditions, with the color gradient representing the degree of association.

"Looking at the colors, you can see that blue is low and red is high, and you immediately get the picture," says Hua Li, Gogol's colleague in Computational Biology. "With numbers it is really hard to see a pattern, but with colors you get it immediately."

Virtually wrapping up the whole package

In the laboratory of Julia Zeitlinger, PhD, Research Specialist Jeff Johnston uses virtual machines both to make sense of their research data and to allow other scientists to reproduce their results. Researchers in Zeitlinger's lab are studying how an

Jeff Johnston, PhD

organism is able to turn on and off the correct genes during development, using the fruit fly *Drosophila* as a model system.

"We go through many different versions of a manuscript before settling on one for publication," Johnston explains. "During this time, many of the software packages we use get updated, similar to how the apps on your phone or software programs on your laptop are regularly updated. Because of all these changes, we can use virtual machines to build a clean computational environment with specific versions of all the software we need, and then repeat our analysis to ensure it is reproducible."

A virtual machine is a program on a computer that works as if it is a separate computer inside the main computer and allows users to run multiple operating systems without interference from each other. For example, a virtual machine would allow a Windows program to run on a Mac.

The Zeitlinger team made one of their first virtual machines public in 2013, with the publication of a paper in *eLife*. The link to the study's virtual machine contained all the software packages, analysis code, raw data, and processed data used to create the figures and tables in the published manuscript.

"Since the virtual machine is essentially self-contained and frozen in time, it will always be able to reproduce our analysis, even years later when much of the underlying software code becomes obsolete," Johnston says.

Sharing data in this way is important because it advances research and paves the way for future developments in how data is analyzed and shared, he says. In this spirit, Johnston and his colleagues also use literate programming, a form of data analysis that mixes software code with descriptive text. When users click on a file, they see a more detailed description of the programming used to analyze data—a document that reads more like a research "how to" than a string of code.

"This makes the resulting analysis much more presentable, easier to follow, and more amenable to use as a teaching tool," Johnston says.

What's next?

The past decade has been one of immense change for biomedical research, and continual innovations in technology and genome engineering promise even more change. It's a future that excites IT experts, analysts, and scientists alike, who look forward to the challenge of using the latest technology to further the Institute's science.

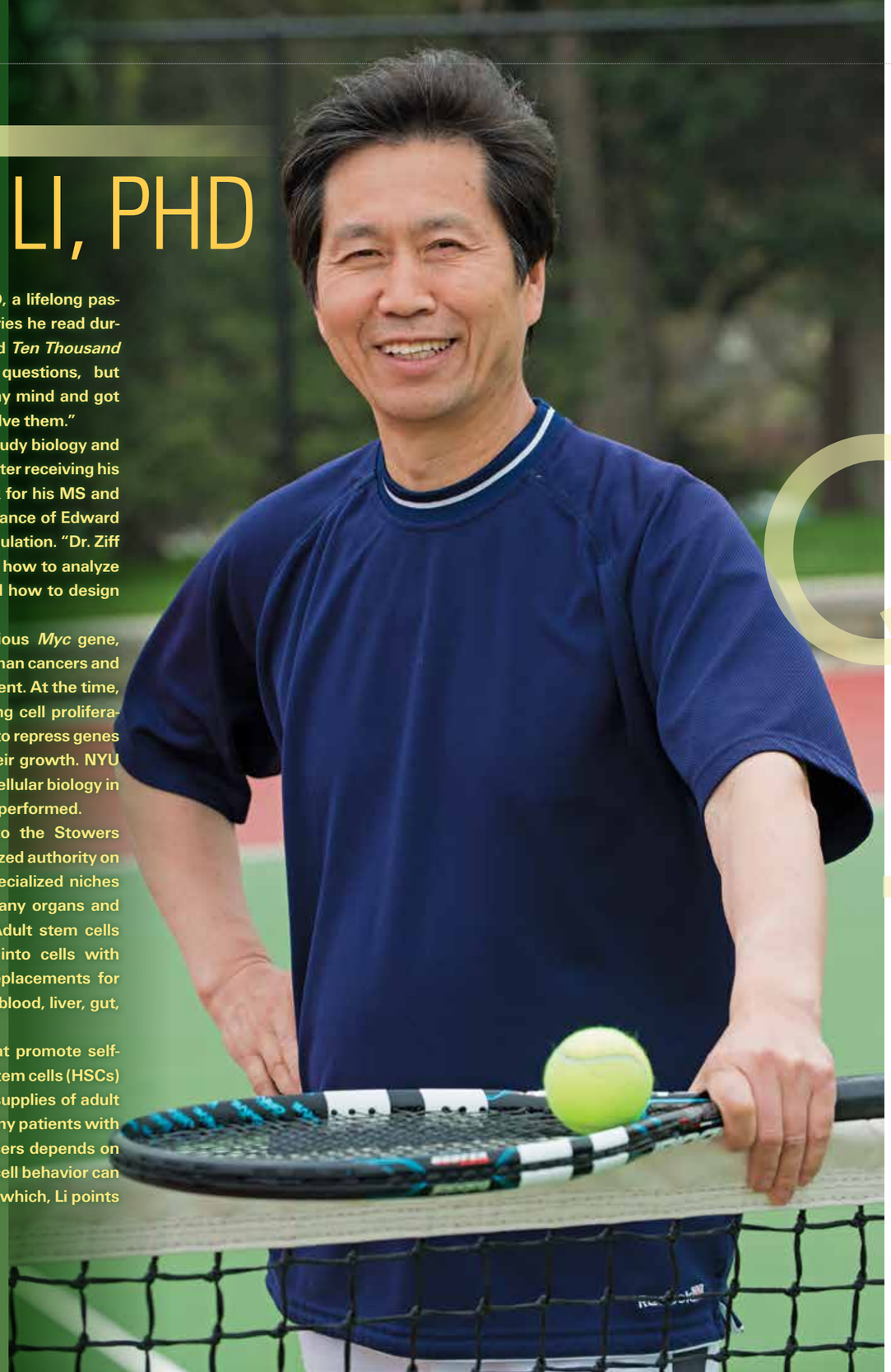
"My basic goal is to help investigators understand and really see their data as quickly and thoroughly as possible, with the underlying hope that it will tell us something interesting and new about the processes of life," Gogol says. "I hope to contribute in my own small way to the discoveries that researchers are making about these wonderful complex biological systems that are going on daily within and all around us."

INFORMATION MANAGEMENT: *Left to right, back row—Steve DeGennaro, Andrew Holden, Dustin Dietz, Chad Harvey, David Hahn, Mark Matson, Jay Casillas, Mike Newhouse, Samuel Burns, Dan Stranathan. Front row—Chris Locke, Jenny McGee, David Duerr, Amy Ubben, Jordan Hensley. (Not pictured Shaun Price and Robert Reece)*

By Cathy Yarbrough

A DISCUSSION WITH

LINHENG LI, PHD



For Stowers Investigator Linheng Li, PhD, a lifelong passion for science was sparked by a book series he read during his childhood in China. The books, titled *Ten Thousand Unknown Questions*, "raised so many questions, but offered no answers." says Li. "It opened my mind and got me thinking about mysteries and how to solve them."

With his curiosity piqued, Li went on to study biology and genetics at Fudan University in Shanghai. After receiving his BS degree at Fudan, Li moved to New York for his MS and PhD at New York University under the guidance of Edward Ziff, PhD, an international leader in gene regulation. "Dr. Ziff taught me how to ask a research question, how to analyze data, how to think in alternative ways, and how to design experiments to test a hypothesis," Li says.

In Ziff's lab, Li investigated the mysterious *Myc* gene, which is mutated in about 20 percent of human cancers and a prime target in anticancer drug development. At the time, *Myc* was known to play a role in promoting cell proliferation. Li discovered another function of *Myc* - to repress genes that instruct cells to specialize and halt their growth. NYU awarded Li a PhD degree in molecular and cellular biology in 1995, based on these and other studies he performed.

Among the first scientists appointed to the Stowers faculty, Li today is an internationally recognized authority on the biology of adult stem cells and the specialized niches that harbor these self-renewing cells in many organs and tissues of humans and other mammals. Adult stem cells are genetically programmed to develop into cells with specialized functions. They provide the replacements for the worn-out or damaged cells of the skin, blood, liver, gut, and other organs and tissues of the body.

Understanding the molecular signals that promote self-renewal of hematopoietic (blood-forming) stem cells (HSCs) could enable clinicians to generate ample supplies of adult bone marrow stem cells. The survival of many patients with leukemia, lymphoma, and other blood cancers depends on these transplants. Insights into adult stem cell behavior can also help explain cancer stem cell behavior which, Li points out, is a newly emerging approach to understand cancer better. Many tumors contain a small population of cancer stem cells, which may underlie the development of resistance to chemotherapy agents that had been effective in the primary treatment. "Cancer stem cells also may play a role in the cancer subsequently spreading from primary to secondary tissues and organs in the body," Li adds.

Li's focus on adult stem cells began during his postdoctoral studies with the legendary scientific pioneer Leroy (Lee) Hood, MD, PhD, co-founder and director of Seattle-based Institute for Systems Biology (ISB) and an early scientific advisor to the fledgling Stowers Institute. "Lee told me that if I wanted to be at the forefront of discovery, I should address only the most leading research questions in biology," explains Li. "He also said that to be on the cutting edge of science, I should identify the technologies that would help me get there. If they were not available, I should obtain them."

Q YOU OBVIOUSLY FOLLOWED HOOD'S ADVICE. AFTER JOINING THE INSTITUTE IN 2000, YOU SPEARHEADED THE DEVELOPMENT OF THE TECHNOLOGY KNOWN AS EX VIVO IMAGING OF STEM CELLS (EVISC), WHICH HAS ALLOWED YOU AND YOUR TEAM TO MONITOR IN REAL TIME THE DYNAMIC BEHAVIOR OF ADULT STEM CELLS. WHAT HAVE YOU LEARNED BY USING EVISC TECHNOLOGY?

A EVISC allowed us to follow the homing of hematopoietic stem cells (HSCs), which are bone marrow-derived adult stem cells, after they were transplanted into laboratory mice. For the first time, we could study the real-time interaction between HSCs and their niches in bone marrow. We were the first to identify an adult stem cell niche at the cellular level and to determine that there are distinct molecular signals that control the size of the HSC niche and thereby the number of HSCs produced in the niche.

Q WHAT IS THE POTENTIAL RELEVANCE OF YOUR LAB'S IDENTIFICATION OF THESE MOLECULAR SIGNALS?

A Physicians' ability to expand, or grow, sufficient numbers of HSCs in the lab for their patients' bone marrow transplants is limited. If we understand how HSCs normally expand in the mammalian body, perhaps we can improve the expansion of these cells in the lab.

In our lab at the Institute, John Perry, a senior postdoctoral fellow, used three small molecules to mimic self-renewal signals to increase by a hundredfold the number of HSCs generated from mouse bone marrow tissue. Recently, John has been able to achieve the goal of expanding human HSCs in the lab.

WHY DO YOU INVESTIGATE THE ADULT STEM CELLS OF TWO SYSTEMS–BONE MARROW AND THE INTESTINES?

We study the hematopoietic system because it is the original and now well-established system for researchers to understand adult stem cells. It's the system I learned from Irving Weissman, MD, the head of Stanford University's Institute for Stem Cell Biology and Regenerative Medicine in Palo Alto, CA. Dr. Weissman was the first scientist to isolate HSCs in both laboratory mice and humans.

Like blood cells, the cells of the mammalian intestinal epithelium are frequently replaced by new cells from their adult stem cell niches. However, unlike the hematopoietic system, the intestines are a solid organ. We want to determine whether our findings with HSCs apply to at least one solid organ system. Although the two systems differ in their developmental origin and anatomic organization, we have found that they share many principles.

YOUR LAB DISCOVERED THAT THERE ARE TWO COEXISTING, DISPARATE SUBTYPES OF HSCS, 'QUIESCENT' AND 'ACTIVE.' WHY DO HUMANS AND OTHER MAMMALS HAVE TWO SUBTYPES OF THESE CELLS?

Our lab and other researchers have found both subsets in the hematopoietic and intestinal systems. Quiescent HSCs are the body's strategic reserve of hematopoietic adult stem cells. They proliferate only when needed to maintain the supply of active adult stem cells in the niche, or in case of an emergency such as massive blood loss in the body. In contrast, active HSCs continually proliferate because the body's supply of blood and immune cells must be replenished continually.

If all adult stem cells in the bone marrow were active, there might not be an adequate supply of these cells in case of emergency. That's why quiescent cells are referred to as the strategic reserve.

DOES THE COEXISTENCE OF QUIESCENT AND ACTIVE STEM CELLS HAVE ANY POSSIBLE RELEVANCE TO CANCER?

Yes. We and other scientists propose that active cancer stem cells in a tumor support its rapid growth, while quiescent cancer stem cells in the tumor maintain the seed of malignancy, and thus are the basis of a tumor developing resistance to drugs. We propose that to treat cancer efficiently, a new method should focus on targeting both the active and quiescent cancer stem cells. And currently, we are actively testing this hypothesis in both bone marrow and intestinal systems.

DID YOU AND YOUR FAMILY CELEBRATE THE 2015 LUNAR NEW YEAR ON FEBRUARY 19?

We did, but not at the level that it's celebrated in China! My family and I observed the Lunar New Year in Kansas City with other members of the local Chinese-American community here. The community is not large, compared to New York, Seattle, and of course China. Celebrating the Lunar New Year is a way my wife, CiCi, and I remind our son and daughter of their Chinese heritage.

WHAT HISTORICAL PERIOD WOULD YOU MOST LIKE TO VISIT, IF IT WERE POSSIBLE?

I can think of two. For my son's sake, it would be great to scope out the Jurassic period and see actual dinosaur colors, as well as some of the earliest birds like *Archaeopteryx*. My own great interest is human evolution, so I'd choose a visit with the Neanderthals to get a better idea of just how similar to modern humans they were, how they communicated, and why they were eventually outcompeted.

HOW DO YOU RELAX AND HAVE FUN IN KANSAS CITY?

I play tennis with my teenage son or with colleagues at the KC Racquet Club. It's one of the few times I'm not thinking about science. I only think about the game when I play. I also enjoy hiking and spending time with my family. We visit local art exhibits and sometimes the City Market.

In Kansas City, it's so easy to drive from one place to another without the stress of frequent traffic congestion. As a result, I can spend more time on my work and with my family. We really like living here.

ANCIENT VERTEBRATE USES FAMILIAR TOOLS TO BUILD A VERY DIFFERENT HEAD

Jawless fish emerged 500 million years ago, 100 million years before jawed fish and well before mammals. Because they're so unlike us, it may be difficult to fathom that the genes that create the primitive "faces" of jawless fish have anything to do with us.

It turns out they do. A collaborative team led by Stowers Investigator and Scientific Director Robb Krumlauf, PhD, has discovered that a gene network governing the vertebrate head and jaw originated in jawless animals.

Krumlauf and his colleagues report that jawless sea lampreys express an array of Hox genes reminiscent of jawed vertebrates. Like mileposts along a road, Hox genes activated along an embryo's axis dictate where structures like arms or legs are built. "Previously, we addressed how these factors make unique structures," explains Krumlauf. "Now, we are excited by how similar sets of genes play common roles in creating a basic structural plan."

The team focused on Hox genes in the embryonic hindbrain, which controls head and jaw construction. To compare their expression in jawed versus jawless creatures, the team inserted fluorescent Hox "reporters" engineered from DNA of jawed animals (zebrafish or mice) into lamprey embryos. The question was whether lamprey embryos emitted embryonic signals required to switch them on.

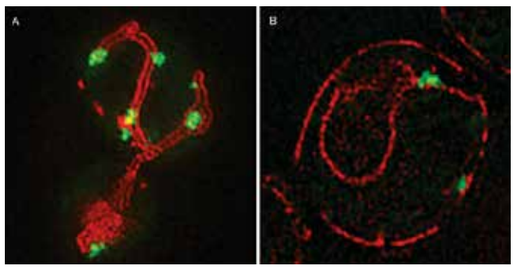
Amazingly, lampreys exhibited hindbrain Hox reporter expression in a pattern much like jawed animals. "That means that the gene regulatory network that governs segmental patterning of the hindbrain likely evolved prior to divergence of jawed vertebrates," says postdoctoral fellow Hugo Parker, PhD, the study's first author.

The study was published in the September 14, 2014, advance online issue of *Nature*.

STOWERS RESEARCHERS CREATE NEW FRAMEWORK FOR PROTEIN AGGREGATION UNDER ACUTE STRESS

Patients with Parkinson's disease, cardiovascular disease, and cystic fibrosis may have something in common - c ells in their disease-affected tissues may produce misfolded proteins that are incapable of functioning normally. Stowers Institute scientists in the Rong Li Lab have studied where the misfolded proteins clump together in a cell, and how the cell can prevent the passage of these defective molecules to its daughter cell.

Investigator Rong Li, PhD, who headed the study, explains that her group has identified the quality control mechanism that limits the spreading of the misfolded protein aggregates to the daughter cell in a budding yeast model. During the mitosis stage of budding yeast's division, aggregates of abnormal protein are tethered to well-anchored mitochondria in the mother cell. The mitochondria acquired by the bud, which will become the daughter cell, are largely free of the abnormal aggregates. As a result, the daughter cell does not inherit the defective proteins that burden the mother cell.

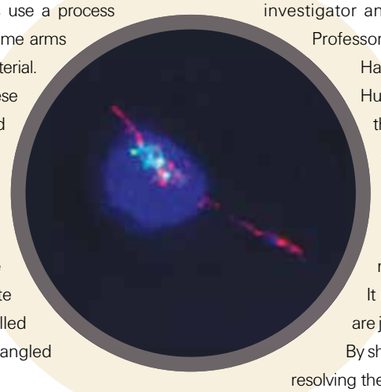


By identifying the quality control mechanisms that normally operate in cells, Li and other scientists are providing information that may prove relevant to treating disorders characterized by misfolded proteins.

These results were reported in the October 16, 2014, online issue of the journal *Cell*.

CUTTING the ties that bind

During the formation of eggs and sperm, the cell's chromosomes must pair up and part in an elaborate sequence that results in sex cells with exactly half the number of chromosomes as the parent cell. In this process, called meiosis, a single misstep can cause infertility, miscarriage, or birth defects.



To stay properly paired, most chromosomes use a process called crossing over, where they loop chromosome arms with their partners and even swap genetic material. Other chromosomes are too short to make these crossovers, but they are still able to stay connected to their partners.

Recent research using a fruit fly model system has shown that some shorter chromosomes stay connected by using thin threads of DNA to tether themselves together, but how they come untied again has not been clear. Stowers Institute scientists now report that an enzyme called Topoisomerase II is required for these entangled chromosomes to be set free.

"It is not surprising there are many ways to segregate chromosomes because there are also many ways to control other molecular events, like gene expression," says R. Scott Hawley, PhD, a Stowers Institute investigator and American Cancer Society Research Professor who led the study.

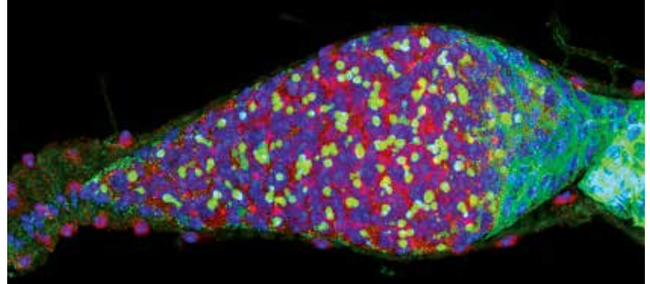
Hawley Lab Research Associate II Stacie E. Hughes, PhD, explains, "Without this enzyme the chromosomes can't come apart, they are stuck together like glue. There are large regions of the chromosomes that are tethered together by these threads, while the rest is stretched out like a slinky as the chromosomes are pulled in opposite directions. It is just a mess. Because the chromosomes are just stuck there, they can't finish meiosis."

By showing that Topoisomerase II is required for resolving these threads so homologous chromosomes can part ways, the Hawley lab team underscores the complexity of the meiotic process.

This study was published in the October 23, 2014, issue of *PLoS Genetics*.

TO MATURE OR NOT TO MATURE

Diverse adult stem cells reside in organisms from fruit flies to humans. Their biology is complex, but their repertoire of behaviors is limited: They either continuously divide (self-renew) or stop dividing and mature, often into replacements for worn-out tissues. Understanding this choice on a molecular level is essential to devising therapies that regenerate diseased tissues.



In a study of adult stem cells from the fruit fly ovary, called germline stem cells (GSCs), Stowers Institute scientists report that the decision to mature, in this case into an egg, versus self-renew comes down to a skirmish between two proteins: - the maturation factor Bam and the multi-subunit COP9 complex, which normally keeps GSCs immature and self-renewing. "Bam is the master differentiation factor in the *Drosophila* GSC system," says Stowers Investigator Ting Xie, PhD, the study's lead author. "To carry out the switch from self-renewal to differentiation, Bam must inactivate self-renewing factors and then activate the differentiation factors."

The team discovered that Bam accomplishes this by binding to and sequestering one of eight COP9 subunits. With that component missing, the remaining proteins in the complex lose their ability to drive self-renewal. As a consequence, GSCs stop dividing and differentiate into eggs.

Mammalian cells also contain COP9 complexes. In fact, there is some evidence that COP9 proteins maintain human stem cell self-renewal. The Xie Lab studies these activities in *Drosophila* because fruit flies can be experimentally manipulated and mirror many aspects of human biology. "As a powerful model system, GSCs have revealed many novel regulatory strategies later confirmed in higher organisms," adds Su Wang, a graduate student from University of Kansas Medical Center who was the study's co-first author.

This study was published in the October 9, 2014, issue of *Nature*.

NEW TECHNIQUE CAN LOCATE GENES' ON-OFF SWITCHES

All the cells in an organism carry the same instruction manual, the DNA, but different cells read and express different portions of it in order to fulfill specific functions in the body. For example, nerve cells express genes that help them send messages to other nerve cells, whereas immune cells express genes that help them make antibodies.

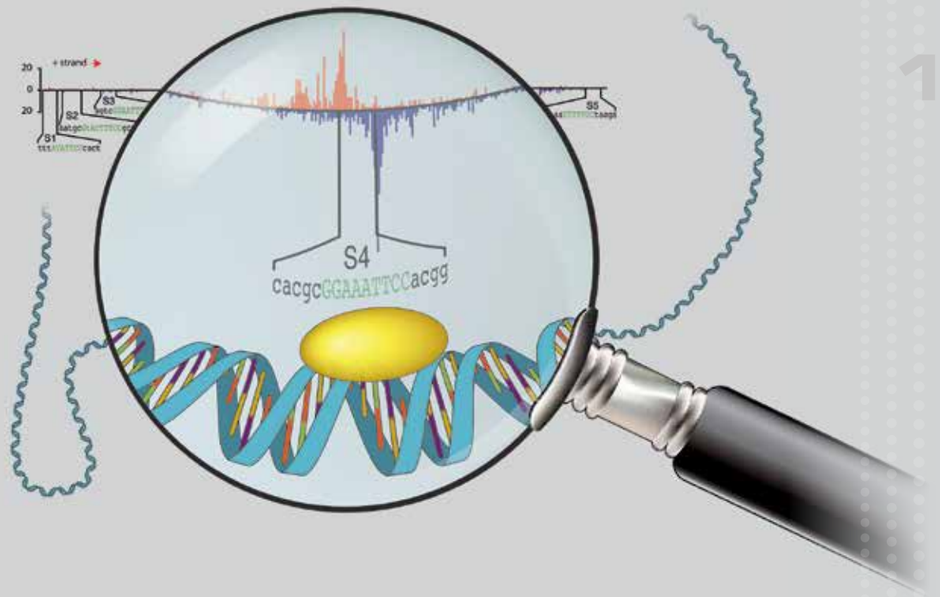
In large part, this highly regulated process of gene expression is what makes us fully functioning, complex beings, rather than a blob of like-minded cells.

At any given time, only a subset of the genes in a given cell are expressed or "turned on." Proteins called transcription factors act as the molecular switchboard operators of the cell, binding specific sites in the DNA to flip different genes on and off. Despite their importance, researchers still have difficulty identifying these transcription factor binding sites.

Recently Stowers scientists reported the development of a new method called ChIP-nexus that can precisely and reliably map these sites, vastly outperforming previous techniques. Stowers Associate Investigator Julia Zeitlinger, PhD, who led the study, explains that researchers can use the new method to understand how transcription factors interact with DNA to control gene expression. For example, the technique has already shown that transcription factors' binding sites are not scattered across the genome as previously thought, but rather appear in specific, predictable sequences.

Zeitlinger thinks the technique represents an important step forward for the field and will ultimately supplant other methods of studying gene regulation.

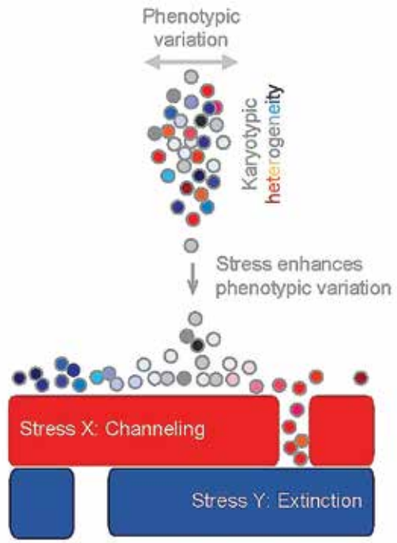
This report was published in the March 9, 2015, issue of *Nature Biotechnology*.



Cancers and human pathogens rapidly evolve and adapt to their surrounding environment–accumulating genetic changes and even gaining or losing entire chromosomes–to develop drug resistance. This ability to adjust

Researchers design "evolutionary trap" to thwart drug resistance

to changing conditions and new therapies can turn the care of patients with these diseases into a game of whack-a-mole, as clinicians hit cells with one treatment after another only to have new drug resistant forms pop up.



Stowers researchers report scientific findings that shed new light on the evolution of drug resistance. The researchers have studied how certain cell populations evolve and evade stresses, such as exposure to drugs. Based on these new insights, the researchers have proposed a strategy called an "evolutionary trap" that is a potential approach to combat human diseases associated with drug resistance.

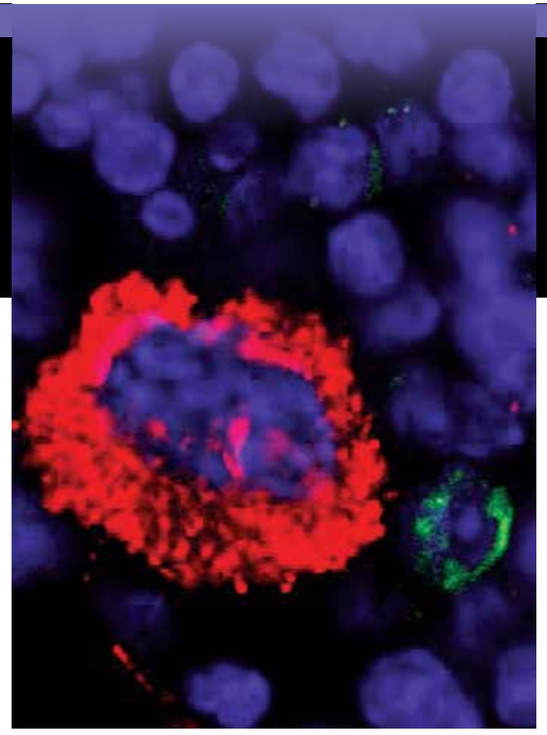
Stowers Investigator Rong Li, PhD, who led the study, explains that this evolutionary trap uses one stress or treatment to steer a population of cells down a single evolutionary path, and then targets a weakness of the less diverse population with another stress or treatment.

"The idea of an evolutionary trap involves training the population so that it has reduced adaptability" says Li. "You take a heterogeneous population of cells and treat it with a drug so that only one specific type of genetic variant will survive. The entire population may be good at growing under that condition, but its homogeneity becomes its Achilles' heel. Then you target that by throwing in a second drug to drastically switch the conditions."

Guangbo Chen, a recently graduated PhD student in Li's lab, tested this approach in a proof-of-principle study with promising results. The strategy may potentially be applied to clinical scenarios where drug resistance is a problem, such as human fungal infections and cancers.

The new approach was reported February 12, 2015, in *Cell*.

"MEGA" CELLS PROMOTE REGENERATION OF BLOOD STEM CELLS



PATIENTS RECOVERING FROM CHEMOTHERAPY OR ORGAN TRANSPLANTATION OFTEN HAVE DANGEROUSLY LOW LEVELS OF BLOOD CELLS, LEAVING THEM WEAK AND VULNERABLE TO INFECTION. RESEARCH FINDINGS FROM THE LAB OF STOWERS INVESTIGATOR LINHENG LI, PHD, DESCRIBE NEW INSIGHTS THAT COULD POTENTIALLY LEAD TO TREATMENTS FOR PATIENTS WITH LOW BLOOD CELL COUNTS.

Li, who led the study, explains that megakaryocytes, "mega" cells found in bone marrow, regulate the function of hematopoietic stem cells—adult stem cells that form blood and immune cells and constantly renew the body's blood supply. He and his colleagues found that in mouse bone marrow, megakaryocytes tell blood stem cells when their services aren't needed and when they need to start proliferating to meet increased demand.

"Megakaryocytes can directly regulate the amount of hematopoietic stem cells by telling the stem cells when they need to stay in the quiescent stage, and when they need to start proliferating to meet increased demand," says Li. "Maintaining that delicate balance is important. You don't want to have too many or too few hematopoietic stem cells."

Engineering a megakaryocyte niche (a special environment in which stem cells live and renew) that supports the growth of hematopoietic stem cells in culture, is the next step for the researchers. Meng Zhao, PhD, a postdoctoral fellow at the Institute and first author on the study, and his colleagues are also investigating whether a megakaryocyte niche can be used clinically to jump-start adult stem cell regeneration and to expand cultured cells for adult stem cell transplants.

These findings were published in the October 19, 2014, issue of *Nature Medicine*.

By Alissa Poh

WHEREVER THE SCIENCE TAKES HER:

MARINA VENERO GALANTERNIK

Like many of the Stowers Institute's young researchers, Marina Venero Galanternik speaks more than one language fluently–in her case, Russian and Spanish, besides English. Venero Galanternik's first seven years were spent in Moscow, before her family's cross-hemisphere move to Lima, Peru, her father's native country.

Oddly enough, "it's because of my father that I still speak Russian," Venero Galanternik says. "He often refuses to answer me in any other language." Otherwise, Spanish conversations are the order of the day during her visits home, even with her Moscow-born-and-raised mother.

Growing up surrounded by a menagerie of pets, Venero Galanternik gave considerable thought to a career in veterinary medicine. "Then one of my dogs died," she says, "and it was traumatic enough to make me change my mind." She opted to major in biology, after a year in dental school convinced her that she was captivated not by the prospect of peering into patients' mouths daily, but by basic science.

Post-college, Venero Galanternik made a bold decision–one that relied on the goodwill of fellow Peruvian Luis Espinoza, PhD, then a researcher at Georgetown University in Washington, DC, whom she'd met during a scientific conference. "He was probably being polite when he said I should contact him if I ever wanted to work in the US," she muses wryly, "but I took him at his word." Espinoza could only offer Venero Galanternik an unpaid research internship.

Barely eight months after Venero Galanternik moved to DC, however, Espinoza's laboratory dispersed. Undaunted, she visited an aunt in Salt Lake City and made her way to the University of Utah. "I walked around the campus, knocking on office doors and inquiring about openings for lab technicians," she recalls. When she learned that developmental biologist Yukio Saijoh, PhD, needed someone who could work with mice, Venero Galanternik didn't let the fact that she had never handled the creatures before stop her from requesting an interview. After successfully isolating and harvesting a mouse embryo on her first try, she was hired.

"He [Saijoh] introduced me to developmental biology, and it was like a light coming on," Venero Galanternik says. "Being able to visualize and study different stages of embryonic growth is truly amazing." Hooked on the field, she eventually enrolled for full-time predoctoral research, choosing Tatjana Piotrowski, PhD, then on faculty there and now a Stowers Associate Investigator, as her mentor.

"She's patient, really dedicated to her students, and never too busy to listen to our ideas," Venero Galanternik says of Piotrowski. "When Tatjana told me she'd be leaving Utah to join Stowers, I simply told my husband he should find a new job in Kansas City, because we were moving there."

At the Stowers Institute, Piotrowski and her team are studying fundamental processes of biological development by examining the lateral line in zebrafish. This sensory system, important in the schooling behavior of aquatic animals, gradually develops from a migrating cluster of cells called the primordium, that migrates from behind a fish's ear to the tip of its tail.

This collective cell migration is a tightly orchestrated developmental process that has implications for cancer research: Wnt/ß-catenin and fibroblast growth factor (Fgf) signaling, two key pathways directing the primordium's journey, also influence metastasis, or the invasive spread of tumor cells. Venero Galanternik recently published a paper in *Cell Reports* showing that heparan sulfate proteoglycans (HSPGs), a type of glycoprotein, modulate cross-communication between Wnt/ß-catenin and Fgf in zebrafish primordium. When HSPGs are rendered nonfunctional, cell migration is truncated, along with subsequent lateral line formation. Examining the subtleties of how these signaling pathways interact in zebrafish development may boost our understanding of molecular and cellular events associated with cancer invasion.

Venero Galanternik successfully defended her thesis this spring and plans to pursue postdoctoral research in lymph vessel development. "Certain cells literally detach themselves from veins to form these vessels alongside," she explains, "and I'd like to figure out the molecular events driving this cell fate specification." Lymph vessels are often damaged during surgical procedures like mastectomy, and sometimes they're genetically defective. Either way, the result is lymphedema, or fluid retention and tissue swelling, Venero Galanternik says, so understanding how these vessels develop in the first place is crucial.

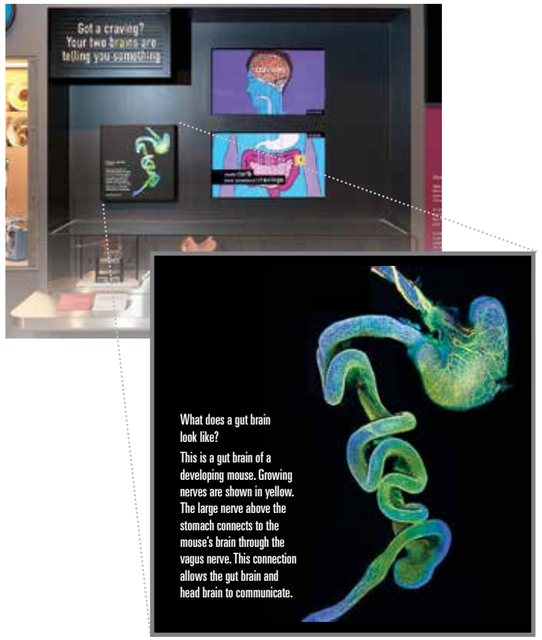
A successful scientist, in Venero Galanternik's view, possesses perseverance, curiosity, and a collaborative spirit–and is amenable to criticism. "In Peru, we say you need to have a big belt," she remarks. "It's similar in concept to being thick-skinned. I was pretty sensitive initially, but I handle criticism much better now." To de-stress or extricate herself from the occasional research rut, she stays active, regularly exploring Kansas City's many parks and trails, often accompanied by her pug dog, Punch–an affectionate reference to his somewhat squashed appearance. She also listens to Bollywood music along the way. "It's a new cultural acquisition, and I'm somewhat obsessed," she confesses.

Encouraged by Piotrowski, Venero Galanternik has now spent several summers at the Marine Biological Laboratory in Woods Hole, MA, immersed in developmental biology. In fact, she recently "graduated" from course attendee to teaching assistant. Educating others about developmental biology is high on her list of career goals, second only to becoming an independent investigator in the field. Ideally, she'll get to do both. "I just enjoy being around people who love science," she says with a laugh.

LONDON SCIENCE MUSEUM SHOWCASES TJADEN'S IMAGE

If you're in London this year, make time to visit the London Science Museum. In February 2015, the museum opened a year-long exhibit titled "Cravings: Can your food control you?" in which former Trainor Lab MD-PhD student Naomi Tjaden's image is prominently featured. The exhibit explores the questions of what drives our appetite and cravings for certain foods and how those foods affect the body and brain.

Tjaden's scientific image results from her research of neural crest cell migration into the embryonic gut, and is a beautiful depiction of the enteric nervous system of a mouse, aptly called the "gut brain." In this stunning image, the nerves of the gut brain are stained yellow-orange. Beyond the top of the stomach, the gut brain connects directly to the brain in the mouse's head via a single nerve called the vagus nerve. Thus, the brain has a direct effect on the stomach and vice versa.



WATT SNAGS FIRST PRIZE FOR POSTER

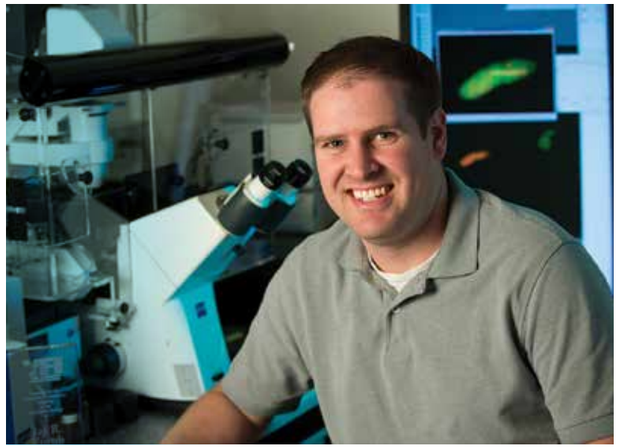
Trainor Lab Predoctoral Researcher Kristin Watt was awarded first prize for her scientific poster at the thirty-seventh annual meeting of the Society of Craniofacial Genetics and Developmental Biology (SCGDB). The SCGDB is a professional society committed to advancing the knowledge, healthcare, and prevention of craniofacial disorders through education and research.

Watt's poster, titled "Examination of the Roles of RNA Polymerase I Subunits During Craniofacial Development," describes her research of genes involved in Treacher Collins syndrome (TCS), a condition involving malformation of the craniofacial bone structures characterized by numerous developmental anomalies such as small jaws, cleft palate, and middle and external ear defects.

"The role of RNA Pol I in embryo development and specifically craniofacial development was previously unknown," explains Watt. "Our studies aid in understanding the function of Pol I so that in the future we can understand how to prevent some of the craniofacial anomalies associated with TCS."

YOUNG FLUORESCENCE INVESTIGATOR AWARD GOES TO UNRUH

The Biophysical Society presented the Young Fluorescence Investigator Award to Stowers Research Advisor Jay Unruh, PhD. This award goes to an outstanding early-career researcher for significant advancements or contributions to the field using fluorescence methodologies. Unruh received a $1,000 honorarium and was invited to present to the Biological Fluorescence Subgroup at its annual meeting in February.



From tracking and quantifying the motion of protein aggregates in yeast cells, to characterizing the flow of cellular components in mouse oocytes, to line scanning fluorescence cross-correlation spectroscopy, to examining protein interactions at the yeast nuclear envelope, Unruh's skills and contributions are an invaluable resource for many of the Institute's investigators.

Research Advisor Brian Slaughter explains, "Jay's made many contributions to fluorescence methodologies. In all cases, they are a direct reflection of his collaborations with the investigators at the Institute, and a reflection of the willingness of our PIs to use biophysical approaches to their questions. That is very important."

NIH funds Exploratory Development Grant for Paul Kulesa

Director of Imaging Paul Kulesa, PhD, received a NIH/National Institute of Neurological Disorders and Stroke grant, which will provide additional funds to study TrkB signaling during development of the sympathetic nervous system. Mistakes during development can result in improper sympathetic nervous system function and can lead to a deadly pediatric cancer of the peripheral nervous system called neuroblastoma.

Recent studies have shown that aggressive neuroblastomas express high levels of the growth factor receptor TrkB. Previously, Kulesa theorized that signaling through TrkB normally functions to regulate the plasticity and invasiveness of the neural crest cell population during a critical period of sympathetic nervous system development—that period when a neuroblast may transform into a neuroblastoma. By studying how normal cell behaviors change when the protein TrkB signaling is disrupted, they hope to learn the functional role of TrkB and details of neuroblastoma progression that may be used to develop clinical strategies to prevent or treat birth defects and neuroblastomas.

The Kulesa Lab is the first to probe the relationship between the neural crest and neuroblastoma by using state-of-the-art imaging to visualize cell behaviors in living quail embryos. Advances in dynamic live imaging will allow them to identify and analyze complex molecular and behavioral traits associated with neural development and neuroblastoma.

Piotrowski Receives Additional HHF Funding

The Hearing Health Foundation has awarded Associate Investigator Tatjana Piotrowski, PhD, additional funds for a project she co-leads along with Stanford researcher Stefan Heller, PhD. Piotrowski's goal is to identify genes that are up- or down- regulated in the support cells of the zebrafish lateral line.

Piotrowski studies hair cell regeneration in zebrafish. Unlike in mammals, when zebrafish hair cells die, support cells can proliferate and replenish them. Piotrowski seeks to uncover the mechanisms that allow zebrafish hair cells to regenerate while mammalian hair cells cannot.

Her research focuses on the lateral line, a sensory organ in zebrafish, that enables a fish to stay righted and correctly oriented and is analogous to the inner ear sensory epithelia of mammals. Previously Piotrowski's lab had determined how genetic pathways change during hair cell regeneration in the zebrafish lateral line as a whole. The additional funds will allow her to analyze support cells at the single-cell level to determine how many support cells exist, what genes are expressed in each cell, and how gene expression changes due to disruption of genetic signaling pathways.

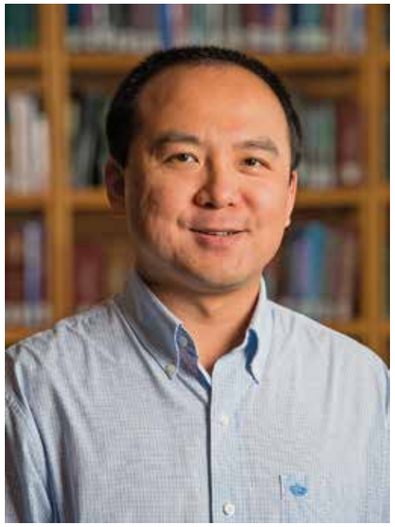
While Heller's research focuses on support cells in chickens, Piotrowski's partnership with Heller aims to provide a comparison of gene expression changes in two different regenerating species as a valuable way to reveal evolutionarily conserved gene interactions required for hair cell growth. This information could prove useful in designing therapies for hearing loss in mammals.

Gerton Lab receives CdLS funding and accolades

Senior Research Associate Baoshan Xu, PhD, has received a grant from the Cornelia de Lange Syndrome Foundation for his research aimed at understanding how defective protein formation contributes to the cause of the Cornelia de Lange Syndrome (CdLS), a developmental disorder characterized by a host of physical and cognitive abnormalities.

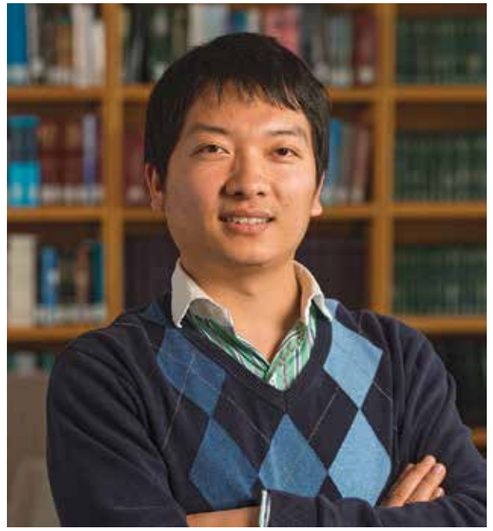
Previous studies from the Gerton Lab suggested that L-leucine, an amino acid that stimulates an important molecular signaling pathway as well as the process of protein formation called translation, may be a potential therapeutic for CdLS. Using zebrafish models of CdLS, they have shown that L-leucine treatment reduces improper cell division and cell death, partially rescuing the developmental defects of the CdLS zebrafish embryos.

Xu plans to examine and measure the effect of L-leucine in tissue derived from CdLS patients with the four common genetic mutations associated with the disorder to determine if and how different gene mutations respond to L-leucine. This study will serve as the basis for assessing the potential for L-leucine to be used as a therapy for CdLS.



It is this innovative experimental work of the Gerton Lab, led by Investigator Jennifer Gerton, PhD, that has earned Gerton and the Stowers Institute recognition as one of the CdLS Centers for Excellence. This designation is awarded to researchers and institutions that pursue research that provides significant scientific contributions to further understanding CdLS, commits to furthering scientific knowledge through collaborations, and shares that knowledge openly with other researchers.

American Society of Hematology Fellow Scholar Award



Pengxu Qian, PhD, a postdoctoral researcher in the Linheng Li Lab was awarded $100,000 over two years for his research that investigates the role of the Dlk1-Gtl2 chromosomal region during blood cell formation (hematopoesis) which may aid our understanding of its potential role in development of leukemia or lymphoma.

Hematopoietic stem cells (HSCs) provide millions of blood cells for circulation each day; however, HSCs must maintain a delicate balance of inactivity and proliferation while maintaining a viable stem cell pool and preventing bone-marrow overgrowth. Therefore, both reserve and active populations of HSCs exist with active HSCs responsible for the daily production of blood cells and reserve HSCs being called into action only when necessary.

The HSC balance is maintained by many important signaling pathways, and it is still not fully understood what signals regulate the different HSC states. Qian has hypothesized that the mTOR pathway that controls mitochondrial function and metabolism is critical for balancing the reserved and active states of HSCs. He plans to explore how non-coding RNAs in the Dlk 1-Gtl2 region act upon the mTOR pathway to achieve this balance.

Viewing science as art

Research Technician Shamilene Sivagnanam and museum visitors.

On a sunny Saturday this spring, visitors to the Nelson-Atkins Museum of Art were treated to a dazzling display of scientific images. In collaboration with the Nelson Atkins Innovation Lab, the Rong Li Lab hosted an exhibit of images and videos showcasing marvels of biology such as the structure of tissues, microscopic components of cells, associations between proteins, and cellular movement. The idea behind the event was to bridge the gap between science and art by exposing museum visitors to the natural beauty of science. Rong Li, PhD, explains, "We wanted to use art to draw attention to science. Science is full of amazing colors and shapes, just like in art."

Vivid images rotated in a larger than life slide presentation where nearby, microscopes were stationed, ready for curious onlookers. Several students and postdoctoral researchers from the lab were on hand to explain the scientific images to unexpecting art patrons. Children and adults alike were mesmerized and intrigued by the visuals but also by the enthusiastic scientists describing their work. "This was a great opportunity for my students and postdocs to present the work that they are proud of to an unfamiliar audience," says Li.

To learn more about the science and art of the Rong Li Lab listen to a KCUR podcast.

http://kcur.org/post/using-cancer-cells-ability-mutate-evolutionary-trap

CELEBRATING 10 YEARS
2004-2014

In January, eleven members celebrated ten years of steadfast service to the Institute.

Left to right, front row: Rebecca McLennan, Robin Bryant, Leslie Lloyd, Jessica Witt
Middle row: Sherry Lockwood, Scott Pettet, Melissa Mathews, Joel Nee
Back row: Patsy Thompson, Jerry Whisler, Mark Parrish

NEW endeavors

Following many years of dedicated service to the pursuit of discovery at the Stowers Institute, both Ali Shilatifard, PhD, and Rong Li, PhD, were selected for prestigious academic leadership positions at distinguished universities.

Beginning last fall, the Shilatifard Lab began transitioning to Northwestern University Feinberg School of Medicine, where Shilatifard had been appointed chair of the Department of Biochemistry and Molecular Genetics. At the Stowers Institute, Shilatifard's group made several significant contributions to the fields of epigenetics (the study of nongenetic cellular memory) and transcription (the first step in gene expression).

Shilatifard's research team collaborated heavily with many members of the Institute's core centers, including proteomics and molecular biology. This collaborative approach, combined with his energy and enthusiasm for science, will serve him well in his new leadership role.

Members of the Rong Li Lab plan to transition to their new location at Johns Hopkins University beginning this summer when Li begins her appointment as the Bloomberg Distinguished Professor and director for the Center for Cell Dynamics. Li's contribution to the advancement of scientific knowledge while at the Institute includes a greater understanding of how cells establish their distinct structures and how they organize themselves in order to divide and function properly. Often, cells that don't organize and divide properly are a hallmark of cancer.

As a Stowers investigator, Li has been a passionate advocate for science education, and will continue her legacy of motivating and inspiring young scientists to explore a variety of biological questions as a director in a strong academic environment.

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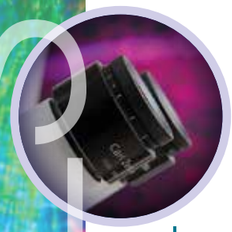

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Cancer. Alzheimer's disease. Diabetes. Cardiovascular disease. Birth defects.

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 ground 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 it's 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.

Any individual or cumulative contribution of $1,000 or more establishes a Hope Shares account, which can be opened in the donor's name or in memory or honor of someone they love. All Hope Shares account holders receive an annual Hope Shares statement and regular updates on the progress our researchers have made.

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 the 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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Herbert & Estelle Adler

INTENSELY INTERESTED IN EVERYTHING

Herbert Adler first heard about Stowers Institute co-founder Jim Stowers back in the 1970s when family members told him about an innovative financial company in the Midwest. Twenty years later, looking for a home for a batch of famous letters he'd owned since childhood, Adler cold-called American Century Investments and spoke to someone who gave him some great advice. Even later, when Jim and Virginia Stowers launched the Institute, these fond memories resurfaced to inspire Adler to donate. "Every time someone I care about dies, I send a bit," says Adler who lives in Brooklyn, New York.

A life-long storyteller, Adler found in the Stowers Institute a new intellectual focus that only added to his already prolific list of interests. He credits his newfound interest in science and health directly to his interactions with the Institute and American Century Investments. "The polio vaccine was developed after years of research," says Adler, "and now it's being studied as a way to shrink cancer tumors. I never followed any of this before, and probably still wouldn't if it wasn't for Stowers piquing my interest in scientific research."

At 87, Adler is still writing and working the phones. He's got a boatload of stories—everything from his time at UCLA with some Watergate notables, to his brief career as a military intelligence officer, to his years as a teacher of English and philosophy in high schools and colleges in California and New England. He's mingled with celebrities in Los Angeles and testified in the U.S. Senate for the Public Broadcasting Act of 1967. He's travelled the globe and married for the first time in his late 50s. His wife, Estelle, is proud that her husband supports the research endeavors at the Institute.

"I believe scientific research is very important and giving to the Institute is the best way I can support that view," says Adler. "And it's good to remember people who've been important to me by donating in their honor."

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David and Eden Thorne

FIGHTING DISEASE WITH DONATIONS

Photo credit: Heidemarie J. Burke, www.heidemariephoto.com

For Eden Thorne, it started with a professional connection. With a freshly minted University of Kansas journalism degree, Eden landed her first job at the Kansas City advertising agency Kuhn & Wittenborn, and soon found herself working with the team that would help create and publish Jim Stowers' first book, *Yes, You Can Achieve Financial Independence*. The project was rewarding and, before long, she was hired to work in marketing at Stowers' mutual fund company Twentieth Century (now American Century Investments).

By the time Jim and Virginia Stowers launched the Stowers Institute, Eden was working as director of publicity at Andrews McMeel Publishing, whose offices were located on the American Century campus. She fondly remembered her time with Mr. Stowers and felt compelled to contribute. "When they opened the Institute, we got involved," says Eden. "David and I are very interested in biomedical research."

Eden and her husband, David—a nationally known attorney with Shook, Hardy & Bacon—believe that biomedical research is the key to solving disease riddles that have claimed the lives of people they care about and people they do not know. Since 2006, the Thornes have donated regularly in memory of the Honorable Elwood Thomas, a Missouri Supreme Court judge for whom David clerked who died of Parkinson's Disease, and Mark Dover, David's former classmate and law partner, who died in his 40s of pancreatic cancer. "And we have a family member who's just been diagnosed with Alzheimer's," David says. "We're big proponents of research that can lead to innovative ways to treat some of these diseases."

In total, the Thornes have gifted the Institute nine times in the past nine years. The couple, who have a 14-year-old son and 12-year-old daughter, believe research is vastly important, a conviction partly influenced by Eden's mother, Donna Blackwood, who has been associated for many years with the Center for Practical Bioethics.

"Judge Thomas was one of the best men I have ever known," says David. "He was a mentor to me. He was well-respected and well-liked. He left too early. That's a major motivator to me for putting money toward research. Maybe we can do a small part to help advance biomedical research."

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Richard Weiss, *including In Memory of Jean Weiss*
Carl Westring
Carl and Ruth Westring in Memory of Mary Baldwin
Geoffrey and Jody White
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BACKSTAGE PASS

Like greenhouse gardeners, the cell culturists in the Stowers Tissue Culture Core Laboratory devotedly care for and cultivate a variety of cells and tissues. Many samples harvested from their original environment can be rendered useless unless properly maintained in conditions that closely mimic their native environment. The expert staff diligently maintains incubators stocked full of roller bottles turning slowly at prescribed speeds that optimize the growth of specialized cells. They also tend to flasks filled with nutrients that nourish tissues and ensure maximum growth.

The Tissue Culture team is skilled at producing large-scale expansions of cell lines, generating cells that carry a genetic modification of interest to a researcher, banking cells for future use, and screening incoming samples for invasive forms of bacteria called *Mycoplasma*.

TISSUE CULTURE BY THE NUMBERS

247,200
milliliters of media used in the last year for roller bottles alone

9,251
vials of cells stored in liquid nitrogen

2,907
vials of cells banked in 2014

1,236
roller bottles cultured each year

1,056
unique cell lines stored in liquid nitrogen

426
orders of cell line 293T fulfilled for researchers in the last year

126
genetically modified cell lines generated in 2014

23
labs requested cultured cells in 2014

9
cell culture specialists

7
days of the week the laboratory is operating