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FOR MEDICAL RESEARCH

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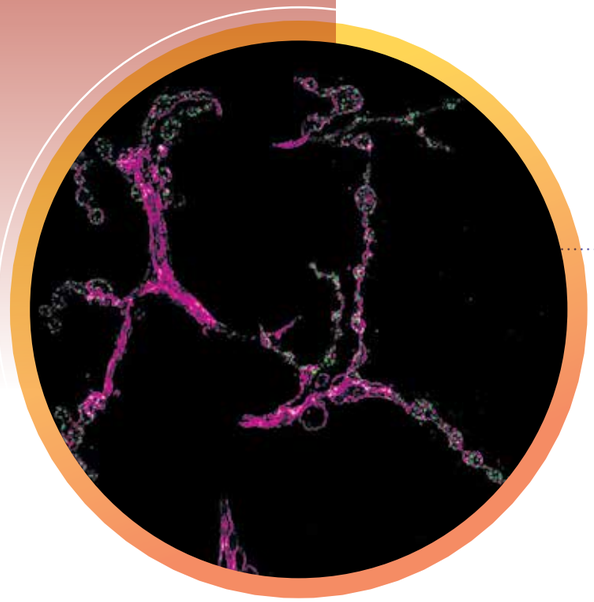
OUR MISSION:

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.



LEARNING AND MEMORY ARE BASED ON A SERIES OF MOLECULAR EVENTS THAT INDUCE LONG-LASTING CHANGES IN THE CONNECTION POINTS OR SYNAPSES BETWEEN NEURONS. ASSOCIATE INVESTIGATOR KAUSIK SI, PHD, USES FRUIT FLIES TO STUDY THE BIOCHEMICAL BASIS OF LONG-TERM MEMORY.

IMAGE: Fly motor neurons (magenta) communicate with muscle fibers via a specialized type of synapse (green) known as a neuromuscular junction.

Courtesy of Liying Li and Brian Slaughter, PhD

BIOMED VALLEY DISCOVERIES
A PHILANTHROPIC MISSION
POWERED BY GLOBAL RESOURCES

STOWERS REPORT

NEWS AND INSIGHT FROM THE STOWERS INSTITUTE FOR MEDICAL RESEARCH SPRING 2013

STOWERS REPORT

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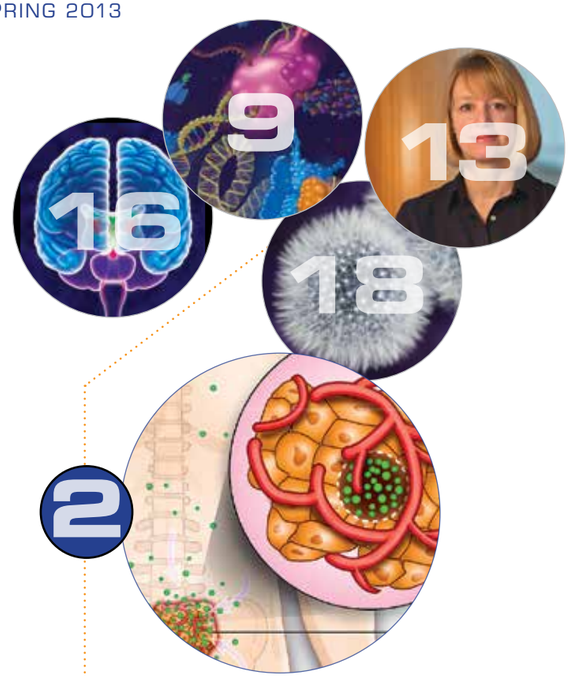

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In perspective

BY DAVID CHAO, PHD
PRESIDENT AND CEO

Biologists' desire to understand how cells work at the most basic level has accelerated the development of new therapies in undeniable and unpredictable ways.

This issue's cover story introduces BioMed Valley Discoveries (BVD), a Stowers organization with the mission of taking basic researchers' findings from the bench to the bedside. BVD has just launched a human clinical trial to test the safety of a new anticancer drug taking aim at a family of growth-promoting enzymes called ERK. While the results of this and future clinical trials won't be known for many years, the ERK inhibitor program holds great promise for the treatment of drug-resistant melanoma and other cancers. The history of the ERK program also illustrates how the combination of basic and clinical research can lead to innovative new therapies.

The origins of the ERK story reach back over a quarter century to basic research in an area as far removed from cancer as one could imagine: the mating behavior of baker's yeast. Baker's yeast comes in two sexes, and when the two meet, yeast cells undergo a characteristic set of changes in their shape and growth. Using mutant yeast cells with mating defects, researchers were able to map the genes and regulatory circuits governing yeast's mating habits.

Independently, researchers working with rat cells identified the ERK gene as a key component of the circuitry controlling accelerated growth in response to insulin exposure. The scientists were surprised and delighted to find the ERK gene was closely related to two genes governing mating behavior in yeast. This unexpected connection dramatically accelerated scientists' understanding of the underlying molecular circuitry in both organisms. When subsequent research showed that mutations in this regulatory circuitry can lead to certain types of human cancer, ERK and its related enzymes became attractive targets for anticancer drugs.

Today, a recently approved drug, directed against a close cousin of ERK, has shown a remarkable ability to shrink melanomas. Unfortunately, over time many melanomas become resistant to the drug and resume their cancerous growth. The new BVD drug aims to overcome this resistance and keep the tumor's growth in check.

Back in the eighties, one would have been hard-pressed to anticipate that research on amorous yeast might someday influence the development of new cancer therapies. The serendipitous path from yeast to cancer illustrates just how hard it is to predict the nature and timing of the inexorable benefits of basic research. As a consequence of science's unpredictability, successful efforts to improve human health need to strike a prudent balance between basic and disease-focused research.

More than a decade ago, Jim and Virginia Stowers founded the institute based on their core belief that basic research will yield long-term, practical benefits for mankind. Just a short while after its founding, the Institute is now joined by a sister organization with a complementary charter of performing disease- and drug-focused research. In the pages that follow, I hope you will enjoy learning about how these two organizations are striving to realize Jim and Virginia's vision of providing Hope for Life®.

Improving human health by combining a philanthropic mission with industrial capabilities

BIOMED VALLEY DISCOVERIES

AT FIRST GLANCE, BIOMED VALLEY DISCOVERIES (BVD) DOESN'T HAVE MUCH IN COMMON WITH TRADITIONAL BIOTECH OR PHARMACEUTICAL COMPANIES. THERE ARE NO RESEARCH LABORATORIES, NO MANUFACTURING PLANTS, AND NO GLEAMING HEADQUARTERS. INSTEAD, A HANDFUL OF OFFICES SPREAD OVER KANSAS CITY, MISSOURI, AND BOSTON, MASSACHUSETTS, HOUSE A NEW KIND OF DRUG DEVELOPMENT COMPANY—ONE THAT GOES ABOUT ITS BUSINESS IN A FUNDAMENTALLY DIFFERENT WAY.

From behind their desks, a handful of physicians and scientists direct a global network of almost nine hundred researchers, clinicians, regulatory experts, clinical trial coordinators, drug manufacturers, and consultants. "We are among the first to execute drug discovery and development on what could be called a virtual basis. This approach minimizes the bricks and mortar infrastructure and enables us to move much more quickly than we otherwise could," explains BVD President Saurabh Saha, MD, PhD. "Most important, the virtual approach allows us to work with very talented and knowledgeable experts from around the world and create an all-star team for the duration of each project."

But BioMed Valley Discoveries is unusual in more ways than one. When Jim and Virginia Stowers' vision of an innovative medical research institute started to take shape, they knew that basic research was just the beginning. They wanted to make sure that the path from basic discovery to practical application was as smooth as possible.

Patients first

Typically, nonprofit research organizations rely on a central technology transfer office to protect and market their discoveries. The tech transfer office facilitates the patenting of potentially valuable discoveries and focuses on licensing the intellectual property to industry partners for further development. But without additional work to make a technology attractive for licensing by drug development companies, many promising potential treatments fail to generate interest and often linger for years on the shelves of universities and research institutes nationwide.

To speed discoveries from the lab to the clinic, Stowers decided to separate "discovery and development" from the institute's basic research activities and create a for-profit company with its own distinct focus on bench-to-bedside translational research. They charged the organization they created, BioMed Valley Discoveries, with developing laboratory discoveries from the institute and elsewhere into new therapies and diagnostics. Although technically a for-profit company, BVD's unique ownership structure means that all profits generated by BVD will be either reinvested in BVD or funneled back to the Stowers Institute to support additional basic research.

With a long-term perspective in mind, Stowers set up BVD with over $50 million in seed funding and a firm

Saurabh Saha, MD, PhD

commitment to a steady stream of future funding. This exceptionally stable source of financing enables BVD to focus on long-term impact rather than short-term returns. "Our unique funding structure allows us to tackle projects that may be considered too early, too risky, or too challenging for traditional biotech or pharmaceutical companies," explains Saha, who directed Novartis Pharmaceuticals' new drug discovery incubator before he was recruited in 2008 to head BVD.

Combining clinical and research training with MD and PhD degrees from the Johns Hopkins School of Medicine and business training from McKinsey & Co. and Harvard Business School, Saha is intimately familiar with the forces that drive the science and business of drug development. "What sets BVD apart is our relationship with the Stowers Institute and our exceptional focus on helping patients. We are a for-profit company, but our first objective is to address unmet medical needs and, in whatever we pursue, our goal is to change medicine. Not incrementally, but substantially."

Filling the pipeline

BVD was originally conceived as the Stowers Institute's "translational arm," a company with the capability to transform Stowers investigators' research findings into new treatments. As BVD's strategy evolved, it became clear that BVD could help patients by advancing discoveries made not only at the Stowers Institute, but also at other institutions. Encouraged by Jim Stowers and the company's board of directors, Saha cast the widest net possible to uncover developable technologies from organizations around the world.

What followed was a very deliberate process of whittling down the list of candidates to the most promising projects. "In addition to the opportunity of addressing an unmet medical need and approaching a problem from a new operational or intellectual angle, we selected projects where we saw the potential of taking the technology not just to the next stage, but all the way to patients," says Saha. Now, barely four years after starting work on the current slate of projects, BVD is advancing seven different drug candidates and diagnostic technologies, ranging from tumor-fighting bacteria to a new imaging tool that detects bacterial infections in artificial joints.

Tracking down intruders

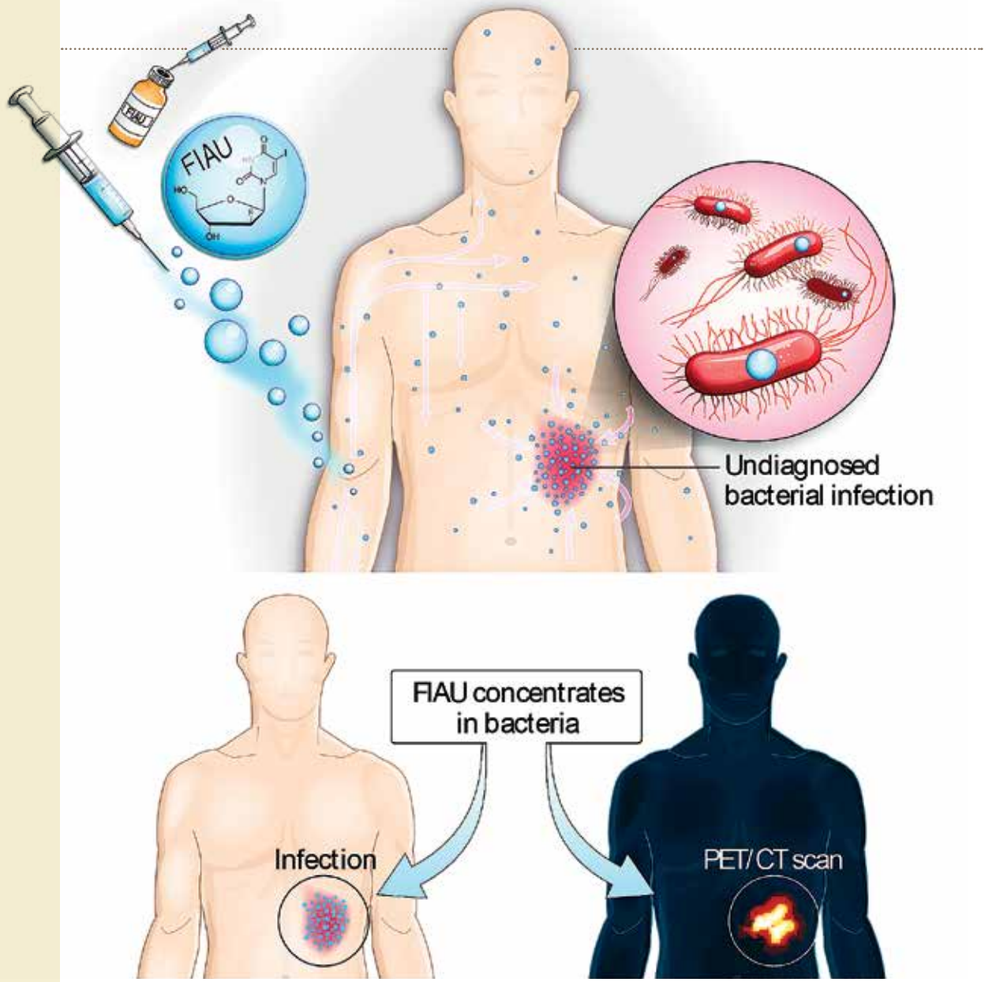
With Phase II clinical trials already in full swing, the imaging project is leading the way. Originally developed at Johns Hopkins, the new imaging technology exploits the difference in enzymatic activity between human cells and bacteria to track down hard-to-detect bacteria before they can cause life-threatening infections.

Many cells, including most species of bacteria, use the enzyme thymidine kinase to construct one of DNA's building blocks. The enzyme's bacterial version prefers a chemical known as FIAU, short for fialuridine, to its natural substrate. When patients are injected with chemically labeled FIAU, bacteria in the body take up the easily tracked molecule. FIAU accumulation can then be detected with high-resolution positron emission tomography (PET) scans to reveal the infection's source.

BVD is currently testing the technology for two different disease indications: prosthetic joint infections and diabetic foot infections. "In the U.S., about one million joint replacement procedures are performed annually," says Michelle Zhang, PhD, who oversees the FIAU project. "Anytime a foreign object, such as an artificial hip or knee joint, is introduced into the human body, patients are more likely to develop an infection in that joint."

Unfortunately, the symptoms of infection—localized swelling, redness, and pain—resemble inflammatory symptoms caused by normal wear and tear or the mechanical failure of an implant. Conventional imaging techniques and other tests often fail to distinguish

TRACKING DOWN INTRUDERS



When patients are injected with FIAU molecules, bacteria in the body take up FIAU molecules and trap them inside. The accumulation of FIAU can then easily be tracked with high-resolution positron tomography (PET) scans to reveal an infection's source. The new technology holds great promise for identifying notoriously hard to detect prosthetic joint infections and determining the extent of diabetic foot infections.

Illustrations: Katie Vicari

between the two since they don't directly detect bacteria. As a result, many patients with misdiagnosed prosthetic joint infections undergo replacement surgeries followed by weeks of rehabilitation when the cause of the problem could have been treated with a simple course of antibiotics. "Often, these revision surgeries are performed without appropriate debridement and antibiotic treatment, which puts patients at risk," says Zhang.

Diabetic foot infections, one of the most common and serious complications of diabetes mellitus, present a different challenge. As many as two thirds of infections will spread to the bone and require amputation if not treated aggressively. MRI scans, the current diagnostic procedure, can only identify a fraction of bone infections. Plus, many diabetic patients have poor kidney function and cannot tolerate the contrast dye required for MRI imaging. "We hope that FIAU will help physicians decide how aggressively they need to treat diabetic foot infections and spare some patients from major surgeries," says Zhang.

Busting tumors

Despite huge inroads into cancer treatment during the last few decades, cancer is still a leading cause of death in the developed world, and scientists are constantly looking for new ways to eradicate tumor cells. BVD has recently been advancing a novel approach developed by renowned cancer researcher Bert Vogelstein, MD, at the Johns Hopkins School of Medicine. In sharp contrast to conventional chemo- or radiation therapy or even personalized cancer treatments, the new treatment relies on bacteria to destroy tumors from within.

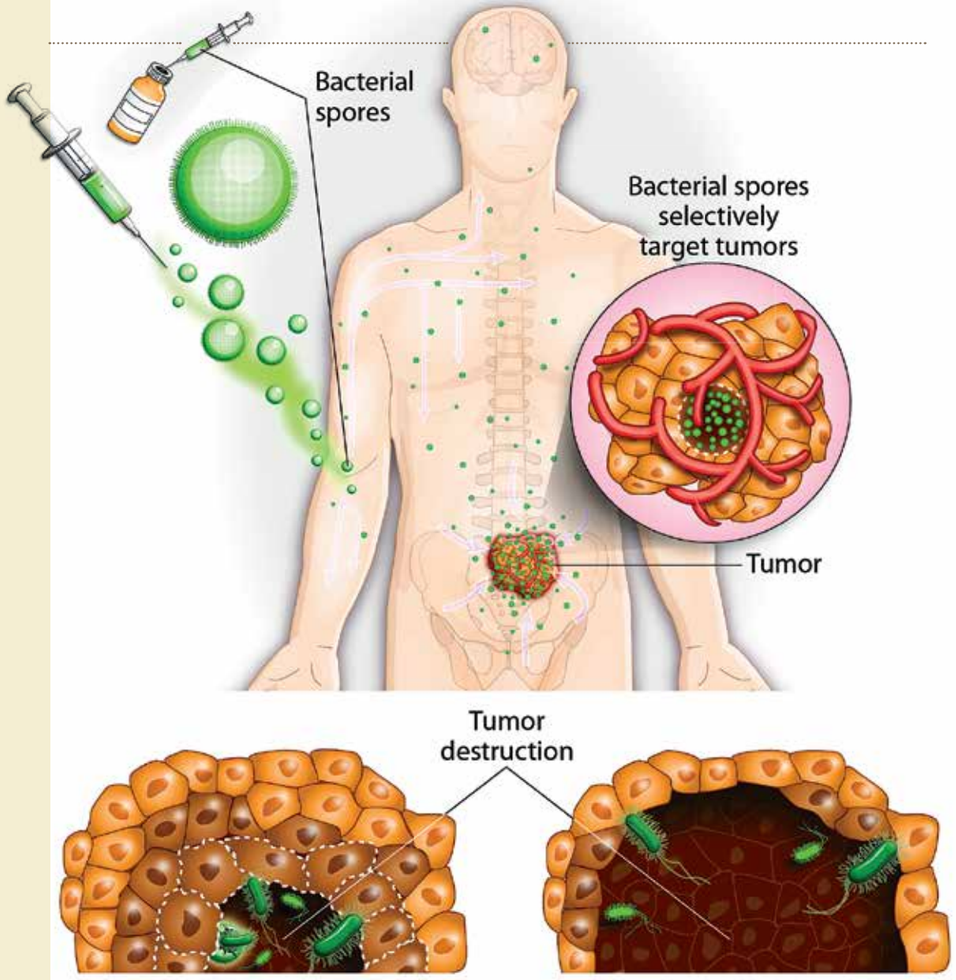
As solid tumors increase in size, they outstrip available oxygen and nutrient supplies. This leads to hypoxic areas inside the tumor that are resistant to conventional radiation and chemotherapy, but still have the potential to harbor cancer cells capable of metastasizing. The bacterium *C. novyi-NT*, however, thrives under these conditions. It hones in on the "dead zone" and destroys tumors from the inside with minimal damage to healthy tissue. When *C. novyi-NT* runs out of cancer tissue to consume, the bacteria stop growing and become inactivated. Subsequently, they are cleared naturally by the body.

Even with its potential as a novel cancer therapy, many pharmaceutical companies consider bacteriolytic therapy, such as *C. novyi-NT*, too unconventional and risky. "Because BVD has a unique source of funding and mission, we have the freedom to pursue promising but unprecedented strategies that require a long-term investment and commitment," says Saha. BVD licensed *C. novyi-NT* from Johns Hopkins, and Linping Zhang, PhD, the project team director, assembled a worldwide group of medical oncologists, FDA regulatory experts, physician investigators, clinical trial leaders, pharmacologists and toxicologists, drug manufacturers, and veterinarian oncologists, among others.

In an unusual complement to traditional preclinical studies, BVD is treating dogs that have developed cancers to assess the safety and effectiveness of *C. novyi-NT*. "Pet dogs naturally develop a variety of cancers for the same reasons that humans do," explains Linping Zhang. With limited treatment options available for canine cancers, most dogs suffering from malignant tumors face euthanasia or amputation. Owners who choose to participate in the *C. novyi-NT* canine clinical study give their dogs a chance to avoid these fates and also help generate valuable data to identify a better therapy for humans. "The opportunity to study our drug in dogs with spontaneously occurring tumors will likely provide valuable perspectives for optimizing therapy in human cancer patients. Even though we are still generating more data, we believe that a drug that works in dogs is much more likely to succeed in human patients than a drug that has only been tested in mice," she says.

Early results from the studies in pet dogs have been encouraging. Human Phase I clinical trials designed to assess the safety of the *C. novyi-NT* therapy and uncover potential side effects have begun in earnest. "The available data has shown great promise, but, as with any novel therapy at this stage, we still have a long way to go to realize that promise," says Zhang.

BUSTING TUMORS



The genetically modified bacterium C. novyi-NT *can only multiply within large tumors whose center is no longer adequately supplied with oxygen. The bacteria hone in on these "dead zones" and destroy the tumor from the inside with minimal damage to healthy tissue. When* C. novyi-NT *runs out of cancer cells to consume, the bacteria stop growing and are subsequently cleared by the body. Certain bacteria produce spores—hardy dormant versions of themselves that can be easily stored.*

Dean Welsch, PhD

Improving human health

In addition to new tools that track down infections and bacteria that attack tumors from the inside out, BVD has several other cancer therapeutics and a pain treatment under development. One of these, a more traditional cancer drug therapy, illustrates the strength of BVD's virtual approach. This drug targets a specific genetic vulnerability frequently found in melanoma, pancreatic cancer, and a subset of colon and lung cancers. About a year after licensing that compound—currently referred to as BVD-523—the company has started Phase I clinical trials in patients with metastatic melanoma and other solid tumors.

In an unexpectedly short time, BVD's global network of partners generated more than thirteen thousand pages of preclinical data on the experimental drug. BVD used this data for the successful submission of an Investigational Drug Application to the FDA, the prerequisite to start clinical trials in human patients. Dean Welsch, PhD, who leads a team of more than a hundred experts, consultants, and fee-for-service partners, says that, "assembling a team of talented people with years of experience in the area you need takes extra effort and coordination, but can make the process very efficient."

In the end, it all comes back to Jim and Virginia Stowers' guiding values—a commitment to excellence and teamwork, a long-term perspective, and an unwavering dedication to improving the lives of others. Those principles drive each entity of the intertwined triad of organizations founded by the Stowerses. Established in 1958, American Century Investments helps its clients achieve their financial goals while its "profits-with-a-purpose" philosophy provides the funding for work at the Stowers Institute and BVD. Opened in 2000, the institute seeks an understanding of life's basic mechanisms to lay the foundation for the development of novel treatments and diagnostics. BVD, the youngest of the three, has the mission of improving human health through medical innovation. Together, the three organizations aspire to fulfill Jim and Virginia Stowers' grand vision of giving people around the world Hope for Life®.

http://biomed-valley.com

By Elise Lamar, PhD

It takes teamwork

POSTDOCS IN THE JERRY WORKMAN LAB COLLABORATE TO SHOW HOW CHROMATIN "RESETS" TO A SILENT STATE AFTER A ROUND OF GENE EXPRESSION, BLOCKING PRODUCTION OF POTENTIALLY HARMFUL RNAS.

Contrary to popular lore, most scientific eureka moments don't come in a flash to a researcher toiling alone in the lab at three in the morning. Instead, the insight required to answer a fundamental question almost always emerges from long-term collaborative effort by teams of investigators who bring varying expertise, different questions, and a lot of conversation to a problem.

Few studies illustrate the power of teamwork better than two papers from the lab of Stowers Investigator Jerry Workman, PhD, published last summer in *Nature* and *Nature Structural and Molecular Biology*. In these companion pieces, two postdocs working collaboratively described how cells protect themselves against aberrant gene expression by transcribing DNA into RNA from start to finish, rather than haphazardly initiating transcription at "cryptic" sites within a gene. These findings are noteworthy, as failure in the system could produce potentially toxic truncated RNAs, which researchers are beginning to associate with developmental defects and even cancer.

Running out of HATs

Jerry Workman has spent three decades characterizing giant protein complexes that modify the structure of chromosomes—or as scientists call it, chromatin—and control gene expression. He says the field exploded in the mid-90s as people began to characterize two classes of chromatin remodelers: the multi-subunit enzymes that activate gene expression, called histone acetylases or HATs, and their de-acetylase opponents, which repress gene expression. Workman's lab began by concentrating on the activators.

"Initially we focused on purifying the six or seven different kinds of HAT proteins that activate gene expression in yeast," Workman says. "At that time, every new postdoc who came to my lab got a HAT complex to characterize and then took it off to start their own lab until there were no HATs left."

At that point, Workman started deploying new postdocs to analyze repressor complexes. By the mid-2000s studies from the lab led by former postdocs Bing Li and Mike Carozza had revealed how a yeast repressor complex called Set2 neutralized HAT activity, thereby inhibiting gene expression. Mechanistically, the Workman team showed that Set2 grabs onto the tail of the enzyme called RNA polymerase (pol II) as it moves down a DNA strand and copies it into RNA transcripts, and then shuts down gene expression in pol II's wake, somewhat like closing the barn door after the cow passes through.

Genomically, the "door" consisted of arraying a barrier of DNA-binding proteins called histones, which when decorated with chemical acetyl groups by HATs, moved aside to allow passage of pol II, but when shorn of those groups (indirectly by Set2) blocked pol II's access to the potentially "wrong" site on DNA.

But how the transition between acetylated versus deacetylated histones occurred at the molecular level remained unknown until the arrival of the next set of recruits to the Set2 team, namely Swami Venkatesh and Michaela (Mischa) Smolle, the authors of the 2012 studies.

Know your neighbors

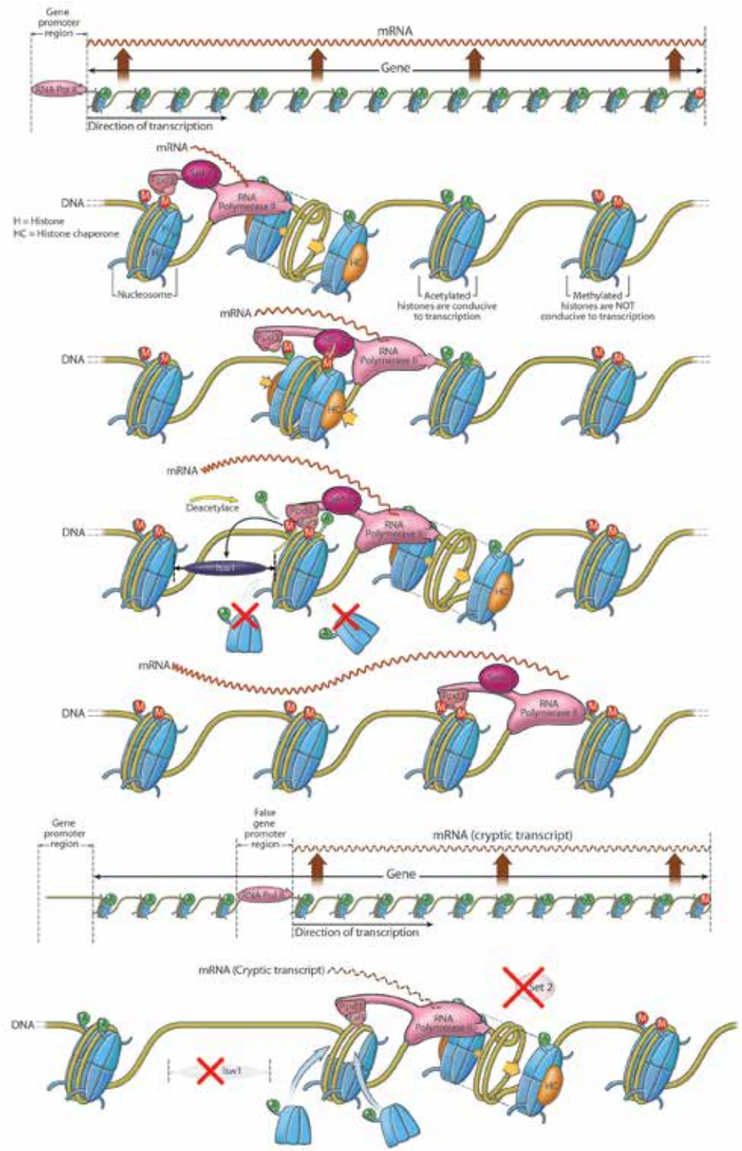
Venkatesh, who led the *Nature* study, joined the Workman lab in 2006 to continue the studies in gene expression he began as a graduate student at Jawaharlal Nehru Centre for Advanced Scientific Research in Bangalore, India. There, Venkatesh had used human cells as a model system, but was motivated, as he says, "to move down the evolutionary ladder" to yeast after Workman visited his mentor in India and talked about Set2. Once at Stowers, Venkatesh took on the task of determining how Set2 acts to reset the histone barrier.

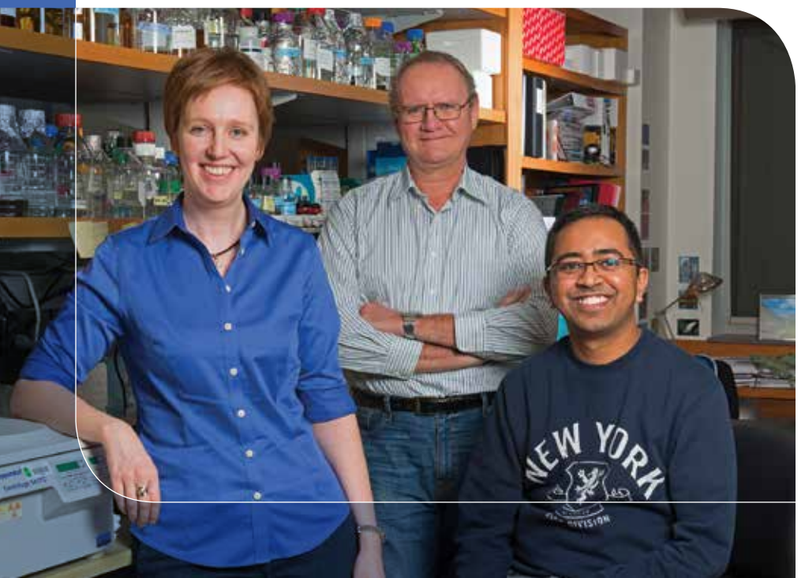
Smolle, the first author of the companion study, arrived a year later after completing graduate work on the structure of glucose-metabolizing enzymes at the University of Glasgow in Scotland. Unlike Venkatesh, Smolle was new to the field of chromatin biology and eager to try something new. Her first task was to conduct a proteomic screen—which she calls a "fishing expedition"—to discover what other proteins might be interacting with histones modified by Set2 in hopes of gaining insight into how those modifications occurred.

Serendipitously, Venkatesh and Smolle were assigned adjacent benches in the Workman lab, and just like lab "baymates" worldwide, they were either condemned or privileged to spend many long hours talking to each other. In their case, it was the latter, and the talk rapidly evolved from what was good in the cafeteria that day to a constant dialogue over molecular mechanisms used by Set2 to modify and shuffle histones.

"Mischa and I come from very different scientific backgrounds," says Venkatesh. "We found it very helpful to have someone from a different field to ask about what to do. That kind of collaboration helped both of us tell a much broader story."

Smolle agrees, noting that the Workman lab is a very team-oriented environment. "It's not like we started out working on the same thing," she says. "We each had our own angle on the project and our own individual





From left to right: Michaela Smolle PhD, Jerry Workman, PhD, Swami Venkatesh PhD

expertise. In the end the two stories just merged very nicely into one."

A new paradigm

The jumping-off point for that story was the knowledge that Set2 terminates gene expression by planting its own biochemical flag, a methyl group, on histones, which then recruits deacetylators to clip off histone acetyl groups, replace the histone barrier, and restore chromatin to a silent state, inaccessible by pol II.

From there, Venkatesh conducted a series of experiments showing that when yeast cells were made mutant in Set2 they derailed this normal gene-silencing mechanism by literally shoving "pre-acetylated" histones (sitting in reserve on the chromatin sidelines) back onto the DNA track, a stealth gene-activation move called "histone exchange." That allowed pol II to sit wherever it liked on a DNA strand and keep gene expression going, whether it was appropriate or not.

"The old paradigm was that histones remain in place and are acetylated by HATs to allow pol II to pass and then deactylated to block it," says Venkatesh. "But we found in a significant subset of genes the HATs weren't required, and that histones remained acetylated as a consequence of histone exchange. That meant that one function of Set2 was to prevent histone exchange from taking place."

The *Nature* study used microarray analysis to determine whether aberrations in histone acetylation were correlated with perturbed gene expression. As expected, the researchers found that unlike normal yeast, Set2 mutants produce variously truncated RNA transcripts, which could potentially gum up normal gene expression.

Meanwhile, Smolle's proteomic "fishing expedition" reeled in a chromatin remodeler known as Isw1, which blocks the histone exchange mechanism—characterized by Venkatesh—by retaining Set2-methylated histones. Strikingly, Smolle went on to show that yeast engineered to lack the Isw1 complex also exhibit perturbed gene expression marked by abnormal expression of RNA snippets rather than complete transcripts, an anomaly similar to that observed following loss of Set2.

Workman notes the studies show that the methylation mark placed on histones by Set2 works in two ways to ensure that RNA transcription does not start in the middle of a gene. "On one hand, that methylation mark recruits Isw1 to block exchange of pre-acetylated histones," he says. "And on the other, it recruits a deacetylase to remove any acetylation marks that might happen to have sneaked in."

The human consequences

These discoveries, made in the yeast *Saccharomyces cerevisiae* model system, have implications for human disease: Excessive acetylation of the histone methylated by the human Set2 counterpart occurs in several tumor types, suggesting that Set2 acts similarly to prevent recruitment of pre-acetylated histones and to ensure that pol II catalyzes RNA synthesis only where it ought to occur in mammalian cells.

"Strikingly, the human homologue of Set2, SETD2, is implicated as a tumor suppressor in breast and renal cancer, and those tumor cells are deficient in the SETD2 methylation mark," says Workman, adding that mutations in the human homologue of Set2 are also associated with a severe developmental disorder known as Wolf-Hirschhorn syndrome. "The point is that genes that contribute to human developmental anomalies or cancer are often involved in chromosome organization. We study them in yeast to figure out what they're doing in humans."

Workman, who analyzes gene expression in multiple systems, says he is contemplating follow-up studies of the Set2 homologue in fruit flies. That work may, however, require a new generation of Set2 recruits, as both Smolle and Venkatesh are nearing the end of their postdoctoral training and are hunting for places to set up their own respective research labs. Venkatesh is searching for positions in the U.S., while Smolle, a native of Austria, may return to Europe.

Their collaboration has a happy outcome, but the partnering of research associates within a lab does not always end in a Hallmark moment. "It is true that highly motivated postdocs sometimes become competitors," says Workman. "But Swami and Mischa get along well and in their case it has always been about teamwork. They spend all day together talking about their work and then come into my office, often with a great new idea I know will cost me a lot of money!"

But since 2003, when the Workman lab first reported that yeast Set2 was a histone methylase, that money has apparently been well spent. "All of these guys working on Set2 have been very interactive," says Workman, noting that Bing Li, who now runs his own lab at University of Texas Southwestern still talks all the time with Venkatesh and Smolle. "I have been fortunate to have such a collegial group working on this project."

By Alissa Poh

A DISCUSSION WITH JENNIFER GERTON

Jennifer Gerton, PhD, first became enamored of science in high school. Growing up near San Francisco, she took advantage of summer programs at several University of California campuses, including Berkeley and Santa Barbara. Also drawn to English and literature, Gerton briefly toyed with a different career path, but science won out. Marine biology might have been another contender, except for one stumbling block: "I liked wading in tide pools and identifying microscopic marine organisms," Gerton observes, "but I have this strange fear of swimming where there are fish."

Gerton's fascination with science coincided with the dawn of the AIDS epidemic in the Bay Area. She recalls her mother, a nurse, being troubled by a young male patient who was dying of the disease. Then, as a Stanford undergraduate, Gerton enrolled in a class called, "Impact of AIDS," taught by Robert Siegel, MD, PhD. Between the epidemic's relevance and Siegel's engaging teaching style, her interest in viruses was piqued. She wound up doing undergraduate virology research with Pat Brown, MD, PhD, and stayed on for her PhD, studying HIV-1 integrase, a protein that enables the virus to insert its genetic material into host cells.

"I still love virology," Gerton remarks. "Each virus is like a short story that tells us something about how the cell works." But her research has since veered in a very different direction. "Viral integration is a process of genetic recombination," she explains. "I became interested in other recombination mechanisms, especially in meiosis. I initially had this naïve notion of finding and purifying all the proteins involved and reconstituting meiotic recombination *in vitro*. Of course, no one's succeeded in doing so yet. But that's how I moved from viruses to studying chromosome segregation in yeast."

Gerton arrived at the Stowers Institute in 2002 for her first faculty position and has been here ever since. She became an associate investigator in 2008.

HOW WOULD YOU EXPLAIN YOUR RESEARCH IN SIMPLE TERMS?

We're studying a couple of different mechanisms that contribute to cell division. The first is chromosome cohesion—the physical adherence of replicated chromosomes to each other until they separate. We're particularly focused on cohesins, proteins that ensure proper segregation of sister chromosomes. Our research has evolved from exploring basic biology to analyzing how cohesin mutations might contribute to genetic diseases like Roberts syndrome and Cornelia de Lange syndrome. Both are cohesinopathies; affected children show growth, cognitive, and limb abnormalities, among many other deficits.

The second mechanism we're studying involves the centromere, a location on chromosomes that, in pinning replicated pairs together, also ensures they separate correctly. Chromosomes are made up of thousands of nucleosomes, but a special type of nucleosome specifies the centromere. So I often compare it to a needle in the haystack.

WHAT'S ONE RESEARCH PUZZLE YOU'VE SOLVED—OR ARE NEARER TO SOLVING IN 2013—THAT PARTICULARLY EXCITES YOU?

We're studying Roberts syndrome from a perspective that's different from what's in the literature, and it's been really fruitful. We now have a pretty good hypothesis as to the cause of this disease, but I can't say more until it's published. As cohesinopathies go, Cornelia de Lange syndrome is more common, but its cause is more elusive. I hope we'll learn much more about the mechanism this year.

WHAT ARE SOME OF YOUR MOST VIVID MEMORIES OF GRADUATE SCHOOL AND OF PAT BROWN AS A MENTOR?

We had regular department retreats where different labs showcased their research. These sessions were simultaneously team-building and competitive, in a good way. I remember worrying about taking questions from Paul Berg (1980 Nobel Prize winner in Chemistry) or (the late) Arthur Kornberg (1959 Nobel Prize winner in Physiology or Medicine). Dan Herschlag (Herschlag Lab, Stanford) could also be pretty terrifying. It was nerve-wracking yet stimulating, and we learned so much.

Pat Brown is incredibly creative and the most brilliant person I've ever met; he operates on a different level than most people. He taught me to think outside the confines of any one field, to not be limited by the available literature. I was in Pat's lab at the height of his enthusiasm for GMS (Genomic Mismatch Scanning); we had this conversation where he said, "I'd love to map the gene responsible for ice cream headaches." The whole point of GMS was to find DNA regions identical by descent – between a grandparent and a grandchild, for instance – in order to map certain human traits. That's how he came up with the idea of microarrays as a readout for what he wanted to study.

DID YOU EVER IMAGINE THEN THAT THE USE OF MICROARRAY TECHNOLOGY WOULD BECOME SO WIDESPREAD?

Not at first; it looked like an engineering project gone really wrong. Pat used capillary action between the ends of tweezers to pick up liquid and print the arrays, but he needed this giant box of tweezers on standby and someone to constantly resharpen them, because after three or four printings, the tweezers would get dull and cease picking up liquid. But it got better after a couple of years. Just before I left, I remember thinking, "This is going to be really powerful."

WHAT INFLUENCED YOUR DECISION TO MOVE TO THE MIDWEST?

I was actually interviewing for a job at Harvard when Doug Melton, then on Stowers' Scientific Advisory Board, opined that I'd be a good fit here. But I was hesitant and almost canceled my initial visit. I'm glad I didn't; Robb (Krumlauf) and Bill (Neaves) impressed me as great leaders, and I felt this would be a wonderful place to work.

GENERALLY SPEAKING, WE AREN'T DOING A GREAT JOB GETTING CHILDREN EXCITED ABOUT SCIENCE. HOW MIGHT WE IMPROVE?

Science is so curiosity-driven. While running a classroom necessarily involves standardized lessons, I also think there should be room, even just a few minutes each day, to tap into kids' innate curiosity, facilitate their imaginations, and let them ask questions. That's the essence of science. It's what my husband and I try to do with our kids. They're five and seven and curious about everything. They know what DNA is, what cells are, and they can grasp more complex details if we go through enough questions and answers.

PERHAPS SCIENTISTS ALSO NEED TO BE MORE OPEN-MINDED ABOUT COMMUNICATING IN SIMPLER TERMS?

Scientists do have their own private jargon, and it's a barrier. We could certainly make more effort to meet lay people at their level and maybe even let them drive the questions, instead of just telling them a whole bunch of stuff.

I have an idea for a book, which I'll probably never write. My colleagues often gripe that lay people don't appreciate the value of basic research. So a series of short stories about basic research that had an enormous impact on how we think about disease or human health would, I think, be immensely helpful. People get the concept of working on a drug against cancer, but it's harder for them to understand how research on yeast cells could be of any value.

WHAT'S THE GREATEST FRUSTRATION IN YOUR WORK? AND THE GREATEST JOY?

The process of getting a paper published is pretty frustrating. It can take a couple of years, by which time you've moved beyond that research and you're working on the next thing. So you're dealing with reviewers and trying to get this "new" idea in print, yet it's no longer new to you.

Joy, for me—and every scientist, really—is when, after synthesizing a lot of information for a long time, I put the facts together and go, "Oh, *now* I understand."

REGARDING A CAREER IN SCIENCE, WHAT'S THE BEST ADVICE YOU WERE EVER GIVEN AND WHO GAVE IT TO YOU?

When I was starting out, David Botstein (former chair of Stanford's Genetics Department and now director of Princeton's Lewis-Sigler Institute for Integrative Genomics) told me to think of publishing papers as getting base hits, not home runs. Better to publish as you go along, rather than save up for this giant story that you hope gets into *Nature*. After all, in science, you're never really done; the story never stops evolving.

WHERE DO YOU DO YOUR BEST THINKING?

I go running a couple times a week, and it really focuses my thoughts. That's when I've had a lot of my best ideas, both scientifically and in terms of managing my lab.

WHAT ABOUT YOU WOULD SURPRISE MOST PEOPLE WHO KNOW YOU?

At a New Year's Eve party last year, I danced to *Michael Jackson The Experience* on the Wii and shocked people by how well I did. I was in a modern dance group during college and still love it. But now I just have tickets to the Kansas City Ballet.

IN A NUTSHELL

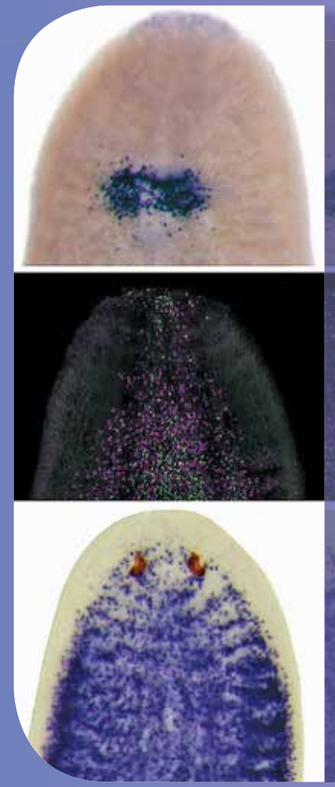
MOVING TOWARD REGENERATION

The skin, the blood, and the lining of the gut—adult stem cells replenish them every day. But stem cells really show off their healing powers in planarians, those humble flatworms fabled for their ability to rebuild any missing body part.

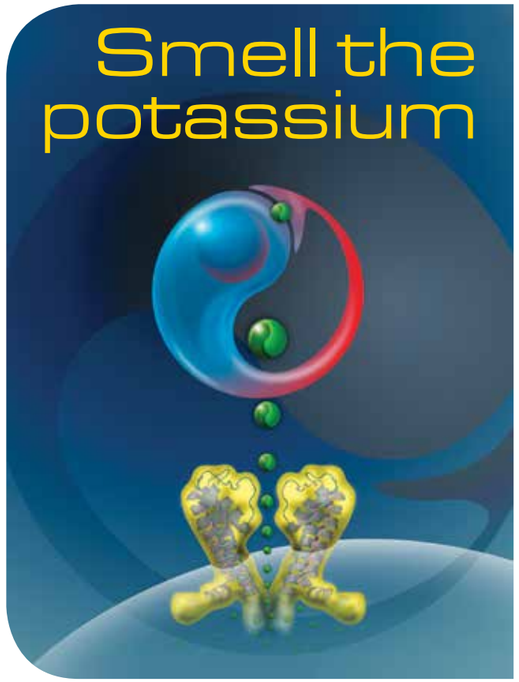
Scientists first hypothesized in the late 1800s that planarian stem cells, which normally gather near the worms' midlines, can travel toward wounds. But the next century produced evidence both for and against that idea. Armed with modern tools, Howard Hughes Medical Institute and Stowers Investigator Alejandro Sánchez Alvarado, PhD, decided to revisit the question.

When they tracked stem cells in the flatworm *Schmidtea mediterranea*, Sánchez Alvarado's team found the worms' stem cells—known as neoblasts—march out, multiply, and start rebuilding tissues lost to amputation. "We were able to demonstrate that fully potent stem cells can mobilize when tissues undergo structural damage," says Sánchez Alvarado. "And these processes are probably happening to both you and me as we speak, but are very difficult to visualize in organisms like us."

Stem cells hold the potential to provide an unlimited source of specialized cells for regenerative therapy for a wide variety of diseases, but delivering human stem cell therapies to the right location in the body remains a major challenge. The ability to follow individual neoblasts opens the door to uncovering the molecular cues that help planarian stem cells navigate to the injury site, and ultimately may allow scientists to provide therapeutic stem cells with guideposts to their correct destination.



The study was published in the October 1, 2012, issue of *Development*.



THE VOMERONASAL ORGAN (VNO) IS ONE OF EVOLUTION'S MOST DIRECT BEHAVIOR ENFORCERS. FROM ITS NICHE WITHIN THE NOSE IN MOST LAND-BASED VERTEBRATES, IT DETECTS PHEROMONES AND TRIGGERS CORRESPONDING BASIC-INSTINCT BEHAVIORS, FROM COMPULSIVE MATING TO MALE-ON-MALE DEATH MATCHES.

A new study by Associate Investigator C. Ron Yu, PhD, and his team extends the scientific understanding of how pheromones activate the VNO and has implications for sensory transduction experiments in other fields.

The VNO works in much the same way as the main olfactory organ that provides the sense of smell. Its neurons and their input stalks, known as dendrites, are studded with specialized receptors that can be activated by contact with specific messenger-chemicals called pheromones, found mostly in body fluids. When activated, VNO receptors cause adjacent ion channels to open or close, allowing ions to flood into or out of a neuron. These inflows and outflows of electric charge create voltage surges that can activate a VNO neuron, so that it signals the brain to turn on a specific behavior.

"We found two new ion channels—both of them potassium channels—through which VNO neurons are activated in mice," explains Yu. "This is quite unusual; potassium channels normally don't play a direct role in the activation of sensory neurons."

Humans have shrunken, seemingly vestigial VNOs, but still exhibit instinctive, pre-programmed behaviors relating to reproduction and aggression. Scientists hope that an understanding of how the VNO works in mice and other lower mammals will provide clues to how these innate behaviors are triggered in humans.

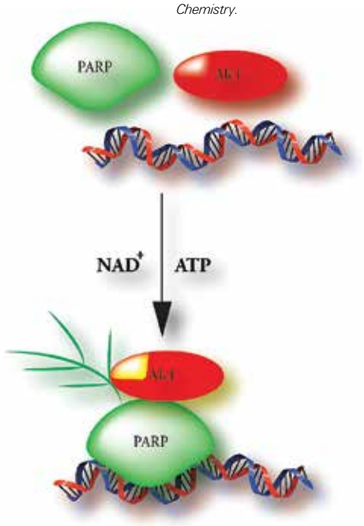
The study was published in the September 15, 2012, in *Nature Neuroscience*.

ACTIVATING ALC1—WITH A LITTLE HELP FROM FRIENDS

CHROMATIN REMODELING—THE PACKAGING AND UNPACKAGING OF GENOMIC DNA AND ITS ASSOCIATED PROTEINS—REGULATES A HOST OF FUNDAMENTAL CELLULAR PROCESSES INCLUDING GENE TRANSCRIPTION, DNA REPAIR, PROGRAMMED CELL DEATH, AS WELL AS CELL FATE. THROUGH A SERIES OF BIOCHEMICAL EXPERIMENTS, STOWERS INVESTIGATORS RON CONAWAY, PHD, AND JOAN CONAWAY, PHD, AND THEIR TEAM CONTINUE TO UNRAVEL THE FINICKY DETAILS OF HOW THESE ARCHITECTURAL ALTERATIONS ARE CONTROLLED.

In their latest study, the researchers discovered that chromatin remodeling enzyme and suspected oncogene ALC1 (short for Amplified in Liver Cancer 1) is activated through an unusual mechanism: In the presence of its activators, PARP1 and NAD+, ALC1 undergoes a structural change, which switches on the enzyme's chromatin-remodeling activity. Apart from its role in modifying chromatin structure, not much is currently known about ALC1. It's regarded as a possible oncogene, being found in excess in hepatocellular carcinoma cells, and because overexpression of ALC1 in mice induces spontaneous tumors. PARP1, on the other hand, has attracted plenty of interest as a potential anticancer drug target, due to its importance in maintaining genomic integrity."A better understanding of the in-depth biochemistry we're uncovering on ALC1 and PARP1 may, in the long term, lead to new or more refined therapeutic strategies," says Aaron Gottschalk, PhD, postdoctoral researcher and the study's first author.

The study was published in the December 21, 2012, issue of the *Journal of Biological Chemistry*.



The face predicts the brain

Craniofacial anomalies or malformations of the face and skull account for approximately one third of all birth defects. The most common among them is the failure of the forebrain to complete the division into the double lobes of the brain's left and right hemispheres, a condition known as holoprosencephaly (HPE). Not all individuals with HPE are affected to the same degree, but in many patients it is closely associated with facial malformations, such as a flattened midface, closely set eyes, as well as clefts of the lip and roof of the mouth. Currently, it is not known whether these defects share a common origin, since only about 20 percent of HPE cases can be attributed to a specific genetic mutation. For all others, the cause remains unknown.

Serendipity led Jennifer Dennis, PhD, a former graduate student in Investigator Paul Trainor's lab and now an assistant professor at the University of Kansas Medical Center, to the discovery that hedgehog acyltransferase (Hhat) plays an important role in craniofacial development. Dennis found that a mouse line already being used in the laboratory unexpectedly carried mutations in Hhat, and that embryos derived from these animals suffered from holoprosencephaly together with a partial absence of skull bones and an underdeveloped or completely absent lower jaw mimicking the severe human condition.

Hhat helps with the processing of Sonic hedgehog (SHH), a protein that is required for the proper migration and survival of neural crest cells. These cells generate most of the cartilage, bone, and connective tissue in the head and face, explaining the link between cranial and facial malformations. "Our work provides new insight into how the most severe craniofacial birth defects may arise and identifies a new gene to screen in humans born with this condition," says Dennis.

The study was published in the October 4, 2012, issue of *PLoS Genetics*.

PATTERNS OF DEVELOPMENT

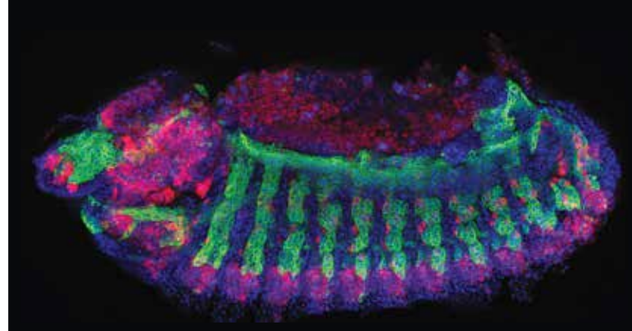
For a tiny embryo to grow into a viable fruit fly, mouse, or human, the correct genes in each cell must turn on and off in precisely the right sequence. This intricate molecular dance produces the many parts of the whole creature, from muscles and skin to nerves and blood.

At the most basic level, genes are turned on when an enzyme called RNA polymerase binds to the DNA at the beginning of a gene. The RNA polymerase copies the gene's DNA into a complementary strand of messenger RNA, which then instructs the cell to make the protein the gene codes for. Several years ago, however, Assistant Investigator Julia Zeitlinger, PhD, made a surprising discovery. The RNA polymerase doesn't just attach to DNA and start copying. Instead, it binds and then pauses, waiting for another signal before it goes to work. Now, new work by Zeitlinger's lab has revealed far more about the role of paused RNA polymerase in embryonic development—and turned up yet another surprise.

The team found that the pattern of genes with poised polymerase in muscle and nerve cells varies depending on the stage of development and not on tissue type as expected. To prevent the wrong poised genes from being turned on, so-called polycomb proteins—a family of proteins whose action varies by tissue type—repress poised polymerase.

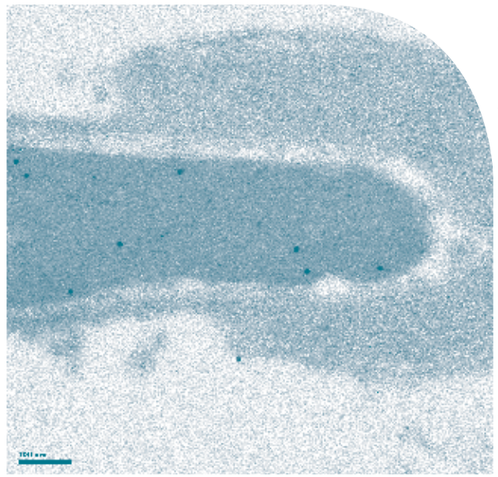
Together, these two mechanisms explain how genes during the development of both muscle and nerves first can be poised to express at the right time by paused polymerase, and then only activate in the right tissue type. And because the researchers were able to show the same mechanisms at work in human cells, too, the findings could eventually lead to a better understanding of disease.

The study was published in the December 27, 2012, issue of *Cell Reports*.



PRIMING GENES FOR FUTURE ACTIVATION

UNLIKE LESS VERSATILE MUSCLE OR NERVE CELLS, EMBRYONIC STEM CELLS ARE EQUIPPED TO ASSUME ANY CELLULAR ROLE. SCIENTISTS CALL THIS "PLURIPOTENCY," MEANING THAT AS AN ORGANISM DEVELOPS, STEM CELLS MUST BE READY AT A MOMENT'S NOTICE TO ACTIVATE HIGHLY DIVERSE GENE EXPRESSION PROGRAMS THAT WILL TURN THEM INTO BLOOD, BRAIN, OR KIDNEY CELLS.



Scientists from the lab of Investigator Ali Shilatifard, PhD, revealed that one way cells stay so plastic is by stationing a protein called Ell3 at stretches of DNA required to activate a neighboring gene, genomic regions known as enhancers.

A few years back, Chengqi Lin, a curious Open University graduate student working in the Shilatifard lab, had started exploring a potential function for the previously neglected gene by initiating a global search for regions occupied by Ell3 in the genome of mouse embryonic stem cells. Lin collaborated with Alexander Garruss, a bioinformatician in Shilatifard's lab, and their work revealed that Ell3 sits on more than 5,000 enhancers, including many that regulate genes governing stem cell maturation into spinal cord, kidney, and blood cells. This finding is significant as many of these same genes are abnormally switched on in cancer.

In a surprising coda to the study, the team discovered that Ell3 and Pol II were present in mouse sperm nuclei. In mammals, gene expression regulated by Pol II, a process known as transcription, does not begin until the formation of a single-celled zygote, that is, well after the union of sperm and egg germ cells. "The presence of Ell3 in sperm suggests that it may serve as an epigenetic marker by bookmarking inactive gene enhancers for future activation in the embryo."

The study was published in the December 27, 2012, online issue of *Cell*.

By Alissa Poh

OF SCIENCE AND SPUNK: MICHAELA SMOLLE, PHD

Michaela Smolle is the only scientist in her family, half of whom are accountants. As a teen, she realized which career she would not pursue when, ten pages into a college accounting textbook, she fell asleep.

Growing up in Graz, Austria's second-largest city, science didn't figure prominently in Smolle's life plan until high school. "I quite enjoyed biology," she says, "but it wasn't until we reached the section on genetics that I really warmed to the subject. Then a wonderful teacher introduced us to biochemistry, and that's where things took off."

Deciding to spend her undergraduate years abroad, Smolle headed off to the University of Edinburgh in Scotland. There, she learned to "totally ignore the weather" and appreciate the panoramic city views from Arthur's Seat, even though she thought her first visit—at sunrise, after a chilly, predawn clamber to the top with fellow freshmen—was "a real letdown." Coffee shops, not smoky pubs, were her frequent hangout spots, including the popular Elephant House where J.K. Rowling first brought Harry Potter's world to life.

Along the way, she delved into biochemistry and investigated factors that influence the formation, positioning, and mobility of chromatin's basic repeating units, or nucleosomes. By the time she graduated with honors, science had gotten enough of a hold on her that pursuing a PhD seemed only natural. She moved to Glasgow and spent the next four years using a variety of biophysical techniques to illuminate the molecular architecture of the human pyruvate dehydrogenase complex—three metabolic enzymes that link glycolysis to the Krebs cycle and are essential to life.

She also cultivated a love for hiking and often drove her aged car, Bertuccio—named after the loyal steward in The Count of Monte Cristo—on exploratory trips to the Scottish Highlands. On a three-week cycling trip along the Outer Hebrides, where Smolle and a friend biked from one restaurant to the next, she discovered that excellent British cuisine does exist. "You just have to know where to go," she says. As for haggis—Scotland's famous dish of sheep's heart, liver, and lungs, minced with oatmeal and simmered in the animal's stomach—"it's really tasty, if you don't think too much about what's inside," Smolle reckons. "When it comes to food, I'll try everything at least once."

While she enjoyed her biophysics-focused graduate research, Smolle afterwards returned to chromatin biology. "There's so much about chromatin that's interesting—how it's packaged to fit into the nucleus and yet has to be rendered accessible for gene transcription to occur," she says. Applying for a postdoctoral fellowship with Stowers Investigator Jerry Workman, PhD, was an easy decision because of his expertise in the field. Other than that, Smolle arrived stateside knowing little about the institute and even less about Kansas City, only that it was "straight bang in the middle of the U.S."

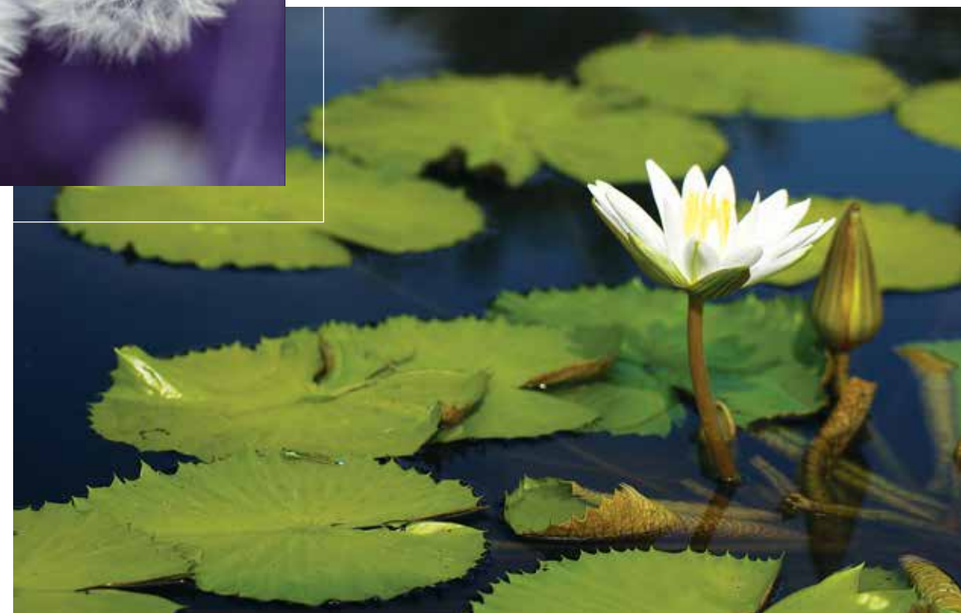
At Stowers, Smolle has been busy figuring out how various chromatin remodeling factors package and unpackage genomic DNA and thereby regulate the process of transcribing genes into proteins. In 2012, she and others in Workman's group published papers in *Nature Structural & Molecular Biology* and *Nature* describing how, in yeast cells, the protein Set2 is responsible for marking nucleosomes with methyl groups at specific points. This signals two other remodeling factors, Isw1 and Chd1, to help maintain chromatin's structural integrity as the enzyme RNA polymerase II passes through and copies information in a lengthening transcript. "If Set2 is suppressed, the system gets messed up and the overall structure of chromatin becomes looser, which results in the production of additional transcripts," Smolle explains.

"I'm fascinated by molecular mechanisms," she adds, "and I also really enjoy analyzing genomewide data sets. You get so much data out of them, but you're usually exploring a very specific question. I can't help thinking ahead about how the rest of that data might be used to answer other questions."

When not working long hours in the laboratory, Smolle experiments with nature and landscape photography. "People are fun to photograph, too, but I lack practice, and while plants don't care how long it takes to get the settings right, humans aren't so patient," she says. Locally, she's captured scenes of the River Market and various stages of the Kauffman Center's construction. The historic West Bottoms, with its funky charm, is another favorite spot.

Languages also fascinate her. Fluent in German and English, Smolle considers her grasp of several other tongues, including Italian and French, "reasonable, if somewhat atrophied by lack of use." She knows enough Spanish to backpack around much of South America, which sits atop her travel bucket list. If she had more time, and despite its complex grammar, she'd love to add Russian to her repertoire. Gaelic, on the other hand, she deems "just impossible."

In another year or so, Smolle will move on with her career. Unfazed by the uncertainties of traditional academia, she's looking at faculty positions and definitely wants to run her own laboratory someday. The world is her oyster—"I wouldn't mind returning to Europe, but I'm open to working elsewhere," she says. "'Just try' is my motto. The answer may be no, but if I don't try, it'll never be yes. It doesn't mean I don't have my doubts occasionally, but so far this guiding principle has worked out pretty well."



Crossroads:
A student and postdoctoral association

Sooner or later all scientific students and postdocs reach a crossroads—a crucial junction in their careers when they must decide which path to take. The decision could be whether to pursue a position in a yeast lab versus a fly lab, whether to choose a career in academia or industry, or whether to leave the bench altogether. During those times of transitions, mentors play a crucial role in providing vital preparation and guidance. At Stowers, the aptly named Crossroads program offers additional resources to help students and postdoctoral researchers broaden their horizons and explore new directions.

Originally started in 2002, for several years Crossroads' primary function was to provide career advice and ideas for trainees. It organized the Young Investigator Research Days (YIRD), which continues to showcase the scientific projects of students and postdocs as well as invite an annual scientific speaker. Since its modest beginnings, Crossroads has matured into an important resource that hosts multiple speakers and events each year, and provides valuable networking and professional development opportunities to young scientists. Talks and training are offered on applying for fellowships, navigating the grant review process, giving effective oral presentations, and teaching a wide variety of other skills important for developing diverse science careers and communications skills.

"The process for obtaining a PhD and completing a postdoc is long and sometimes even discouraging, especially when experiments don't work out as planned or you face difficulties you hadn't expected," says Crossroads postdoc chair Annita Achilleos, PhD. "Crossroads can serve as a source of support for young scientists during this phase of their careers."

This year, under the leadership of Crossroads committee chairs Achilleos and Rushi Trivedi, the group hosted panel discussions and special lectures that highlighted a variety of science careers. "The reality is that not every scientist will end up with an academic appointment," says Achilleos. "It is important for our members to know that there are many great opportunities for well-trained scientists outside of academia." In fact, driven by member interest the 2013 YIRD keynote speaker was chosen from a select group of scientists who excel in careers outside of academia.

But the group's agenda doesn't stop with panelists and speakers. To emphasize professional networking, committee members added social events to the annual line-up. In addition to a social gathering during the National Postdoc Appreciation Week in September, Crossroads hosted a screening of *PhD Comic: The Movie*, a humorous take on life in graduate school. "The social events are an important component of our group, says Achilleos. "They provide opportunities for our members to connect with other scientists in a relaxed environment."

Rallied by the positive response of its members and the enthusiastic support of Scientific Director Robb Krumlauf, PhD, and his staff, Crossroads leaders hope to expand events and activities next year, focusing on interactions with investigators and greater member participation. "Crossroads is an integral organization that offers phenomenal opportunities to learn and develop many of the non-bench-based skills that are an important part of a scientist's overall development," says Krumlauf.

Rushi Trivedi and Annita Achilleos, PhD

ADVOCATING FOR SCIENCE

Last fall, Danny Miller, an MD-PhD student in Scott Hawley's lab, participated in "Hill Day" as part of the semi-annual trek to Capitol Hill sponsored by the American Society for Biochemistry and Molecular Biology (ASBMB) Public Affairs Advisory Committee. Hill Day is an opportunity for a select group of young postdocs and students to deliver a pro-science message to congressional representatives and their staff members.

A thoughtful and unassuming young researcher, Miller is a passionate and strong advocate for science and science education. So it is no surprise that he jumped at the chance to talk directly with representatives drafting and voting on legislation that impacts the future of science in our country.

As part of the ASBMB brigade of young scientists marching up the hill, Miller carried with him a message for his Midwest representatives. "Don't cut science funding is what it boiled down to," says Miller. Miller's approach with his representatives was one of education itself. "I tried to explain to them the value of biomedical research and well-funded research programs on human health."

While Miller was cordially welcomed by all representatives and staff—even a few well-versed in research and science—he found some of his interactions a bit discouraging. "Most of our elected officials have little or no background in science," Miller shares, "and they have no fundamental understanding of how a scientific research program works."

A chance interaction on the flight home from Capitol Hill provided Miller yet another opportunity to educate a fellow citizen on the value of scientific research. When the conversation veered to Miller's profession and his trip's purpose, his fellow passenger complained that she just didn't understand why government funds should be used for things like fruit fly research.

Miller spent time explaining the fundamental genetic similarities between humans and fruit flies and how what we learn from flies often can be applied to human health. His efforts were rewarded when the woman thanked him and said, "No one ever explained that before. Now I understand it." In the end, Miller scored at least one small victory advocating for science.

Abiel Trevino Garza (standing, sixth student from the left) with other winners in Taiwan.

A CURIOUS MIND

Abiel Trevino Garza exudes excitement for science. When the undergraduate researcher talks about his research project, his eyes light up and his words and gestures become animated. His scientific curiosity is palpable.

Trevino Garza arrived at Stowers late last fall to complete the research component of his undergraduate work from the National Autonomous University of Mexico's Center for Genomic Sciences (CGS) in Cuernavaca, Mexico. The specialized program at CGS is designed more like a graduate program than an undergraduate one. Experts from around the world teach various components of the curriculum, and each student is required to undertake an independent research project.

Intrigued by neuroscience since high school, Trevino Garza decided to seek out a research program focusing on memory. "The brain is magnificent," he says. "It gives us the remarkable ability of self-recognition." When he discovered the work of Associate Investigator Kausik Si, PhD, on the formation of stable, long-term memories, he knew he had found a fit. And Si was glad to gain another young researcher so enthusiastic about science.

His research project, "Experience ex-specific long-term memory in *Drosophila melanogaster*," is based on the lab's previous work. It focuses on external experiences that elicit specific behavioral responses that get stored as a long-term memory and then guide future behavior. In other words, Trevino Garza wants to determine why fruit flies develop a long-lasting memory of some natural sugars, but not others, by identifying the underlying gustatory receptors and the corresponding neuronal circuits. "We are particularly interested in this question because it may help us to understand how we form long-lasting memory of only some, but not all, experiences," Si explains.

Trevino Garza has long been interested in finding out the "why" of things. During high school, he worked as a clinical lab technician and spent many hours at a microscope viewing cells from patients suffering from leukemia and other blood disorders. It was then that he decided he wanted to know more about the origin of disease rather than just how to identify and treat it. "Research science focuses on the basic questions," he shares. So, he immersed himself in a high school research project titled "Prototype for production of mycorrhiza as a natural bio fertilizer" that earned him top honors in his local science fair and third place at an international fair in Taiwan.

During his early undergraduate work, Trevino Garza, along with other like-minded young students, continued his curious scientific pursuits as they developed research projects for the International Genetically Engineered Machine (iGEM) Competition. Award-winning projects took the team to competitions in South America and the United States.

But it is at the Stowers Institute that the globetrotting scientist believes he is doing his best work. "The people are so kind and willing to discuss projects, and the resources here allow you to focus on the research, which leads to a faster pace of science." The diversity of scientific minds is just another reason he emphatically believes that "Stowers is the best place to do science!"

Stowers Summer Scholar wins summer innovation award

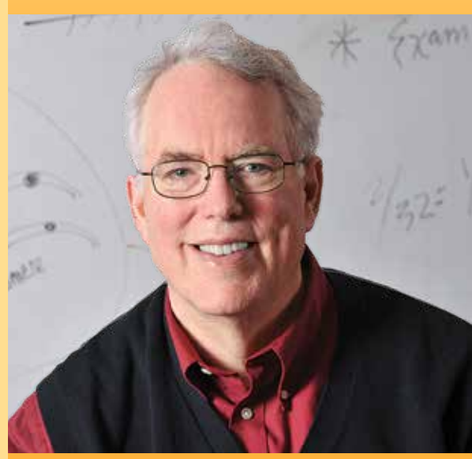
Karthikeyan Murugesan, a student in the Department of Biological Sciences & Bioengineering at the prestigious Indian Institute of Technology in Kanpur (IITK), India, won the coveted BSBE Summer Innovation Award for research performed during his ten-week stint at the Stowers Institute last summer. In addition to bragging rights, Karthikeyan received a cash prize, a certificate, and the opportunity to present his work during an IIT-wide symposium.

During his summer internship in the lab of Associate Investigator Ron Yu, PhD, Karthikeyan, who is particularly interested in bioinformatics, used bioinformatics tools to sift through gene expression data from mouse olfactory epithelia. He was looking for genes that guide growing axons—the slender projections nerve cells use to communicate with each other—to their final destination. Within a sea of data originating from 22,000 genes, he successfully zoomed in on fifteen genes that help axons stay on track.

"It probably surprised no one that Karthikeyan got this honor," says his mentor Yu. "We always have very high expectations for the summer scholars. Karthikeyan clearly surpassed them."

Along with seven other summer scholars, Karthikeyan was part of what became known as the "Yu lab brigade." They helped each other, discussed their research, cheered together during the European soccer tournament, and generally had fun in and out of the lab. "The summer internship at Stowers is one of my most memorable events in my life," says Karthikeyan. "I loved the research environment at Stowers. I have never seen such an open, friendly culture anywhere else."

SCOTT HAWLEY WINS GEORGE W. BEADLE AWARD



R. Scott Hawley, PhD

The Genetics Society of America has selected R. Scott Hawley, PhD, Stowers investigator and dean of The Graduate School of the Stowers Institute for Medical Research as the recipient of the 2013 George W. Beadle Award for his outstanding contributions to the community of genetics researchers.

"No one is more deserving than Scott," says Scientific Director Robb Krumlauf, PhD "Scott has had a profound impact on the field of genetics through his groundbreaking discoveries, but maybe even more so through his unrelenting enthusiasm for teaching, which has inspired generations of students to consider a career in science."

Many of those students agree. "Working with Scott both before entering medical school and during my graduate phase has been a wonderful experience. I consider myself fortunate to have a mentor who is a highly respected scientist, ardent supporter of my work, and an enthusiastic teacher," says Danny Miller, an MD-PhD student in Hawley's lab. "Scott has both validated my decision to pursue a career in science and given me a career model to strive for."

Hawley, a member of the National Academy of Sciences, is known worldwide for his seminal work on meiosis, a specialized type of cell division that sets the stage for sexual reproduction. In an orderly, stepwise fashion, maternal and paternal chromosomes pair up, exchange genetic material, and then separate. The tightly controlled process halves the number of chromosomes carried by sperm and egg cells and thus allows the genes of two parents to be combined without increasing the total number of chromosomes.

In recognition of both his research and teaching activities, Hawley was selected as an American Cancer Society Research Professor and is also the recipient of the GSA's 2008 Excellence in Education Award. Indeed, he is one of only a handful of people who have won two awards from the GSA.

THE CUBE

An RFID-equipped supply room—the first of its kind—streamlines the distribution of scientific supplies at the institute.

Jennifer Johnson stocking supplies in The Cube.

For many years the Stowers Institute stocked the most frequently purchased lab supplies in a convenient on-site location. By logging into a biometrically controlled computer system, researchers could retrieve and purchase items from locked cabinets, freezers, and refrigerators. The system was sufficient as long as the number of items stocked and demand remained small. When both of those grew, however, so did the institute's need for a more efficient and dynamic system that would integrate with current institute software.

As the Stowers team began looking for ways to improve and expand the supply system, a chance encounter with an unmanned snack kiosk was all it took to plant the seed of ingenuity. Head of Research Systems Jessica Witt had traveled through a Florida airport that used radio frequency identification (RFID) as inventory control at a self-checkout snack stand. She thought the same technology might prove useful with scientific supplies at the institute.

"I tracked down the company that had installed the system in the airport," Witt says, "but they had no experience with scientific products and reagents." Undeterred, Witt sought out other companies with specialized experience in scientific research. In fact, one of the scientific vendors the institute already used had a prestocked mini-fridge that employed similar technology, but it was too limited for the needs of an entire research campus.

"Our team met with the company, Terso Solutions, to explain our needs," says Witt, "but the scale of the project was much larger than anything they had ever done before and they did not have existing technology to support it." But Terso was willing to give it a shot. In close consultation with the Stowers research systems and purchasing teams, Terso Solutions engineered a fully integrated RFID scientific stockroom that has been coined, "The Cube – Stowers Scientific Supplies."

STATS:

- **Most frequently purchased items are pipette tips, gloves, and media prep items.**
- **Busiest shopping days of the week are Mondays and Wednesdays with an average of 57 transactions each day.**
- **The Cube really is open 24/7—a purchase was recorded at 12:06 a.m. on New Year's Day.**
- **Average total checkout time is only 15 seconds.**

The RFID technology allowed Stowers to create a walk-in, open-display, supply room where bright lighting, organized shelving, fridges, and freezers encourage researchers to browse all items. "The new system gives scientists the opportunity to pick up an item, look it over, and read the information on the box before making a decision to buy," says Witt. "With the old system, that was not at all practical."

Now, each item on display is labeled with an RFID tag that is synced with information in a computer tracking system. When finished selecting supplies, shoppers simply place them on a check-out table equipped with an RFID reader. It automatically scans everything and provides a list on the touch screen computer display. After the researcher selects the billing destination lab and grant, a detailed receipt is automatically e-mailed to the lab and the process is complete.

With this technology, The Cube is designed to be part stockroom, part convenience store and part showroom. The increased space allows for more items and new vendors, but there is a benefit bigger than just a greater variety. Labs no longer have to order large supplies to keep on hand or find storage space for them.

Labs also enjoy the convenience of on-site shopping, no shipping delays, or additional shipping charges. For Renju Nair, a research technician in the Rong Li lab and one of the most frequent shoppers in The Cube, "The biggest convenience is not having to enter each item one by one into a computer." The RFID scanning eliminates the need for data entry and reduces the checkout time to mere seconds rather than minutes.

Vendors are pleased to have an expanded space where they can display products and interact with scientists. VWR International representative Danny Murphy says that he plans to take advantage of the RFID technology to feature new products in The Cube. "My goal is to give the researchers more hands-on opportunities to consider new products that potentially may save them time and money," he says, "while limiting the intrusion on their research."

BASED ON THEIR EXPERIENCE

IN JANUARY, CROSSROADS HOSTED TWO PROFESSIONAL DEVELOPMENT EVENTS FEATURING STOWERS ALUMNI AS GUEST SPEAKERS. THE INFORMAL TALKS PROVIDED CURRENT POSTDOCTORAL RESEARCHERS WITH INSIGHTFUL INFORMATION ON THE DO'S AND DON'TS AS THEY PREPARE TO NAVIGATE THE SCIENTIFIC JOB MARKET.

Former Stowers postdocs and current assistant professors Lisa Sandell, PhD, (University of Louisville), Vikki Weake, PhD, (Purdue University), and Erika Geisbrecht, PhD, (University of Missouri-Kansas City), distilled their firsthand experiences into three nuggets of advice for young scientists pursuing an academic career: apply for external funding, focus on developing a full body of work, and gain teaching experience. All agreed that completing a grant application as a postdoc, even if it goes unfunded, provides invaluable experience since most academic positions require some sort of competitive funding. Geisbrecht strongly believes that showing you have previously maneuvered the grant process can give a candidate's application an edge.

In addition, while a paper published in a top-tier journal may be what researchers strive for, these alumni believe it is more important to develop a body of work that shows a breadth of knowledge and skills, even if it means publishing in lower-impact journals. Finally, each encouraged Stowers postdocs to take advantage of opportunities to learn and practice teaching skills. "Most academic positions require some level of teaching responsibility, and it is vital to be able to communicate information and skills to the next generation of young researchers," emphasized Weake.

The second event featured three alumni who successfully pursued careers outside academia: staff scientists Justin Grindley, PhD, (Regeneron Pharmaceuticals) and Brian Sanderson, PhD, (Ambion), and technology innovation and development expert Christof Bausch, PhD, (POET, Kieon Group, and Nanopore Technologies). Advice from the industry professionals focused on taking advantage of summer internships and fellowships as an opportunity to showcase talents, considering the use of a professional search firm, and never underestimating the power of networking.

In the panelists' experience, the adage that "sometimes it's not what you know, but who you know" should not be discounted. After many failed attempts at securing an interview via an online application system, Sanderson forwarded his interest and qualifications to an acquaintance within the company. By the next day he had an interview scheduled. Bausch went even further, "The key to a great position for me was the networking skills of a hired agent." He explained that the agent's established connections and knowledge of the industry simply proved to be more powerful than his own.

Investing in tomorrow's cures: THE HOPE SHARES® ENDOWMENT

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

Chances are, you or someone you know has been affected by at least one of these conditions, which are all too common in our society.

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

Today, Stowers scientists are at the forefront of unraveling the mechanisms behind health and disease and preparing the 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, Stowers uses every gift, no matter how big or small, to add to the institute'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, which shows how the value of their gift has grown with the Stowers Institute's endowment and provides 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®.

LIFETIME CONTRIBUTIONS

The information listed below represents contributions from, in memory of, or in honor of the following as of December 31, 2012.

$10 Million+

Pamela Stowers

$1 Million+

American Century Investments Foundation

William Neaves to establish the "Priscilla Wood Neaves Endowed Chair in Biomedical Sciences"

Helen Nelson Medical Research Fund to establish the "Helen Nelson Distinguished Chair"

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

Richard and Jeanette Brown

Cerner Corporation (in kind)

Country Club Bank

The Richard H. Driehaus Charitable Lead Trust

Frederick and Louis 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+

William and Priscilla Neaves

Polsinelli Shughart PC

Marilyn N. Prewitt Trust in Memory of Marilyn Prewitt

Jim and Michele Stowers

Roderick and Linda Sturgeon

Jonathan and Cyndi Thomas

A caring soul PAMELA STOWERS

Generous, compassionate, and kind, Pamela Stowers cared deeply about the well-being of her fellow humans through gestures both big and small. "She was the most kindhearted person, who would do anything and everything for any of us," says her younger sister Linda Stowers. "No matter what, she would always take the time to send a birthday card, a card for Valentine's Day or any other holiday, especially to her nieces and nephews."

The eldest child of Jim and Virginia Stowers, Pam was born and raised in Kansas City, Missouri. She earned an emergency medical technician certification from Penn Valley Community College and joined her father's company, American Century Investment—then called Twentieth Century—after graduating. She spent the next sixteen years as a customer service representative witnessing firsthand the early days of the company's explosive growth in Kansas City.

When Pam moved to Newport Beach, California, she felt the pull to help others in medical need. She initially volunteered in admissions at Hoag Memorial Hospital, but soon moved to the emergency room. As a liaison between nurses, patients, and their families, her warm smile and caring nature helped ER patients feel at ease and reassured their worried families. Her co-workers loved her, and she loved them right back.

After leaving Hoag, Pam shifted her attention to substance abuse counseling in hopes of having a positive impact on the lives of struggling addicts. She spent many exhausting and emotionally draining hours trying to make a difference, as in the life of a young addict whose mother's note simply stated, "I owe you dearly. You saved my daughter's life."

Giving hope to the disheartened gave Pam Stowers' life meaning. But she wanted to fill the world with hope long after she was gone. When she died in 2010, she left a significant bequest to the Hoag Hospital Newport Beach Emergency Department and a generous gift to the Rose Brooks Center, a domestic violence shelter in Kansas City. She bestowed her biggest legacy on the Stowers Institute for Medical Research, which her parents had championed and realized against many odds. "She always was a big supporter of what our parents were doing, and was able to make a meaningful contribution to a cause she felt was worthy due to the extraordinary success of American Century Companies," says her brother Jim Stowers, III.

$25,000+

David Chao and Julia Zeitlinger

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JE Dunn Construction Company (in kind)

Irving Kuraner

Labconco Corporation

Menorah Medical Center Inc. (in kind)

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In Memory of Robert Ruisch Jr.

John and Shirley Wagner

Bruce and Laurie Wimberly in Memory of Virginia Wimberly

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Bo Kreiling in Memory of Helen Jayne Kreiling

In Memory of Helen Lebens

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Thomas Kmak Family

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John Whitten

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$1,000+

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Alexander Family Foundation

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Jonathan Bauman

Janice Beatty

Bert and Joan Berkley

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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

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

Cathryn and Jay Linney in Memory of William Cordes

Jody Craven

Alan Critchell

Jim and Virginia Stowers in Memory of Walter Day

Marshall and Jill Dean

In Memory of Carol Denicole

Terrence and Peggy Dunn

In Memory of Dana Eckles

In Memory of William Edwards

Ron and June Estabrook

Jill Farrell

Banning Flynn

David Ford

David Ford in Memory of Theresa Ford

Brett Hart in Memory of Theresa Ford

Stephen Thune in Memory of Theresa Ford

Jody Anne Frederickson

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Stephen Garcia

The William George Family Charitable Trust

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Marsha and Jules Goldman

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Stephen and Patricia Gound

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Mary Louise Greene

Edward Jr. and Jody Griffin

Bernard Hamblin

Andrea Lynn Hazle

Henson Trust Fund

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Jim and Virginia Stowers in Memory of Paul Henson

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Robert and Lynette Jackson

Harrison Jedel

Jeff Johnson

Leroy Larsh Johnson

Wes and Nancy Kabance

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Kelly Kerr

Mark Killen

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Bob and Myrna Krohn

Kuhn and Wittenborn Advertising

Kathie Nelkin in Memory of Edward Lane

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Mary Kay McPhee

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Brendan Murray

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Jennifer Noland

Stephen Novak

Frank Leo O'Gara

James Olson

Parris Dobbs Spirit of the Heart Fund

WILLIAM "BO" KREILING

Holding out hope

As an insider at American Century Investments, William "Bo" Kreiling knows firsthand the emphasis company founder Jim Stowers, Jr. places on hiring the finest people to do unsurpassed work. "American Century's guiding principle is to hire the very best and provide them with the best resources to do their jobs well," he says. So it came as no surprise to Kreiling that the Stowers Institute also recruits only the brightest scientific minds and equips their laboratories with the most advanced technologies.

In fact, as a vice president in the Intermediary Sales Division for ACI, Kreiling often shares the institute's story and goals to motivate his team members and to inspire and encourage clients to invest. But it was something more personal that acted as his own call to action.

Although she'd never smoked, Kreiling's mother developed lung cancer. As he helped navigate her ensuing medical treatments and doctors' appointments, a simple comment from one of her physicians set Kreiling on the path of giving to the Hope Shares Endowment. "That doctor remarked to me about how unique the Stowers Institute is because rather than looking for a way to cope with cancer, it is looking for a way to cure cancer."

That cure didn't come in time for his mother; however Kreiling is confident that Stowers' research will unlock the cure to cancer and provide hope for his and his children's generations. So he continues to give. But recently, he realized that he could have a far greater impact by participating in the employee-matching program at American Century, thereby doubling his gift to the Hope Shares Endowment.

Kreiling's contributions are in memory of his mother, Helen Jayne Kreiling.

Robert Pearson

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

Michael Green in Memory of Mary Lee Prico

Michael and Terese Raddie

Michael J. Rainen Family Foundation

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Katherine Richardson

Craig and Maryanne Roepke

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In Memory of Eleanor Smith

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In Memory of Paul Stoffel and Aimee Stoffel

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Sierra Aviation in Honor of Jim and Virginia Stowers

Merriman Foundation in Memory of Pam Stowers

Mark A. Susz Revocable Trust

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In Memory of Arthur Weitzmann

Jon Zindel

Every attempt has been made to ensure the accuracy of the lists of contributors. 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.

Amy Noelker, fresh off the back of her Honda Cruiser in Grand Teton National Park near Jackson Hole, Wyoming.

AMY NOELKER

Waging a battle

Amy Noelker has survived cancer more than once. Although it has never invaded her body, cancer has come close enough for her to know the pain it can inflict. Instead of being the one with a diagnosis, Noelker has been the supportive daughter, niece, cousin, in-law, and friend.

In the late 1980s Noelker came face to face with the enemy for the first time when her mother was diagnosed with breast cancer. Although she fought a hard battle, she eventually succumbed to the disease. And over the next fifteen years, cancer relentlessly attacked Noelker's other loved ones: Her brother-in-law was diagnosed with non-Hodgkin's lymphoma, a college roommate's mother and her cousin developed breast cancer, her aunt fought leukemia, and a close friend struggled with thyroid cancer.

Sure, Noelker wants to beat cancer for her loved ones, but she doesn't want anyone else to experience cancer either. That's why she is a passionate supporter of the Stowers Institute's Hope Shares Endowment and its goals to generate new therapies, prevent suffering, and save lives through basic biomedical research.

Even before the institute officially opened its doors, Noelker had pledged her support. "The research at Stowers is something I believe in—fundamentally believe in," she emphatically states. Since then she has regularly contributed to the endowment because she knows researchers don't yet have all the answers. "I still feel motivated to give because there is still a need."

But Noelker readily admits that some part of her desire to give comes from the respect and gratitude she feels for the institute's founder and her former employer, Jim Stowers, Jr. "It is partly because of Mr. Stowers that I have been afforded the opportunity to be philanthropic."

And when not waging battle with her loved ones against their enemy cancer or working as a data analyst, Noelker finds time to take cross-country motorcycle trips with her husband. She has experienced Yellowstone National Park, Jackson Hole, Wyoming, and the Southwest's Four Corners region all by the seat of her Honda VTX1300 Cruiser.

2012 CONTRIBUTIONS

In 2012, contributions were received from, in memory of, or in honor of the following:

$1,000,000+

William Neaves to establish the "Priscilla Wood Neaves Endowed Chair in Biomedical Sciences"

$100,000+

American Century Investments Foundation

Helen Nelson Medical Research Fund for the "Helen Nelson Distinguished Chair"

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William and Priscilla Neaves in Memory of Pam Stowers

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Janice Beatty

Country Club Bank

Alan Critchell

Phillip Davidson

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Stephen and Patricia Gound

Allan and Margot Huber

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Wesley and Nancy Kabance

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Up to $999

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Mary Breed Brink

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Douglas Stafford

Kevin Stone

Stephen Thune

Bob Weisensee

Carl Westring

Winfried Wiegraebe

William and Teresa Wong

Jerry Workman

Congrong Yu

BACKSTAGE PASS

The humble fruit fly *Drosophila melanogaster* is the granddaddy of all model organisms. Since it helped launch the science of genetics more than a century ago, it has been used to study everything from embryonic development, learning and behavior, human disease, and even for drug discovery. But the fruit fly's true power lies in its long history as a research object and the tens of thousands of genetic lines that have been created over the last hundred years. The fly-stock facility at Stowers feeds and cares for more than 1,700 unique lines, some with distinguished histories of their own.

DROSOPHILA BY THE NUMBERS

50,000,000
estimated number of fruit flies reared annually

437,000
number of fly food vials prepared annually

169,056
number of fly-transfers to fresh food vials made by the fly-flipping robot last year

16,000
liters of fly food prepared annually

1,728
number of unique genetic fly lines maintained by the fly-stock facility

100
average number of eggs laid by a female fruit fly each day

60
number of gallons held by the kettle used to prepare fly food

30
average lifespan of fruit flies in days

18
number of incubators used to maintain flies

8
number of research labs working with flies