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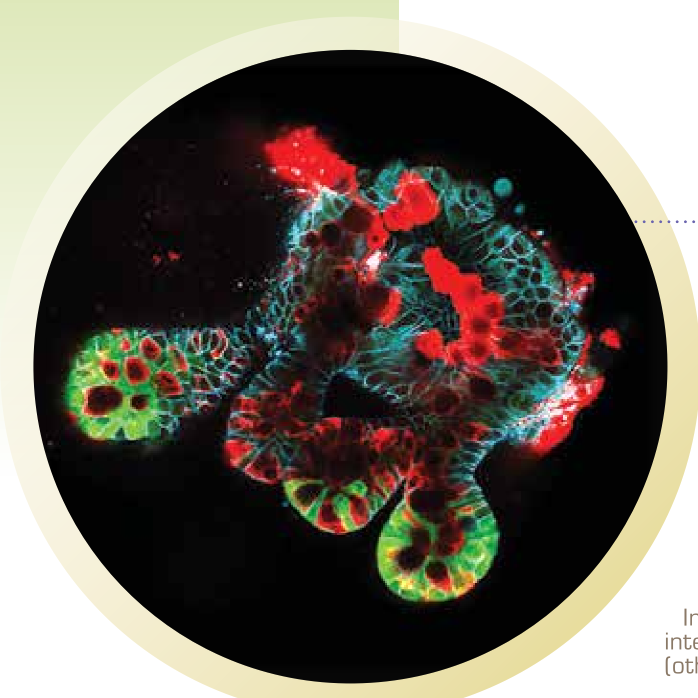
TO MAKE A SIGNIFICANT CONTRIBUTION TO HUMANITY THROUGH MEDICAL RESEARCH BY EXPANDING OUR UNDERSTANDING OF THE SECRETS OF LIFE AND BY IMPROVING LIFE'S QUALITY THROUGH INNOVATIVE APPROACHES TO THE CAUSES, TREATMENT, AND PREVENTION OF DISEASES.



A SINGLE MOUSE INTESTINAL STEM CELL HAS GIVEN RISE TO A MULTICELLULAR STRUCTURE RESEMBLING A MINIATURE SMALL INTESTINE. BY IMPROVING CELL IDENTIFICATION AND CULTURING METHODS, INVESTIGATOR LINHENG LI ADVANCES THIS MODEL TO BETTER UNDERSTAND INTESTINAL STEM CELLS AND THEIR FUTURE CLINICAL APPLICATIONS.

Image: A small intestinal mini-organoidal structure with intestinal stem cells (green) and differentiated cells (other colors).

2 MUCH MORE THAN PRETTY PICTURES
THE STOWERS MICROSCOPY CENTER CAN SUGGEST JUST THE RIGHT SCOPE FOR YOU.

STOWERS REPORT

NEWS AND INSIGHT FROM THE STOWERS INSTITUTE FOR MEDICAL RESEARCH

FALL 2014

STOWERS REPORT

PUBLISHED BY THE STOWERS INSTITUTE FOR MEDICAL RESEARCH
FALL 2014

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In perspective

BY DAVID CHAO, PHD
PRESIDENT AND CEO

The frontiers of scientific research are often pushed forward by the ability of scientists to make observations not previously apparent to others.

As part of his studies on light and optics, the seventeenth century English experimentalist and philosopher Robert Hooke improved upon the primitive microscopes of his day, to open up a whole new world of study. The enhanced performance of his new microscopes allowed him to make unprecedented observations of a multitude of tiny objects. For instance, his observations of a slice of cork revealed honeycomb-like pores for the first time. Because these pores reminded him of the cells used as living quarters in a monastery, Hooke called the structures "cells"—the first use of the term to describe the basic unit of life.

Since Hooke's early example, the demands of biological applications have pushed microscopists to make steady progress in magnification, illumination, and resolution. With each advance, more and more of the inner workings of the cell have become visible. Most recently, this year's Nobel Prize in Chemistry recognized the work of three scientists in achieving resolutions smaller than half the wavelength of light—a limit previously presumed to be insurmountable.

This issue's cover story describes how the centuries-long tradition of collaboration between biologists and microscopists takes form at the Institute. The article highlights the activities and achievements of the Microscopy Center, one of the Institute's largest scientific support centers. The Institute's scientists have access to eighty microscopes, which vary greatly in purpose and complexity. Eleven resident experts ensure that the instrumentation is used to maximal benefit.

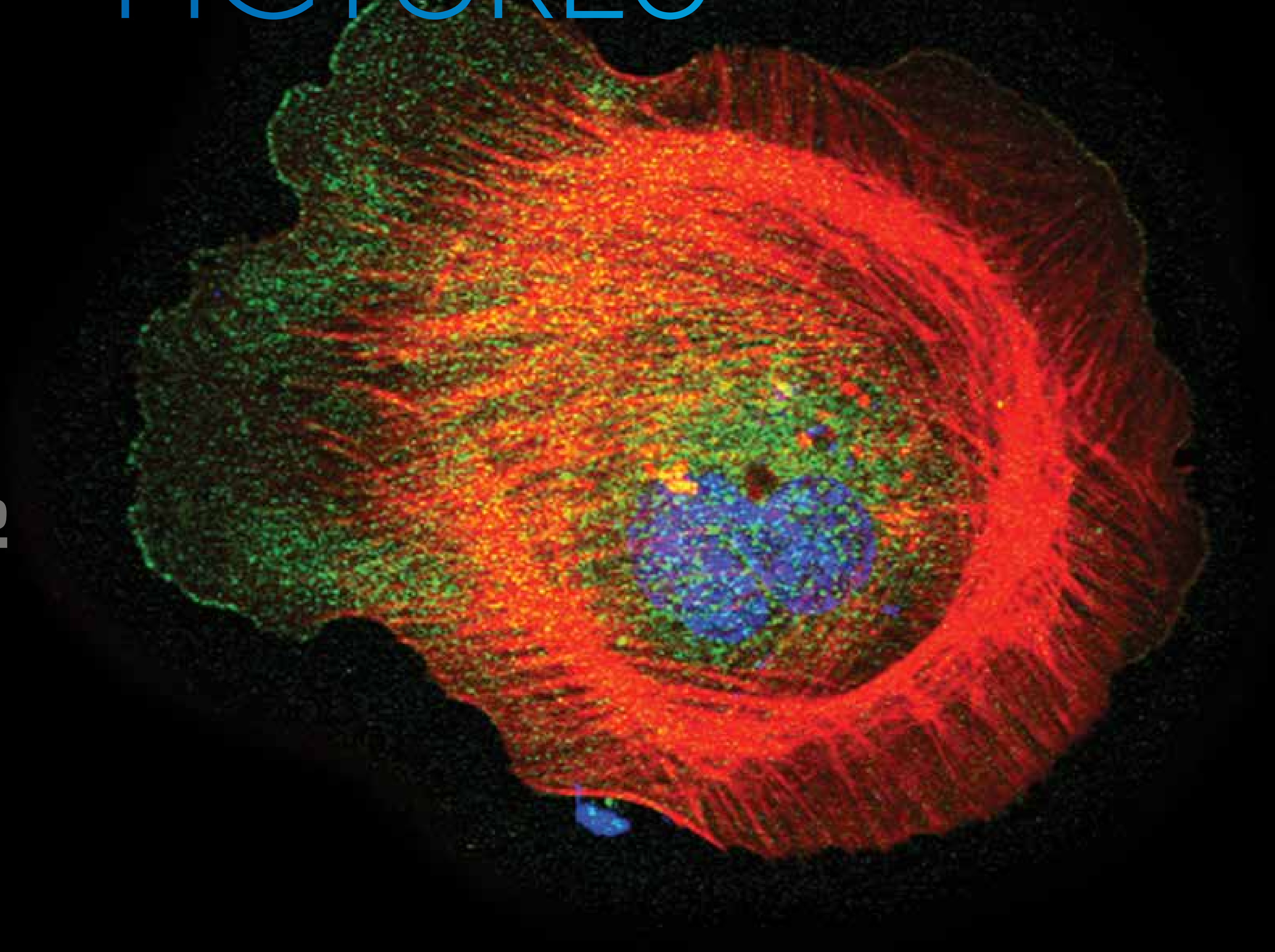
Yet, a keen ability to make significant observations requires more than just cutting-edge instrumentation. As Louis Pasteur said, "In the fields of observation, chance favors the prepared mind. "Training is required for scientists to learn how to set up experiments to maximize the chance of making an interesting observation and how to recognize when a chance observation might have special significance.

The Institute has a variety of training and mentoring programs to help prepare the minds of the next generation of scientists. A second story in this issue highlights the intensive research opportunities for postdoctoral researchers—scientists embarking on the post-PhD phase of their careers. In recent years, Investigator Jerry Workman, who heads the postdoctoral affairs program, has led a set of distinctive initiatives focused on enhancing the postdoc experience and preparing these scientists for the next step in their careers.

Centuries ago, scientists like Hooke made their own simple instruments, worked largely in solitude, and taught themselves whatever was needed. In contrast, the modern practice of biological research, especially at the Institute, involves advanced technology, teamwork, and training. I hope you enjoy reading the stories that follow and will reflect upon how new observations can arise from the confluence of technological, organizational, and intellectual advances.

By Elise Lamar, PhD

MUCH MORE THAN PRETTY PICTURES



GOT A BIOLOGICAL QUESTION THAT COULD BE ANSWERED BY MICROSCOPY? THE STOWERS MICROSCOPY CENTER CAN SUGGEST JUST THE RIGHT SCOPE FOR YOU. THEN, AFTER THEY'VE SHOWN YOU HOW TO TURN IT ON WITHOUT DESTROYING A HALF-MILLION DOLLAR PIECE OF EQUIPMENT, THE TEAM MEMBERS WILL MARSHAL THEIR DIVERSE TALENTS TO HELP YOU ACQUIRE, PRESENT AND MAKE MATHEMATICAL SENSE OF YOUR STARTLING IMAGES. SOME MAY EVEN BE SUITABLE FOR FRAMING.

Tools used to conduct biological experiments, such as microscopes, computers, or DNA sequencing machines, have become mind-bogglingly expensive. So most research centers have "core facilities" in which investigators pool resources to purchase big-ticket items.

But unlike core facilities in many academic institutions, the Stowers Microscopy Center team members, many with advanced degrees in physics or chemistry, often work with investigators to acquire and analyze microscopy data in an extraordinarily collaborative manner. And, if none of the microscopes they have in-house suit your needs, they can custom build one.

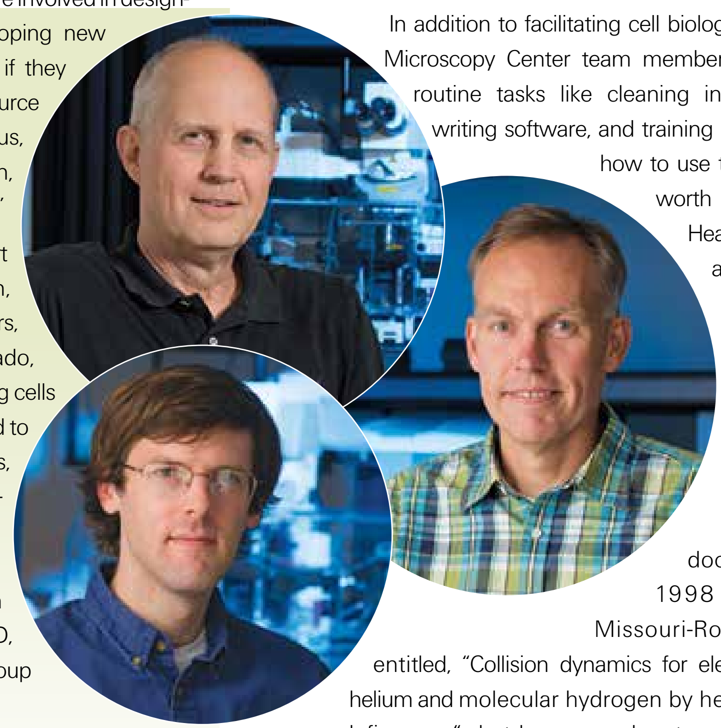
A Stowers core value: supporting scientists

Over 100 individuals work in the Institute's twelve core facilities, which offer expertise in specialties from reptile husbandry to computational biology. The Microscopy Center is among the largest. Their team is on a mission to train their colleagues in all matters relevant to light microscopy, plus keep Stowers' eighty plus microscopes up and running 24/7. They also supply software for image processing and data analysis, or can even write it themselves if there is a need for something more specialized.

Winfried Wiegraebe, PhD

Winfried Wiegraebe, PhD, leads the Center. He studied microscopy in Germany as a biophysics student at Max Planck Institute for Biochemistry in Martinsried and then completed a postdoc at the Institute for Molecular Biology in Jena. Wiegraebe is a former R&D engineer and product manager at Zeiss, a German company that is to microscopy what Mercedes Benz is to auto manufacturing. At Stowers, Wiegraebe runs the Center assisted by three Group Heads and says his primary purpose is to keep current on new technologies that could be brought to Stowers. In interacting with scientists, he wants the Center staff to go above and beyond. "The members in my group and I are involved in designing experiments and developing new methods," he says. "In fact, if they want, Stowers labs can outsource complete experiments to us, including experimental design, data acquisition and analysis."

Case in point: as one part of a study of regeneration, HHMI Investigator at Stowers, Alejandro Sánchez Alvarado, PhD, needed to count dividing cells after a manipulation designed to activate flatworm stem cells, so his group stained thousands of worms with a green fluorescent dye that marks dividing cells. They then asked Sean McKinney, PhD, one of the microscopy Group Heads, to help with analysis.



From top:
Steve Hoffman,
Chris Wood, PhD,
Sean McKinney, PhD

McKinney imaged a very large number of glowing green dots marking dividing cells in worm tissues using a confocal microscope, an instrument built to reject background fluorescence that might obscure details. He pieced images back together to create pictures of entire worms aglow with fluorescent specks. He and a colleague then wrote a computer program to compare speck number in normal versus experimentally manipulated worms.

McKinney has a doctorate in physics from University of Illinois Urbana-Champaign and completed a postdoc in a protein-engineering lab at the Howard Hughes Medical Institute's Janelia Farm Research Campus, where he developed novel fluorescent proteins. He calls himself a "hired gun" on the Sánchez Alvarado study, which was published in *eLife* in 2014 with McKinney as a co-author. To McKinney, this kind of cooperation to solve a problem is business as usual: "We regularly go beyond the routine core operations of maintenance and training."

Sánchez Alvarado is more expansive: "Sean designed a customized protocol that allowed us to get the most information possible from our data and provided an infrastructure to carry out more complex experiments," he says. "This is where the Microscopy Center shines brightest. Without them, these efforts would lead to significantly fewer insights."

Finding problems before the users do

In addition to facilitating cell biology breakthroughs, the Microscopy Center team members spend time doing routine tasks like cleaning intricate components, writing software, and training Stowers scientists on how to use the millions of dollars worth of equipment. Group Heads Chris Wood, PhD, an expert in image processing, and Steve Hoffman, who oversees scope maintenance, supervise many of these tasks.

Wood earned a doctorate in physics in 1998 from University of Missouri-Rolla with a thesis entitled, "Collision dynamics for electron removal from helium and molecular hydrogen by heavy ions," which he defines as "what happens when two particles smash into each other." He then spent eight years working as a software developer at consulting companies, where, among other things, he designed computer simulations to assess fluid flow.

Most days, Wood, assisted by Research Specialist Richard Alexander, teaches researchers how to manipulate multiple software packages that quantify imaging data so they can create meaningful plots and tables of the data. This is a non-trivial task, because for some applications, processing an image is more demanding than acquiring it. In some instances, Wood or Alexander might offer to look at the data from an experiment and compile results for the researchers.

Hoffman also brings eclectic training to his job as overseer of equipment. In the 1980s, he earned a business management degree at Kansas State University and then a master's degree in education at University of Missouri-Columbia, where he specialized in counseling and even worked briefly as a psychologist.

Over the last twenty years, Hoffman has learned to digitize physiological signals, such as brain waves, acquired by medical equipment for computer analysis and become adept as a programmer, first at a contract research institute and then at Cerner Corporation, a supplier of health-care information technology located in the Kansas City metropolitan area. He joined the Microscopy Center in 2007.

Hoffman spends his days "finding problems before the users do" and drives microscope repair when needed. *Drive* is the operative term, because the Center is structured such that the maintenance of instruments, some of which cost nearly a million dollars, is a group endeavor. Each staff member, regardless of job description, is assigned one scope as their baby, an instrument they know inside-out, as part of what Wiegraebe calls "the expert principle."

"Maintaining and evaluating a system helps us understand how to design better experiments," says Wiegraebe. "It's as important for successful science as developing cutting-edge imaging approaches or analysis algorithms."

To FRET, SPIM, or TIRF?

Most of the Center's instruments are fluorescence microscopes, meaning that they beam light of a certain wavelength at a specimen, whose components, such as nuclei, membrane proteins, or microtubules, have been stained with dyes that glow when struck by light of that wavelength, making structures visible. Specimens treated with multiple stains resemble collages of glowing red, green and blue patterns revealing the relationship of cellular components. Images are two-dimensional, but confocal microscopes and their cousins called "two-photon" microscopes—often used with very thick specimens—can optically section through a piece of tissue, while a companion computer "stacks" images to create a 3D view.

Beyond that, more specialized techniques are available, depending on whether one needs a flat or 3D image, whether tissue is fixed or living, and (if living) how cells need to keep functioning to answer the question at hand. These applications go by acronyms like TIRF (Total Internal Reflection Fluorescence), FRET (Förster or Fluorescence Resonance Energy Transfer), or SPIM (Selective Plane IlluminationMicroscopy), to name a few. Whatever the technological details, a Center team member knows how to apply it and advise you on whether it's best for each application.

The Axioplan is capable of acquiring both fluorescence and transmitted light images that utilize various contrast enhancement methods. The motorized filter turret permits multi-channel acquisition.

Take TIRF. One would only apply TIRF to answer a question that required limiting your view to a very thin 2D plane with no confounding signals intruding from above or below that plane. As a graduate student in the lab of Investigator Rong Li, PhD, Sarah Smith, PhD, employed TIRF to analyze how vesicles moved into and out of yeast cell membranes. For one study, Li's group needed to be 100% sure that two proteins resided in different cellular membranes. By confocal microscopy, the proteins appeared to coalesce into a single blob, but TIRF analysis revealed that the proteins were actually embedded in closely apposed but different membranes.

After earning her doctorate in 2013 from the University of Kansas Medical Center, Smith joined the Microscopy Center as a research specialist. Her expertise in microscopy (as an undergrad she won an award from the National Society of Physics Students for building an instrument called a scanning tunneling microscope) plus her familiarity with Stowers science has given her a leg up in establishing collaborations with multiple Institute scientists.

One collaborator is Associate Investigator Sue Jaspersen, PhD, with whom Smith worked in applying FRET, a completely different application of microscopy. FRET measures the transfer of energy from one fluorescing molecule "excited" by light to a nearby molecule. Thus, biologists doing structural studies might use FRET to figure out whether proteins actually touch each other. In this case, Jaspersen, who studies multi-protein nuclear structures that help organize chromosomes in yeast, worked with Smith to use FRET to determine how these structures insert into yeast nuclear membranes and then reconstruct themselves protein-by-protein when cells divide.

Another fruitful Stowers collaboration occurred recently between the Microscopy Center and Associate Investigator Matt Gibson, PhD. Gibson needed to image embryonic fruit fly cells residing in epithelial sheets to determine if a specific mutation disturbed how cells divide within that sheet. Doing that imaging required a strategy to view components of a living cell's mitotic spindle (the machinery that drags chromosomes into daughter cells during mitosis) long enough to capture individual cells dividing.

So McKinney, working with Center Laboratory Assistant Amanda Kroesen, scavenged parts from other confocal microscopes to build an in-house SPIM microscope. This is an instrument that allowed them to illuminate tissues from the side, rotate them to view from all sides, and image them for long periods of time without the laser "bleaching" or fading the fluorescent signal—all while quantifying the extent to which the mitotic spindle tilted.

The Gibson Lab published that work, complete with time-lapse films of dividing cells, in *Nature* in 2013, with McKinney and Kroesen as co-authors. It reveals that alignment of a cell's mitotic spindle relative to the surface of a cell layer is critical for epithelial integrity and that mutations that cause the spindle to list significantly disrupt an epithelial sheet. The work has implications for cancer: disorderly division of epithelial cells is a hallmark of carcinomas.

For experiments that require imaging of developing cells and organisms, sometimes over the course of several days, the Microscopy Center calls on fellow Research Specialist Jeffrey Lange, PhD. Lange uses advances in materials science learned during his PhD studies in analytical chemistry at Kansas State University to design and fabricate devices tailor-made to specific live samples ranging from tiny yeast to whole worms. His goal? To keep them under the lens of the microscope while still remaining free to move about. Lange's devices have enabled Stowers researchers to capture and study the details of processes such as fruit fly ovary development and flatworm locomotion.

Until recently, this kind of robust scientific cross-talk between biologists and people who provide technical support has not been common. But that cultural divide may be dissolving given the enormous technical know-how required to analyze biological data today. Wiegraebe notes with pride that historically physicists have often demonstrated a "let's-get-the-job-done-as-a-team" spirit, enabling them to rack up significant accomplishments, such as the moon landing. "The management at Stowers knows that people are more productive when they work together," he says. "So they established the core services to provide investigators with collaborative help from specialists or consultants."

A new kid on the microscopy block

Although a powerful tool, conventional light microscopy can't yet hold a candle to electron microscopy (EM) when it comes to resolution. EM (the purview of a different Stowers core) can distinguish features of particles less than a nanometer in size and take snapshots of large protein complexes, like Jaspersen's centrosomes. But EM sample preparation is onerous and tissue must be fixed (dead): so if you need EM level magnification, you won't be twirling living tissues around making movies of them.

But stay tuned: new "super-resolution" light microscopes can image structures smaller than 200 nanometers, the limit of conventional light microscopy. Jaspersen recently used one to figure out how a dividing yeast cell knows to make just one copy of its centrosome. She and collaborators from University of Colorado, Boulder, suspected that the nuclear factor Sf1 controlled centrosome duplication. Thus, they mutated, or disabled, Sf1 in yeast and applied a super-resolution technique called SIM (for Structured Illumination Microscopy) to peer into the nuclei of dividing cells and check if they contained the right number of centrosomes, namely two.

Sure enough, many didn't. Some yeast harboring mutant Sf1 exhibited more than two centrosomes, sometimes separated by less than 100 nanometers. Conventional microscopy would simply have mistaken these two dots for one, just as a double star might appear as a single point through a backyard telescope. Moreover, super-resolution imaging gave the team a way to count centrosomes in large numbers of cells to allow statistical comparison of mutant and control cells. This work tagged Sf1 as a key factor controlling centrosome duplication, which is important, as aberrant centrosome duplication occurs in several diseases, including cancer. Jaspersen and collaborators published the study this summer in *PLoS Genetics*.

Zulin Yu, PhD, research specialist in the Microscopy Center, was a co-author on that paper. Yu joined the Center in 2010 after earning a biophysics doctorate at the Chinese Academy of Science in Beijing and worked as a postdoc with Stowers Associate Investigator Ron Yu, PhD. Zulin Yu easily made the move from postdoc to core center because he can be an expert on multiple projects and is currently the Center's super-resolution point person. This year, for example, he contributed not only to the Jaspersen study, but was co-author on a paper published in *Genetics* from the lab of Investigator Scott Hawley, PhD. That study applied SIM technology to show how components of another multi-subunit nuclear complex called the synaptonemal complex were arranged.

"As a postdoc in Ron's lab I used to stop by the microscopy office and ask Winfried and Sean questions all the time," says Yu. "They were always glad to help me. Now it's my job to help many different scientists solve problems that are often quite challenging."

More beautiful than the real thing

Rong Li, a cell biologist, agrees: "The job of a microscopy core now is not just to help us acquire beautiful images and time-lapse movies but to develop unbiased and reliable methods to quantify signal intensities, fluctuations, and dynamic movement of cells and intracellular structures."

Although he is a microscopist first and foremost, Wiegraebe is adamant that mathematical analysis is where it's at: "The days of just pretty images are over!" he says. "Go to any cell biology meeting and you'll see that the future of microscopy is quantification: this field is no longer descriptive."

Paradoxically, however, both Li and Wiegraebe relish microscopy's aesthetic side. Li was delighted when "data" from her lab was chosen for display at "Life: Magnified," an exhibit this summer at Washington DC's Dulles Airport. That project featured dazzling microscopy images from labs around the world, among them portraits of tick mouths, lizard toe hairs, liver cells, and (from the R. Li Lab) a single skin cell radiating fluorescent red and green cytoskeletal filaments like a medusa head from a royal blue nucleus. (*See page 24 for related story.*)

Wiegraebe loves contemporary art and has worked as a docent at Kansas City's Kemper Museum of Contemporary Art for eight years and more recently at Kansas City's Nelson-Atkins Museum of Art. (Unsurprisingly, the Microscopy Center website has links to pages showing the historic relationship of art to science.)

He argues that artists and scientists have more in common than one might think, because both make sense of the world by looking at things carefully. As examples he cites nineteenth century biologists, such as German microscopist Ernst Haeckel who made delicate sketches of micro-organisms that people still admire, as blurring the line between art and science.

"Haeckel was a Romantic scientist and promoter of Charles Darwin who thought that being a good scientist meant being a good artist," says Wiegraebe. "His drawings were often more beautiful than the real thing, probably because many in the nineteenth century believed that the perfection of the world is reflected in its beauty."

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A basic fluorescence scope that uses a conventional light source and colored filters to observe biological processes.

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By Carina Storrs

WHAT'S UP, POSTDOC?

To land the most prestigious and demanding jobs out there, a classroom education alone often does not cut it. Many professionals like physicians and pilots must first complete years of specialized training, clock thousands of hours of practice, and gain experience in other roles. The same goes for many of the top positions in the life sciences. After earning a doctoral degree or PhD, the next step in becoming a professor at a university or scientist in a biotech company is usually to do postdoctoral research, or as it is more commonly called, a postdoc.

From left to right: Carrie Adler, PhD, Jerry Workman, PhD, Baoshan Xu, PhD, and Juston Weems, PhD

A postdoc is typically a period of three to five years that gives researchers the chance to apply the knowledge and critical thinking skills they gained in graduate school to different biological questions. For example, someone might go from studying cancer in their graduate research to embryonic development during their postdoc, or switch to a different aspect of how cancer genes commandeer cells.

Along the way, postdocs (postdoc is also the term used for the person in this position) will ideally flex their independence more than they did in graduate school, independently choosing the scientific questions to ask and experiments to do. They also learn new techniques to expand the types of questions they can propose.

As Jerry Workman, PhD, a Stowers investigator and head of the Stowers postdoc affairs program, puts it, "A postdoc is a chance to prove yourself. If a university is going to hire a new assistant professor, they want to know that the person they hire has a good research plan and is able to carry it out." Thirty percent of Stowers postdocs score a faculty position, slightly better than the national average of about twenty-five percent according to the Biomedical Research Workforce Working Group Report from the NIH. Another twenty percent or so go on to work as staff scientists in academic labs or at biotech or pharmaceutical companies. Close to forty percent choose to expand their scientific repertoire and do another postdoc.

In some ways, a postdoc at the Stowers Institute is similar to postdocs at other research institutes and universities. Freshly minted PhDs come from all over the country and world to tackle new research projects in a new environment and with newfound independence.

But in other ways, the Institute sets itself apart as a highly coveted postdoc destination. Most importantly, thanks to opportunities for scientific support from core facilities, technology centers, and research advisors, postdoc researchers "can do more and more different types of experiments here than just about anywhere else," Workman says. This helps satisfy one of the biggest demands on postdocs: to generate ample data and publications. For those aspiring to become a professor and run a lab, data will lay the foundation for their own research. But data and papers can provide a boost to any kind of post-postdoc career.

Unwavering support

At the Institute, postdocs have access to support for tissue culture, screening, proteomics, or other techniques. There are no fewer than a dozen expert-led core facilities on campus that many of the Institute's approximately 100 postdocs collaborate with to speed up experiments and build up stocks of reagents and solutions.

Carrie Adler, PhD, has been a Stowers postdoc for three years and is exploring how genes control regeneration in the planaria flatworm. "I am benefiting enormously from the expertise of the molecular biology and microscopy cores," Adler says. The molecular biology core routinely clones and screens

Head of postdoc affairs Jerry Workman, PhD discusses experimental data with postdocs Arnob Dutta, PhD and Fu Huang, PhD.

hundreds of genes for her in one fell swoop. "The time advantage is on a scale that you can't imagine," she says.

Because of their skill, dedication, and streamlined approaches, working with the core center teams can mean not just doing more, but doing better. This capability is on full display at the Laboratory Animal Services Facility (LASF). But in addition, the LASF is particularly adept at making "knockout" mice, in which a gene has been inactivated, to study how the absence of a gene may perturb biological processes. Meanwhile, the Reptiles & Aquatics Facility has developed a novel tank system that vastly improves planaria growth and reproduction, which Adler hopes to set up, perhaps on a smaller scale, when she starts her own lab.

For postdocs seeking expert experimental design, the research advisors at the Institute are standing by. They are in-house consultants specializing in microscope-based assays and mathematical modeling. When Postdoc Juston Weems, PhD, arrived three summers ago, he set out to study how cells halt gene expression after they are exposed to dangerous levels of UV light, a damage control strategy. Weems knew that data from microscopy could provide important insight into which proteins interacted with others in the process, and when. But Weems, with a background in biochemistry, had "zero experience" with microscopy, and the effort to get these experiments off the ground would be time-intensive.

Weems promptly began collaborating with Research Advisors Brian Slaughter, PhD, and Jay Unruh, PhD. The research advisors have gone far beyond teaching Weems how to use the microscopes. They help him figure out how to select the best assays for his questions and set up experiments, and then help analyze the resulting data. "I'm certainly proficient in microscopy now and comfortable directing similar experiments myself when I have my own lab," Weems says.

No-holds-barred

Even with the extensive scientific support at the Institute, research is not an easy undertaking. But the Institute strives to remove all barriers, big and small, to asking the most ambitious questions and doing the best experiments.

One obstacle removed is the need to secure funding. Due to the Institute's sizable endowment, Stowers investigators are not dependent on outside grant support. As a result, postdocs' experiments are not limited to fit within a narrow grant budget.

However this luxury can be a liability for postdocs because hiring committees at universities and institutes sometimes evaluate a candidate based on ability to get funded, says Weems. To counterbalance, Workman and the Stowers Postdoctoral Association have teamed with Stowers Grants Administration to organize workshops on applying for competitive awards. A workshop was held earlier this year that focused on K99 awards, which are NIH grants that allow the funds to travel with postdocs when they complete their work at the Institute and set up their own labs elsewhere. At the workshop, two members of a recent K99 review panel provided tips on writing the application and what makes a good candidate for the K99 Award. Weems says some of the suggestions were eye-opening. Workman plans for similar workshops to be held periodically.

Xu believes that when postdocs worry less about funding and resources, they are more available to help their fellow researcher: case in point, the informal request for reagent (RFR) system. Say you want to try out a reagent to see if it works before buying it. All that is required is a RFR via email that goes to all Stowers scientists. "In very short time, a lot of people will get back to you and, as a result, you will get to know a lot of people," Xu says.

Numerous other perks give postdocs the chance to meet each other and make life easier all around. In addition to free beverages 24/7, every Tuesday night, postdocs and other researchers who work late can gather in the Stowers Café where dinner is provided courtesy of the Institute. The twenty-four hour fitness facility offers free classes such as yoga and total body conditioning. "It's those little things that really make it nice to be a postdoc here," says Adler.

For Weems, it is the ease of working and chatting with scientists in other labs and core centers and the research advisors that he will miss the most. "It is a great atmosphere, and when I leave Stowers, I don't know if I'll be at a place with the same collaborative feel," he says.

Moving on

While the Institute makes it relatively easy for postdocs to do research, it also has several programs to help prepare them for the transition into more challenging environments. "We want to keep postdocs on their toes and a little more aware of the pressure of the outside world," Workman says. Indeed, Stowers postdocs have moved on to faculty positions at numerous prestigious and highly competitive institutions including New York University, Rutgers University, Kyoto University, Albert Einstein College of Medicine, Arizona State University, University of Texas Southwestern Medical Center, and Yale University School of Medicine.

When Workman became head of the postdoctoral affairs program a few years ago, he put in place several opportunities to help postdocs stay on track. While postdocs have always been required to complete an annual evaluation with their advisor to ensure they are working toward their career goals, postdocs can now select a co-mentor or a committee of several investigators to help them navigate their research project and subsequent steps. Having a larger sounding board can reveal new and different options and opportunities.

"As the head of postdoctoral affairs, Jerry has taken the Institute's postdoc program to the next level," said Scientific Director Robb Krumlauf, PhD. "Jerry has led and coordinated numerous initiatives that help postdocs stay focused on their research as well as build important skills beyond the bench to advance their careers."

One of the biggest changes afoot is the new faculty search group. For the second year in a row, postdocs who plan to apply for faculty positions in the fall can compile their application materials (cover letter, CV or resume, and research plan) a few months in advance for Stowers investigators to critique. In addition, a group of professors from other institutions and universities convene at Stowers to give the postdocs feedback on their "job talks" or interview seminars. "It is the feedback from outside scientists that I don't think exists at many other places," Adler says, who is participating in this year's group.

Not that postdocs don't get ample chances to present their work throughout their tenure to other researchers at Stowers and to outside scientists. Almost since the opening of the Institute, the Crossroads program, run by postdocs and predoctoral researchers, has held Young Investigator Research Days (YIRD). The Crossroads members invite outside scientists to give seminars, and also to hear presentations from predocs and postdocs at the Institute. The Crossroads team has also started organizing Professional Development Days so postdocs can network with scientists outside of academia, from pharmaceutical companies or consulting firms for example.

For Workman, the motivation for creating the mentoring programs to help postdocs move on to the next stage of their career is clear: The postdocs that train here will publish a lot more science as a group than the Stowers investigators that trained them. In addition to the discoveries made here, training the next generation of scientists could be one of this Institute's biggest contributions to science."

Sheng Xia, PhD and Masataka Nikaido, PhD, now a research assistant at the University of Hyougo, discuss research projects at the annual Young Investigator Research Days event.

By Alissa Poh

A DISCUSSION WITH KAUSIK SI

The rural village where Kausik Si, PhD, grew up may have lacked electricity and running water, but one thing it *did* have was a good school—comparable, in fact, to those in nearby Calcutta, courtesy of India's one-size-for-all education system. Because Si's father taught high school physics and mathematics, and the family lived right next door, students were used to seeing their teacher's young son hanging around the laboratory, entranced by the likes of color-changing chemical solutions or watching a Van de Graaff generator produce visible electric currents. Si also struck up frequent conversations with his father's colleagues on assorted topics, from Mendelian genetics to Darwinian evolution.

"One of them would tell me, 'No, you don't really understand [genetics],'" Si recalls wryly. "It made me mad, because I was sure I did, but he reminded me that having answers didn't necessarily mean actual comprehension."

His parents being far from the helicopter variety, Si was never asked if he'd done his homework, or otherwise pushed academically. Of his own accord, he haunted the village library and read voraciously—including books perhaps questionable for his age. Once, the youngster asked his father what "passion" meant, after the dictionary's definition proved rather obscure.

Si's propensity for independent thinking eventually propelled him to the United States for graduate education. "I didn't arrive with the clearest notion of what to study," he says, "but I quickly decided that what I *didn't* want was to pursue problems with fairly clear-cut solutions." He settled on neurobiology—figuring that the field would never lack interesting questions—which led him to the laboratory of Nobel Laureate Eric Kandel, PhD, at the University of Columbia, for a postdoctoral fellowship. There, Si and Kandel proceeded to turn conventional understanding of prions, long regarded as nothing but bad news, upside down. Prions are proteins that can exist in two shapes–one shape that is stable on its own and another shape that can form self-propagating aggregates. They proposed that the protein CPEB was important for long-term memory in the marine mollusk *Aplysia*—precisely *because* of its prion-like ability to form self-aggregating amyloid structures that could hang out indefinitely at, and stabilize, new synaptic connections necessary for consolidating information into more permanent storage.

There seems to be an oxymoron here, because amyloid—the aggregated protein deposit—is a known factor in multiple neurodegenerative diseases where memory loss is one of the earliest symptoms," Si says. "We're suggesting that prions and prion-like proteins evolved to serve regular biological functions, and diseases like Alzheimer's are anomalies of such normal phenomena."

After joining the Stowers Institute in 2005, Si turned his attention to the fruit fly *Drosophila* as a scientific model for his research. Among other discoveries, he has found that when controlled stacking up of Orb2, the fly version of CPEB, is disrupted, long-term memory formation is impaired in these flies. Now an associate investigator, Si is content to wander—and steadily ascend—what Kandel has described as "the foothills of a great mountain range," learning ever more about the molecular whys and wherefores of memory storage.

WAS IT DIFFICULT FOR YOU TO BE CONVINCED OF YOUR POSTDOCTORAL HUNCH THAT CPEB'S PRION-LIKE PROPERTIES MIGHT BE ESSENTIAL FOR *APLYSIA* TO FORM LONG-TERM MEMORIES?

It was actually easy, because I was young and naive. Prions had long struck me as highly unusual, particularly their self-perpetuating ability. But if I'd been studying them from a disease-related perspective, I probably wouldn't have concluded what I did. Eric [Kandel] and I had a great relationship by then; I was full of wacky ideas, and somehow that's why we got along really well. So he wasn't surprised, nor did he pour cold water on my suggestion. Nearly everyone else thought it was ridiculous. After we published our findings, I got multiple e-mails along the lines of "you're completely out of your mind," and "this is so wrong for so many reasons." I never responded, but it was a nerve-wracking process to go through.

The naysayers are slowly coming around, partly because our experimental evidence has been very consistent, even independently corroborated; and also because several unrelated publications have illustrated the same principle—of prion-like proteins capable of normal functions—over the last several years.

HOW WOULD YOU SUMMARIZE YOUR CURRENT RESEARCH INTERESTS?

I'm intrigued by two questions. How do you keep a memory, for years, of something that happened in a short time? And what is it about some experiences that makes us remember them for so long? There's no apparent rhyme or reason for many of my lasting memories; were they randomly retained, or did my brain perceive some implicit information as important, although I wouldn't consciously think so?

I'd also like to tease apart what forgetting really means. Is it truly a blank slate, or are the details somewhere in the recesses of your brain, just inaccessible? It might even be that you *could* access the information, but there's no meaning or context associated, so you don't.

ARE YOU ABLE TO VISUALIZE MEMORY IN *DROSOPHILA*, USING ORB2?

We're working on it. We've developed a probe, where Orb2 has to oligomerize, or form a protein complex, in order for two inactive halves of an enzyme to come together and produce a fluorescent product. So wherever Orb2 stacks up in the fly brain, there'll be enzyme activity and increased fluorescence.

It's a molecular "signature" of memory—in flies, anyway. We got lucky because this process is selectively engaged and, other than food and choosing a mate, flies don't form long-term memories of most experiences. In research terms, it means we were dealing with low background noise. Things get more complex with higher organisms, and because there's no such thing as a naïve brain, tracking down subtle changes in certain neurons over others, as representative memory "signatures," would be a needle-in-the-haystack quest.

CAN MEMORY STORAGE IN THE BRAIN BE COMPARED TO A LIBRARY?

It's frequently used, but neurobiologists dislike this analogy, because it implies a catalog—that information is stored alphabetically, which is not necessarily true with memory. There's likely some pattern, but it might be very difficult to figure out because it is unlike any of the typical organizational patterns we encounter in our everyday lives, such as information organized alphabetically or chronologically. It's one reason why people are so interested in mapping the brain.

WHAT DO YOU THINK OF THE WHITE HOUSE'S BRAIN INITIATIVE?

I think it's simultaneously exciting and daunting. The challenge is even bigger than sequencing the human genome, because when you've mapped a brain—well, you've mapped *a* brain. If I record your brain activity and mine, both will be vastly different, yet we have nearly identical genomes. However, this initiative should enable a better understanding of the basic neural connections and circuitry we do share, and that itself will be a huge achievement.

WHAT FASCINATES YOU ABOUT THE HUMAN BRAIN?

Language; if you want to find out how scribbled words provoke such profound feelings as joy, loss, or anger, you can't look to yeast for answers. A rat is never going to write *One Hundred Years of Solitude*.

DO YOU THINK THE GENERAL PUBLIC PERCEIVES "SCIENTIFIC KNOWLEDGE" DIFFERENTLY THAN YOU AND YOUR PEERS?

Definitely. To us, it's an intellectual quest to understand how biological systems work, for example. To the public, it's more about fixing problems, and helping people live longer and better. We need to change this perception.

After all, what's the probability that by studying a fly's brain, I'll come up with a solution for human psychological disorders? Zilch, honestly. But could I provide insight as to how, fundamentally, an organism assesses its external environment and stores that information to guide its future behavior? Yes, I think so. To me, uncovering this knowledge is just as important. Fixing problems is generally more a *consequence* of achieving understanding.

SCIENTISTS ARE OFTEN THOUGHT OF AS OBJECTIVE. DO YOU AGREE?

No, we have plenty of prejudices and our basic instinct is one of neophobia. Like anyone else, we have two choices when we come across something new—pursue it and see where it takes us, or decide we're not going down that road. But it's difficult to know how rarely or often the unknown route is actually taken, because you never hear of the failures, only the successes.

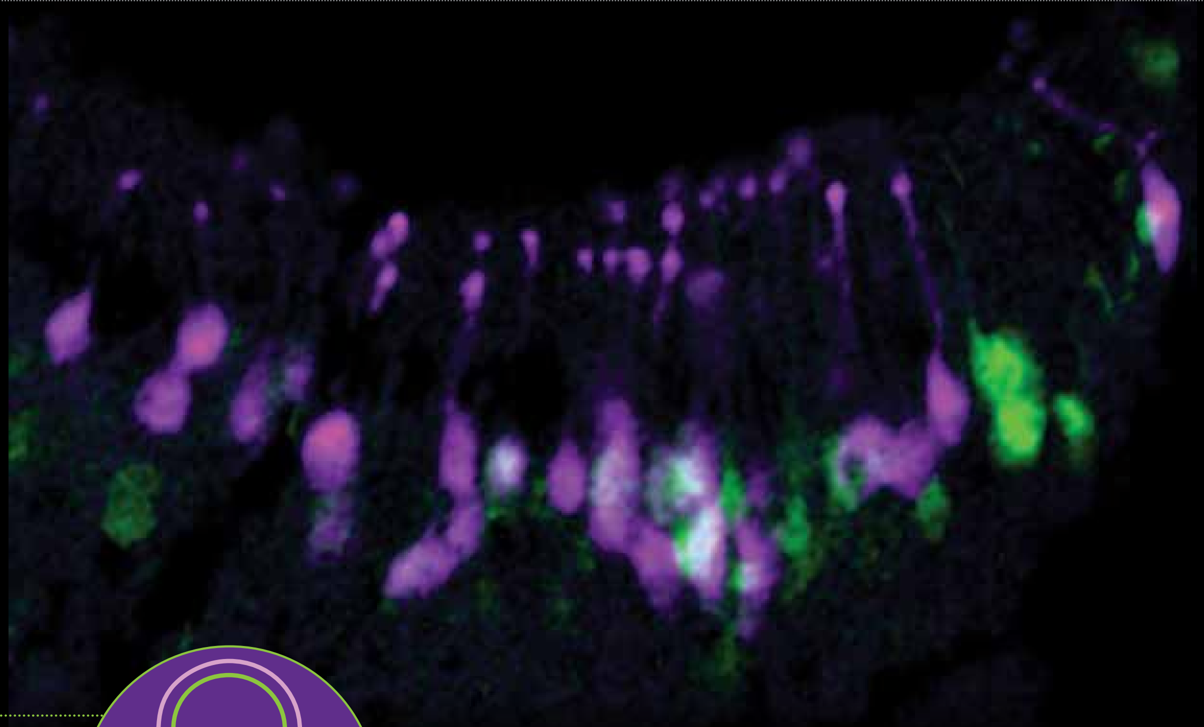
Pulitzer-winning author of *American Pastoral*, Philip Roth, says "character is destiny, yet everything is chance." I think it's so true; in my opinion, saying you're destined to do something isn't necessarily accurate because most decisions are evaluated retrospectively, with a great many chance events involved along the way.

IF YOU WEREN'T A SCIENTIST, WHAT WOULD YOU LIKE TO BE?

A soccer player who writes great literature. My dream career would fuse the talents of Diego Maradona, a former Argentinian soccer player, with the late Gabriel García Márquez, a Colombian novelist and Nobel Laureate. I love sports, and I'm envious of anyone who has a way with words.

WHICH THREE FAMOUS PEOPLE, LIVING OR DEAD, WOULD YOU DINE WITH, IF IT WERE POSSIBLE?

Galileo, Linus Pauling, and one of my favorite authors, Saul Bellow. It'd be a very interesting conversation, as they'd bring such different perspectives to the table.



It takes 2 to court

PHEROMONES ARE CHEMICAL SIGNALS THAT STIMULATE SOCIAL RESPONSES IN OTHERS OF THE SAME SPECIES.

These chemical signals are detected by pheromone receptors located in nasal tissue. Pheromones can let an animal know when a suitable mate is near and activate the release of hormones that encourage the animal to mate.

Researchers at the Stowers Institute led by Investigator C. Ron Yu, PhD, have identified the functions of two classes of pheromone receptors. They found one class of receptors helps a male mouse detect pheromones that indicate when a female is present. The other class of receptors lets him know if the female mouse is ovulating and ready to mate. Both sets of pheromones are critical to trigger mating. Stowers' researchers believe mice developed this system through evolution to maximize the chance of their reproductive success.

"Interestingly, the pheromone that tells other mice that 'I am female,' or the one that tells others, 'I am ovulating,' do not do much on their own," says Yu. "But when the two are presented together, the male mice showed great interest in courting and mating with the female."

Yu and his colleagues plan to build on their research to identify other pheromones and receptors, and map out the neural circuitry that transmits information from the pheromone receptors to the brain. Their findings open the door for the discovery of the neural pathways that activate inborn behavior in mammals, including humans.

"These next steps will help us understand how mammalian brains integrate multiple pieces of information to make critical decisions in their lives," says Sachiko Haga-Yamanaka, PhD, the study's lead author.

The study was published in the July 29, 2014 issue of the online journal *eLife*.

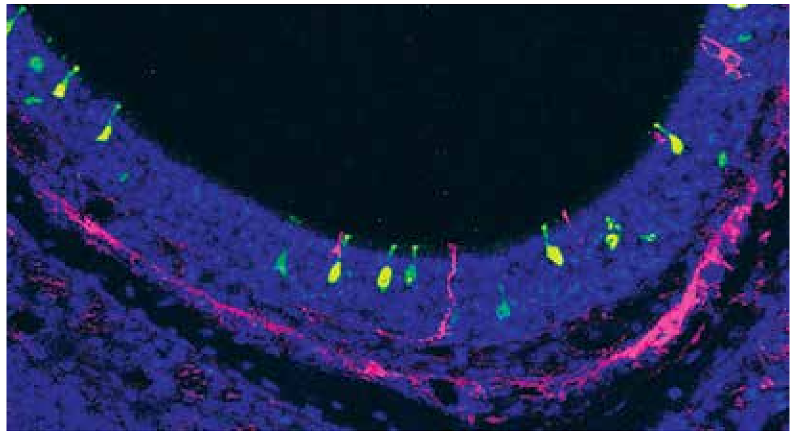
FINDING THE TARGET: HOW TIMING IS CRITICAL IN ESTABLISHING AN OLFACTORY WIRING MAP

THE HUMAN NOSE EXPRESSES NEARLY 400 ODORANT RECEPTORS, WHICH ALLOW US TO DISTINGUISH A LARGE NUMBER OF SCENTS.

Each olfactory neuron displays only a single type of receptor and all neurons with the same receptors connect to the same spot in the brain. This wiring pattern is often described as an olfactory map and serves as an important code book that allows the brain to distinguish between food odors and the scent of a predator, for example.

Unlike other types of sensory cells, which cannot be replaced once damaged, olfactory neurons have a unique regenerative capacity. More remarkably, the regenerated neurons must dispatch their axons on a path through the nasal epithelium to the brain through a distance a thousand times the length of the cell in order to make the proper connections. If regenerated neurons are wired to the wrong location, odor perception would be altered.

Investigator C. Ron Yu, PhD, and his team have identified a developmental window during which olfactory neurons of newborn mice can form a proper wiring map. They have shown that if incorrect neuronal connections are maintained after this window is closed, then regenerated cells will also be mis-wired.



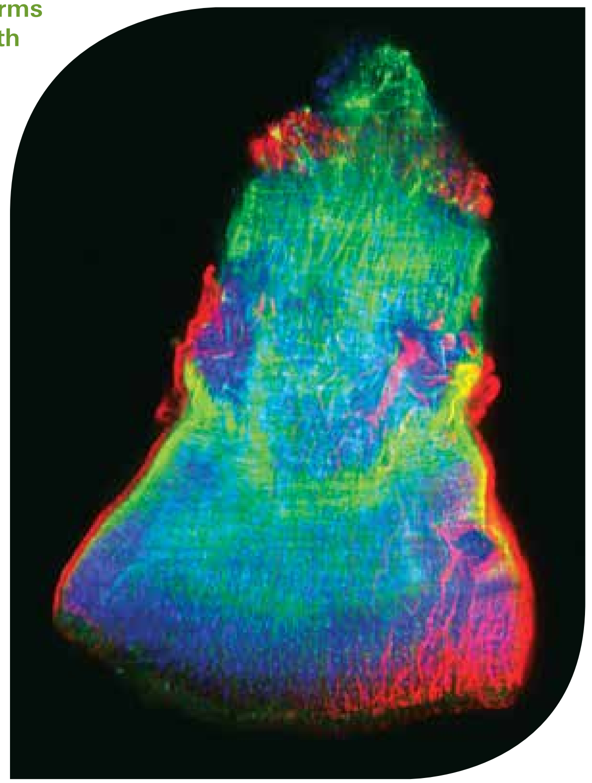
This work has potential implications for understanding the regeneration of other types of cells as well, such as for newly generated neurons that repair the brain or spinal cord.

"To repair a damaged spinal cord, you will need to ensure that newly generated motor neurons target the right muscle," says Yu. "The next goal is to identify the molecular cues that enable correct projections to be established."

The study was published in the April 11, 2014, issue of the journal *Science*.

PLANARIA DEPLOY AN ANCIENT GENE EXPRESSION PROGRAM IN THE COURSE OF ORGAN REGENERATION

It's hard to feel kinship with planaria worms, the tiny aquatic flatworms most often found in standing water and resembling brown tubes with rudimentary "eye-spots" and a feeding apparatus – the pharynx – that doubles as an excretory tract. And yet, the Sánchez Alvarado Lab has used them as a promising model system for accelerating mammalian regeneration.



"When mammals are severely injured, they just heal the wound and call it a day," explains Alejandro Sánchez Alvarado, PhD. A planarian, however, has the ability to heal injured areas and regenerate its body. This capacity is not what's surprising, as biologists know that thirty percent of planarian body cells are stem cells; the ability of these cells to identify what has been lost and regenerate the correct cells, however, has mystified researchers.

Stowers researchers shed light on this mystery by identifying the genes worms use to rebuild an amputated pharynx. They report that near the top of the pharynx regeneration hierarchy is a master regulator called FoxA and go on to reveal how planarian stem cells sense the loss of a particular structure on a molecular level.

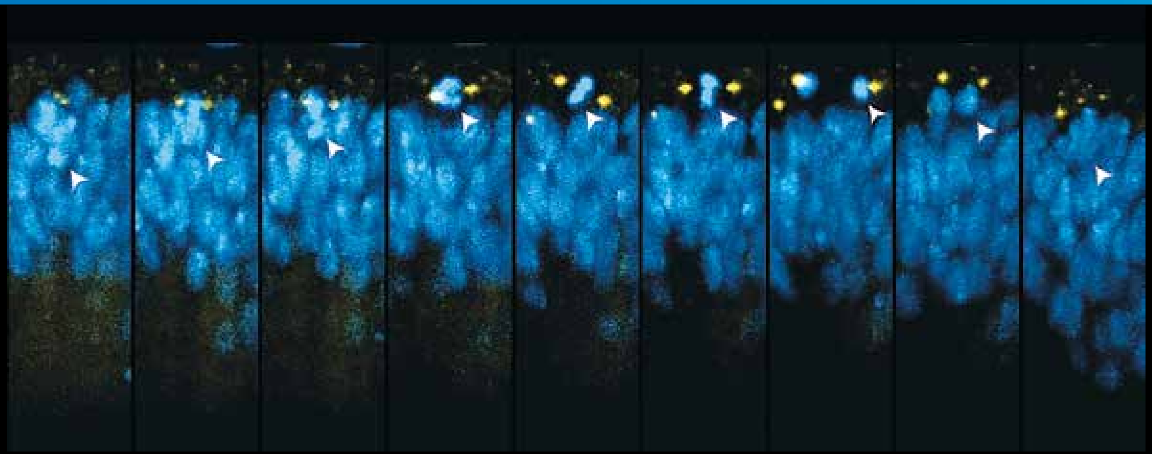
"Currently, we think that FoxA triggers a cascade of gene expression that drives planarian stem cells to produce all of the different cells of the pharynx, including muscle, neurons, and epithelial cells," says Carrie Adler, PhD, a postdoctoral fellow who led the study. "The next question is *how* FoxA gets stimulated in the first place in only *some* stem cells."

Beyond the newly identified role of FoxA, Sánchez Alvarado concludes that his lab's work cements planaria's place as a key model system to analyze regeneration or stem cell activity. "Planaria's simplicity is what makes it such a fruitful system," he says. "If we used salamanders for these studies it would take ninety days to do an experiment. I want answers to these questions *yesterday*, not years from now."

The study was published in the April 15, 2014 issue of the online journal *eLife*.

GOING GLOBAL:

STOWERS TEAM REPORTS GENOME-WIDE ANALYSIS OF GENES THAT DRIVE CELL DIVISION IN A MULTICELLULAR ORGANISM.



"Before, you sailed from place to place for hundreds of years establishing landmarks to create a map," Genomic Scientist Chris Seidel, PhD, says when equating modern genome mapping with using satellites and GPS for navigating the earth. Today, a few hours' worth of data collection offers a comprehensive, global view. Stowers Investigator Matt Gibson, PhD has taken full advantage of these advancements to explore gene expression during cell division and made some compelling discoveries.

Mitosis, the tug-of-war in dividing cells as duplicated pairs of chromosomes get dragged in opposite directions into daughter cells, occurs only after essential safety steps in the cell cycle. Almost any disease, from autoimmunity to neurodegeneration, is marked – if not caused – by some kind of cycle malfunction, making these quality control steps essential for proper cell division.

Halting abnormal cell division thus requires knowing where in the cell cycle genes should be active, a task pursued by the Gibson Lab as they undertook a genome-wide comparison of genes in fruit fly larval tissue that are expressed during these steps. Their work successfully catalogued over 300 genes differentially expressed in the cell cycle – a notable first in a multicellular organism.

"What was exciting was the plasticity we saw in cell cycle regulation of gene expression," says Liang Liang, the predoctoral researcher who led the Gibson Lab's efforts. "Every animal uses the same cell cycle machinery, but that machinery may be regulated very differently depending on the cell type, even in the same organism."

With a nod to the pioneers in the cell cycle field, Gibson pointed out that they "provided immense insight into how cell division works. Now we have tools to determine how that fundamental process is fine-tuned to operate in the complex and varied contexts present in a multicellular animal."

The study was published in the April 14, 2014, issue of the journal *Developmental Cell*.

By Carina Storrs

AISSAM IKMI, PHD:

INTERNATIONAL MAN OF BIOLOGICAL MYSTERIES

Aissam Ikmi was hooked from the first photograph of a mutant fly that he spotted in a textbook in college. Ikmi, with his penchant for science and visual learning, had already gravitated toward the subject of biology. But it was not until that moment in his junior year, staring down at a fly possessed of four wings instead of the normal two, that he knew he had to study how animals develop different body parts.

That epiphany moment might have come sooner, but where Ikmi grew up, in Agadir, a port city in Morocco, libraries would only let visitors see the specific books as requested by title. When he went to university in Paris, Ikmi could peruse all the titles he wanted in the school library. "This slight difference of giving access to books makes a big difference," Ikmi says.

For Ikmi, the difference certainly *was* big. After college, he stayed in Paris and headed directly into a master's degree program, then a PhD program, to study—what else?—animal development using fruit flies, or *Drosophila melanogaster*, a popular laboratory animal model system. He even managed to convince his mother and father, a housewife and an automobile mechanic, of the little flies' value and that there are things worth doing with flies other than ridding the kitchen of them.

"I told them that we are using flies to study relevant questions of human diseases and that, you know, flies can get diabetes too. They were surprised and impressed," Ikmi recalls. They might also have been a receptive audience. "My parents are always supportive if they see that I'm passionate about what I'm doing," he says.

But the questions that really electrify Ikmi run deeper than studying a single disease and get to the heart of how species have originated. For example, when in evolution did animals acquire a body part? What genetic changes happened to give an old part new or better function?

During his graduate research, Ikmi figured out, by mutating genes of interest in *Drosophila* and studying the animals' development, how the naturally occurring duplication of a gene endowed flies with more robust bristles on their thorax, which help them sense the environment, and thus has probably been naturally selected for.

While Ikmi pursued his big, bold research questions, he spent his free time in more light-hearted endeavors. One of Ikmi's favorite things to do in Paris was to cross the Seine river and take in a one-man comedy show in one of the little theaters in the northern parts of the city.

When it came time to find a lab for his postdoctoral research, Ikmi knew he wanted a break from bristles and gene duplication. For a while he had been beguiled by another big-picture question: Why are some animals huge and others tiny? With that in mind, Ikmi discovered the work of Stowers Investigator Matthew Gibson, PhD, who focuses in part on growth control in flies.

What absolutely convinced Ikmi to move across the Atlantic and join the Stowers Institute, though, was when Gibson told him that he was thinking of working with a type of animal that is not usually found in the lab, the sea anemone *Nematostella vectensis*. Ikmi immediately saw the potential for *Nematostella*, because it is thought to resemble an ancient ancestor shared by all animals, to offer exciting insights into how pathways that control growth have evolved in organisms such as flies and humans.

Gibson, on the other hand, was not so sure. "I tried to warn him off of this scientific question because it's a pretty risky enterprise," he recalls. "We needed functional tools and basic descriptive studies and all the foundational work for what Aissam wanted to study."

Hardly deterred, Ikmi joined the Gibson Lab for his postdoctoral research six years ago. Since then, he has developed tools, based on cutting-edge gene-editing systems such as CRISPR/Cas9 and TALENs, to manipulate genes–delete them or add to them–in sea anemone as seamlessly as researchers have been doing for decades in *Drosophila*.

Now Ikmi is starting to wield these tools, which he described in a paper he recently accepted for publication, to study tentacle growth in *Nematostella*. He has already added a fluorescent marker to genes to visualize which ones are expressed, and when, as new tentacles bud. Next up, he wants to turn his tools on genes involved in the animal's insulin pathway, and see which gene disruptions render the animal unable to make tentacles.

In retrospect, Gibson feels that Ikmi made the right decision to work on *Nematostella*, but only because he was so clever and relentless in setting up the system. The effort will hopefully pay off in spades. This type of gene editing "has really huge implications for the field of evolutionary developmental biology," Gibson says. "Historically the field has been very descriptive in nature...CRISPR opens up the possibility of manipulating genes and comparing their function between different species."

With a suite of questions that he can now tackle with the *Nematostella* system, Ikmi plans to apply for faculty positions at research institutes in France this fall. Although returning to Paris and its small theaters is appealing, Ikmi would be happy anywhere in France because he would be so much closer to his family.

In the meantime, Ikmi will continue to embrace life in Kansas City. Although previously never really a runner, he discovered that running is a great way to socialize and relax. He even races, and has a half marathon under his belt.

And if research and running weren't enough, he takes full advantage of the University of Missouri-Kansas City campus pool across the street from his lab. Being in the water brings Ikmi back to his boyhood in Morocco, where he did very little other than swim in the ocean and play soccer on the beach. In fact, if Ikmi were to envision a life outside of science, it would probably be connected to the water. "Being a fisherman would be great!" he says.

Sea anemones, Nematostella vectensis

ON COMMON GROUND

Joining the current crew of predoctoral researchers in the Stowers Institute Graduate School program are eleven new individuals who bring diverse backgrounds to the group: from growing up in one of the frigid, northern-most areas of China near the Russian and Mongolian borders, to working a variety of side jobs including drapery installer and door-to-door salesman to finance a college education.

Diverse, too, are their research experiences: from analyzing oncogenic mutations in lung cancer to comparing cyanobacteria strains found in rivers. Yet common to all is a choice to expand their scientific knowledge and research experiences through the Stowers graduate program.

Raquel Barajas Azpeleta was introduced to the Stowers graduate program by a fellow Madridian. While her first trip to the United States, for her interview at the Institute, was nerve-racking, it was confirmation that she had found a place where she could realize her scientific goals.

Cheng-Yi Chen is fascinated by regeneration. He even helped pioneer an emerging model, the segmented worm *Aeolosoma*. Not surprisingly, it was the regeneration work of the Sánchez Alvarado Lab that first captured his interest in the Institute.

Matthew Christenson may not have ever considered a career in science had it not been for a torn ACL and the physical therapy that ensued where he discovered the world of biomedical science. After briefly considering pre-med studies, a genetics course turned his interests to research.

Gerald Dayebga Doh is certain he will weather the cultural transition of moving to the United States well once he finds a market that sells the right kind of cornmeal for his favorite Cameroonian dish, fufu.

Darrick Hansen is a globetrotter. He's lived in various parts of the United States, Aruba, Singapore, Scotland, and England. But he's happy to call Kansas City home for the next five years.

Shuonan He credits a devastating fire at Peking University that destroyed his research project with making him a better scientist. With his research temporarily curtailed, he had time to attend more seminars and learn more about other fields of science.

Get to know this diverse group of 2014 predoctoral researchers at www.stowers.org/gradschool/predocs

Yanfeng He became interested in science while competing in his high school's Science Olympiad. With that same competitive spirit, He went on to compete on a collegiate level in the International Genetically Engineered Machine competition (iGEM).

Ahmet Can Karabulut was encouraged by colleagues at Seattle's Fred Hutchinson Cancer Research Center to apply to the Stowers graduate program. His parents are thrilled that the move from Seattle will provide a sunnier climate and be 2000 miles closer to home in Tarsus.

Xingyu Liu was a standout science student in high school. But during her undergraduate years, it was a failed experiment that provided the most valuable lesson when a hypothesis she proposed didn't hold up.

Linhao Ruan shouldn't have trouble with time management in the Stowers graduate program. For his undergraduate degree he pursued dual majors, while serving as President of the Student Union at his university and graduating valedictorian in a class of 7300.

Karla Yadira Terrazas plans to pay it forward when she completes her graduate degree and postdoc. Her pursuit of science was supported by a young scientist initiative at the University of Texas-San Antonio, so she wants to give back in the best way she can. She plans to teach.

Back row: Linhao Ruan, Yanfeng He, Matthew Christenson, Cheng-Yi Chen
Middle row: Raquel Barajas Azpeleta, Gerald Dayebga Doh, Karla Yadira Terrazas, Xingyu Liu
Front row: Darrick Hansen, Shuonan He, Ahmet Can Karabulut

STOWERS RESEARCHERS RACK UP AWARDS

Once again, KUMC graduate students conducting research in labs at the Stowers Institute were awarded prizes at the University of Kansas Medical Center Student Research Forum. This multi-day event, similar to the Stowers Young Investigator Research Days, highlights the research of students studying in medical and biological disciplines.

Naomi Tjaden, an MD-PhD student based in the Trainor Lab received a first place award for her poster in the Poster Session II competition. The winning poster described Tjaden's research of retinoic acid, a metabolite of vitamin A, which affects the migration of neural crest cells to locations in the intestinal tract. When neural crest cells don't develop properly and colonize the nervous system of the gastrointestinal tract a condition known as Hirschsprung disease may result. This disease occurs in 1/5000 live births, and typically requires surgical resection of the bowel. Tjaden believes that gaining a greater understanding of the role of retinoic acid to intestinal development may lead to innovative non-surgical treatment approaches to reduce the occurrence of this common congenital disease.

Conaway Lab student **Rushi Trivedi** received the Joe R. Kimmel Award. This award recognizes the most outstanding research presentation by a student in the University of Kansas Medical Center Biochemistry and Molecular Biology Department. Trivedi captured the prize with his presentation on the regulation of ALC1 (Amplified in Liver Cancer 1), encoded by a suspected cancer-causing gene and a member of the SNF2 ATPase superfamily of proteins that contains a SNF2 ATPase domain and a regulatory *macro* domain. Trivedi's project focused on a small patch of amino acids that was previously thought to act only as a simple linker of these domains. His research revealed within that linker potential regulatory elements including a DNA binding region that could facilitate communication between two structurally independent domains and help regulate the SNF2 ATPase. With this discovery Trivedi is concentrating on better understanding the regulatory mechanism of ALC1 which could ultimately be useful in developing drug therapies for liver cancer.

WEB SPECIAL:

Biological treasure hunters

To the untrained eye /baɪoʊˌɪnfərˈmætɪks/ appears as an unfamiliar language or maybe even gibberish, but to a linguist it is a systematic representation of the sound that the letters B I O I N F O R M A T I C S make.

Just as linguists can identify the sound of individual letters from phonetic notation and combine it with other sounds to create a recognizable word, a bioinformatician can extract and identify meaning from massive sets of biological data that might also appear to the untrained eye as gibberish.

As modern scientific techniques such as DNA sequencing produce vast amounts of information about genes, proteins, nucleotides and amino acids, a relatively new form of science called bioinformatics has developed.

Left to right: Interns Kirsten Gotting, Ben Story, Vasha Duttel, Summer Elasady.

Bioinformatics scientists or bioinformaticians are trained to use computational tools and statistical methods to sort through mountains of biological data to visualize data and find meaning in the patterns that emerge. And by revealing the behavior of individual genes and proteins within genomes, they can provide researchers a better understanding of biological processes.

"Bioinformatics scientists are a bit like biological treasure hunters," says Chris Seidel, PhD, who in his role as genomics scientist works closely with bioinformaticians to optimize analysis strategies for experiments that involve massive data. "They have to sort through all the sand to find the nugget of gold that reveals a bigger treasure."

In a collaborative internship program with the University of Oregon aimed at producing highly trained bioinformaticians, four master's level students have spent the better part of a year embedded in Stowers labs learning and refining biological, statistical, and computational skills and applying them to biological questions posed by our scientists.

Learn about this program, what motivated these students to pursue a degree in the field of bioinformatics, what they hope to achieve, and how training at Stowers has influenced them by visiting www.stowers.org/stowers-report/fall-2014/bioinfo

HHF RENEWS SUPPORT FOR TATJANA PIOTROWSKI'S RESEARCH ON HAIR CELL REGENERATION

Through its Hearing Restoration Project (HRP), the Hearing Health Foundation is continuing to fund a study co-led by Associate Investigator Tatjana Piotrowski, PhD, that aims to characterize the molecular mechanisms underlying regeneration of sensory hair cell populations along the zebrafish lateral line. Lateral line hair cells are similar to mammalian inner ear hair cells that enable hearing, but in contrast to mammalian hair cells, lateral line hair cells regenerate after damage.

HRP scientists are part of a consortium that emphasizes collaboration across multiple institutions, with the goal of developing new therapies for hearing loss. Several ongoing HRP projects have generated large data sets illuminating the transcriptomes—which reflect all the genes being actively expressed at any one time—of hundreds to thousands of chicken and mouse hair and support cells.

Since their study took off in 2012, Piotrowski's group has produced similarly extensive information for zebrafish. They will now apply the power of bioinformatics in cross-comparing and mining these data sets. Their overarching goal is to identify key genes and biochemical pathways that trigger hair cell regeneration in non-mammals like zebrafish and chickens, while simultaneously searching for mammalian genes that block this important process. They hope to use the knowledge gleaned from non-mammals to one day direct hair cell regeneration—first in mice, then ultimately in humans.

MARCH OF DIMES FUNDS JENNIFER GERTON'S RESEARCH ON COHESINOPATHIES

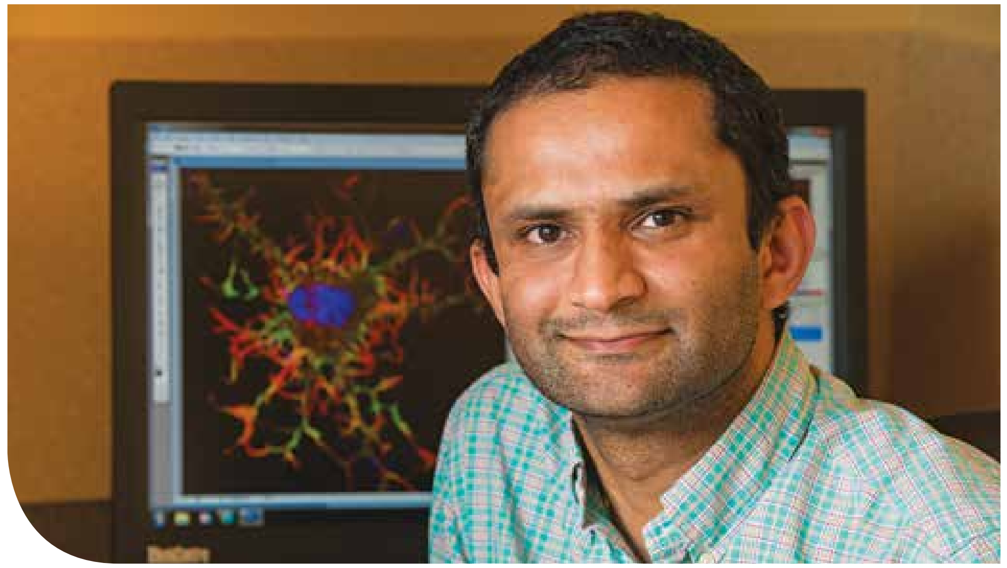
The March of Dimes Foundation has awarded Investigator Jennifer Gerton, PhD, a three-year grant to study Cornelia de Lange Syndrome (CdLS), a genetic disorder caused by mutations in the cohesin complex. It is present but not always diagnosed at birth, and associated with a wide range of developmental abnormalities.

Besides regulating the separation of duplicated chromosomes during cell division, cohesin interacts with chromosomes at many other regions to influence their function. For instance, it regulates the production of ribosomal RNA and the organization of the ribosome factory, which ultimately affects translation. Gerton hypothesizes that cohesin mutations, in affecting translation, ultimately contribute to changes in gene expression that drive cohesinopathies like CdLS.

Using zebrafish models and human CdLS cell lines, Gerton will examine both the mTOR pathway, key in regulating translation; and p53, a major cell cycle regulator. She has preliminary evidence for a pattern of p53 activation and mTOR inhibition in this disorder. She will also determine if the amino acid L-leucine ameliorates some of the effects seen with CdLS and ribosomopathies, another group of inherited disorders where translation is defective.

First established by Franklin D. Roosevelt to combat polio, the March of Dimes Foundation took on birth defects prevention in 1958, a mission that now encompasses every level of perinatal health.

PROCRASTINATION PAYS OFF



It's not everyone who enjoys the complicated theories or the perplexing language of science, but ***one aspect of science that anyone can enjoy is the spectacular images of life captured through the lens of a microscope.*** Today's imaging and visualization techniques allow scientists to not only peer into the microscopic world, but to capture and share the beauty that lies hidden within.

From June through November of this year, travelers from all corners of the world who traverse the corridors at Washington Dulles International Airport have been treated to forty-six of the most stunning images of modern science. What began as an effort to improve the aesthetics of airport corridors and introduce visitors to public art became a public science lesson when the Metropolitan Washington Airports Authority's Arts Program teamed up with the National Institute of General Medical Sciences (NIGMS) and the American Society for Cell Biology (ASCB).

Hundreds of scientists heeded the call when the ASCB and NIGMS organized and publicized an image competition and exhibition dubbed "Life: Magnified". For one Stowers scientist, a heavy experimental workload combined with the time-consuming process of applying for postdoctoral positions, meant the idea of submitting an image had to be placed low on his list of priorities.

Praveen Suraneni, PhD, who completed his graduate degree through the Open University program in the Rong Li Lab at the Stowers Institute and has started postdoctoral training in the Department of Medicine at Northwestern University, explained that on the final day for submissions, a lab mate's reminder sent him scrambling. To meet the deadline, he had to select among his own images for the one that was "the most visually appealing, but also told a great story."

Suraneni settled on an image of a fibroblast. While a normal fibroblast, which is a connective tissue cell that is important in wound healing, has smooth edges with properly functioning lamellipodia that motor the cell along, Suraneni found an image of a disabled fibroblast far more striking. His selection lacked a protein necessary for proper development of the cell's skeletal structure; the result is a cell replete with jagged looking, tentacle-like appendages with no ability for normal cell movement. And with only minutes to spare, Suraneni uploaded his image, went back to his other work and thought little more of the competition.

Imagine his surprise when weeks later, Suraneni was notified that his image had been selected from over 600 others to be one of the forty-six for display. "What an honor! I knew I had a great image," shares Suraneni, "but I imagined there were lots of great images." Investigator Rong Li was equally delighted. "These images are so captivating you can't help but want to know more about them," she says. "This provides scientists a valuable opportunity to spark interest and educate the public about our work."

Not only will an estimated 1.5 million people pass by Suraneni's eye-catching image at Dulles, even more have an opportunity to view it online. Impressed with the images in the Dulles exhibit, NIH Director Francis Collins is also featuring several on his own blog (http://directorsblog.nih.gov/2014/07/).

RONG LI RECEIVES NINDS FUNDING TO STUDY ANEUPLOIDY'S IMPACT ON NEURONAL CELL BEHAVIOR

The National Institute of Neurological Disorders and Stroke has given Investigator Rong Li, PhD, a two-year award to probe the effect of having different numbers of chromosomes (aneuploidy) on brain cell development and function. These cells exhibit an unusual level of diversity in their chromosome numbers, Li says, which could contribute to the likes of learning, cognition, and other complex functions. Even within one neuronal cell type, variations at the individual level can be found. Li hypothesizes that aneuploidy, a form of genetic diversity, could be a source of the functional diversity of brain cells. Specific aneuploidy karyotypes, or chromosome numbers, could even prove advantageous under certain acute stressful conditions.

Using mouse neuronal stem cells, Li's team will examine questions encompassing aneuploidy's effect on neuronal development, from growth through differentiation; changes in gene expression as a result of altered chromosome dosage; and whether aneuploidy plays a role in how neurons respond to different kinds of stress.

"Aneuploidy is usually associated with disorders like cancer or congenital birth defects, but normal brain cells can also be aneuploid," Li says."It's intriguing to think that aneuploidy may actually confer important beneficial effects during development and normal organ function, while its dysregulation could drive some diseases. It's an idea we'll explore with this project."

POSTDOCTORAL RESEARCHER EARNS K99 AWARD FROM THE NATIONAL CANCER INSTITUTE

Hans-Martin Herz, PhD, was selected to receive a Pathway to Independence award from the National Cancer Institute. This two-phase award is designed to facilitate, even speed the transition of promising post-doctoral fellows to fully-fledged investigators: they are first provided up to two years of mentored research support (K99 phase), followed by three years of their first independent research support (R00 phase) in an approved tenure-track or equivalent faculty position.

Herz is studying the role of *Drosophila* Trithorax-related (Trr) and its human homologs, MLL3/MLL4, in enhancer-mediated tumor formation. Enhancers are DNA elements that regulate tissue-specific gene expression; the enzymes MLL3/MLL4 function at enhancer regions. There, they decorate histones—responsible for rendering DNA inaccessible, or uncoiling it to allow gene expression—at a particular location, H3K4, with a methyl group. MLL3/MLL4 are frequently mutated in leukemia and other cancers, which is thought to result in malfunctioning enhancers and, therefore, dysregulated gene expression. Herz wants to identify the specific enhancer-mediated processes that are misregulated in cancers bearing MLL3/MLL4 mutations, which they hope might lead to the development of specific drugs targeting these processes.

KAUSIK SI AND MARCO BLANCHETTE LAND FIVE-YEAR NIMH AWARD

The National Institute of Mental Health, through its Research Project Grant (RO1) program, will fund the joint foray of Associate Investigator Kausik Si, PhD, and Genomics Scientist Marco Blanchette, PhD, into the molecular whys and wherefores of long-term memory formation.

Si and Blanchette are studying Orb2, a protein that, in the fruit fly brain, stacks up to help stabilize new synaptic connections formed to consolidate information into more permanent storage. Orb2 comes in two forms, of which one, 2A, may be a critical determinant of whether a learned experience becomes a stable memory. They have observed that the immature, unspliced transcript for Orb2A is prevalent in fruit flies not trained to retain a long-term association of specific chemicals with food. But spliced, protein-coding Orb2A transcript levels increase after such training, and the researchers have identified Nova, an RNA-binding protein, as a potential player in this event. They hypothesize that Orb2 transcript splicing and maturation, mediated by Nova, is important for long-term memory.

"We want to find out what engages this process, whether it's needed continuously for memory maintenance over time, and how it's regulated," Si says. "Perhaps one day this will help us understand memory-related diseases."

American Century Championship 25 YEARS

Charles Barkley, Annika Sorenstam, John Elway, Ray Romano, Denny Hamlin, Bode Miller, Jack Wagner, Alex Smith... just a small subset of the eighty celebrities who gathered this summer to enjoy golf and good times at the American Century Championship near Lake Tahoe in the scenic Sierra Nevada mountains. For twenty-five years, this annual golf tournament has offered a chance for the public to mingle with sports and entertainment legends, and has also raised substantial funds—about $4.2 million over the years—for charitable organizations.

This year, tournament title sponsor American Century Investments (ACI) honored the memory of their founder Jim Stowers, Jr., who passed away earlier this year, by naming the Stowers Institute as the tournament's national beneficiary. Stowers President and CEO David Chao, PhD, attended the event. As an invited speaker, Chao shared some of the latest research from the Institute and from BioMed Valley Discoveries with American Century clients.

"Jim was an amazing person who focused his entire life on helping others," said Jonathan Thomas, president and chief executive officer of American Century Investments. "In tribute to Jim and his unparalleled generosity, we were proud to direct a portion of the 2014 proceeds to the Stowers Institute."

The week-long event, owned and broadcast by NBC Sports, drew nearly 40,000 people to Edgewood Tahoe Golf Course in Stateline, Nevada. Former NFL quarterback Mark Rypien won the event, and Jeremy Roenick and Annika Sorenstam tied for second place.

"The American Century Championship is known for its high-profile sports heroes and celebrities," said Thomas. "But, thanks to his achievements in business and life sciences, and the enduring legacy he left the world, Jim Stowers is as big a star as any hall-of-fame athlete or award-winning actor."

DON'T CALL IT PING PONG

Table tennis is serious business for participants in the Kansas City Corporate Challenge competition. Many competitors arrived at the event equipped with custom paddles and extra practice balls. Some even donned special athletic shoes designed especially for the sport. For one Stowers member, it was a bit less serious. She just wanted to have fun participating in a sport that she had learned from her grandmother and grown up playing with her siblings. Nonetheless, former Sánchez Alvarado Lab Research Tech Carolyn Kaufman took first place in the women's single event.

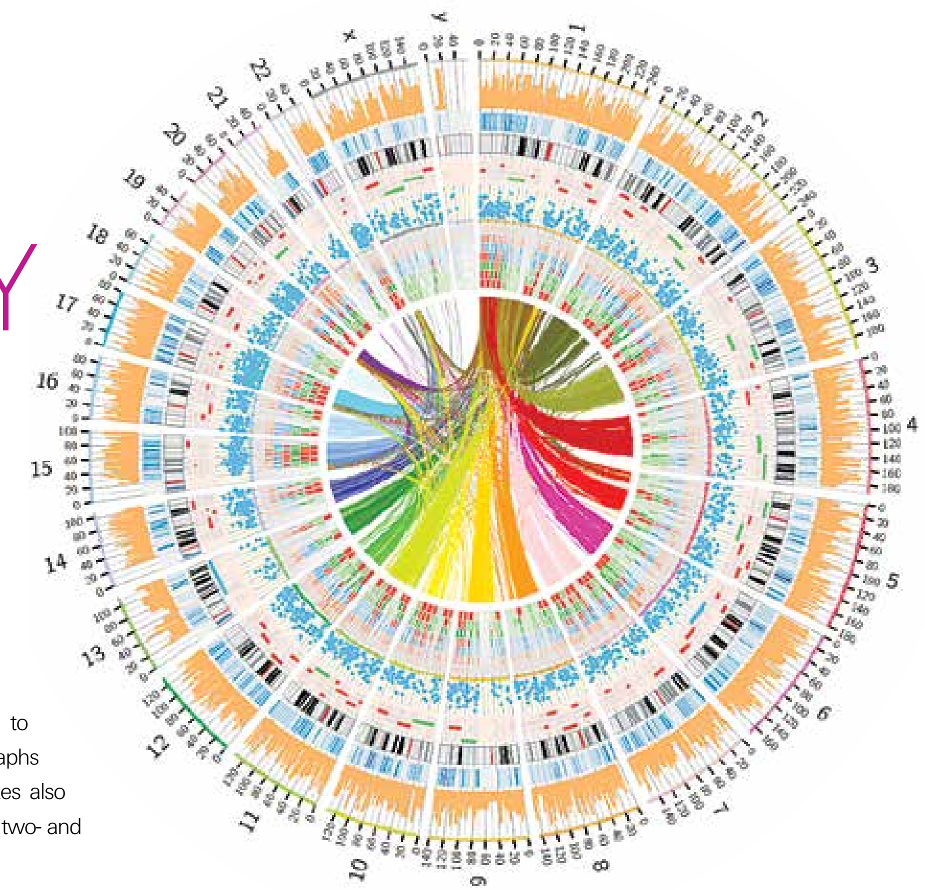
The Corporate Challenge is designed to promote health, wellness, camaraderie, and a spirit of corporate competition through organized sporting events.

BASIC RESEARCH
TEAM SIMR
HOPE FOR LIFE

"It was exciting to get out there and participate in something I enjoy and represent Stowers in such a positive way," says Merry McLaird, lab manager of the Conaway Lab. McLaird competed in multiple swimming events, finishing first in her age group and division in backstroke, butterfly, and individual medley. "Participating on the Stowers relay team was a great opportunity for me to get to know some of my co-workers better, too."

From April through June this year, nearly 150 Stowers Institute members competed in a variety of Corporate Challenge events, including bowling, softball, volleyball, horseshoes, darts, and golf. And although not everyone or every team walked away with a win, many Stowers members enjoyed their participation and left with a heightened sense of camaraderie.

MORE THAN A GAME OF PICTIONARY



Draw me a picture. Have you ever been asked to do this when explaining a complicated idea or concept? That is just what researchers were asked to do for this years' Young Investigator Research Days (YIRD) Data Visualization competition. But when you ask a scientist with advanced visualization tools to do this, you get more than a doodle or stick figure drawing.

Researchers regularly use a variety of scientific software to simplify and represent data that is abstract and complex. Bar graphs and scatter plots are common fare, but researchers' toolboxes also contain tools such as interaction maps, Voronoi diagrams and two- and three-dimensional imaging.

The first place winner of the 2014 inaugural event, Kobe Yuen, a predoctoral researcher in the Gerton Lab, used a bioinformatics software program to show the results of ChIP-seq experiments which reveal where protein binding occurs on DNA.

In his visualization, the outer orange histogram shows the binding of Nipped-B-like (NIPBL) protein in the genome of human B cells. The blue scatter plot shows the enzyme Pol II binding and the heat map shows the distribution patterns of different proteins and protein modifications.

By comparing a side-by-side visualization of his experimental results, Yuen was able to extrapolate that "the binding of NIPBL is strongly correlated with Pol II and may, in fact, play a role in Pol II dependent gene expression."

Another winning visualization technique that has gained mainstream popularity uses the Wordle web application to plot a frequency map in the form of a word cloud. Rushi Trivedi, a graduate student in the Conaway Lab, mined PubMed, a clearinghouse of scientific publications, for titles of all Stowers Institute published papers.

Using font size, he represented the 150 most frequently occurring scientific terms. The larger the word, the more frequently it appears. "I think the word cloud provides a clear picture of the focus of research at Stowers," explains Trivedi. "Words like cells, protein, genes, histones, development, signaling represent the basic scientific focus of our research." View this and other winning scientific and data visualization images at www.stowers.org/yird2014.

YIRD event winners include:

Poster Session I:
WINNER – Yuichiro Nakajima (Gibson Lab)
RUNNER-UP – Takuya Akiyama (Gibson Lab)
HONORABLE MENTION – Swaminathan Venkatesh (Workman Lab)

Poster Session II:
WINNER – Andres Romero-Carvajal (Piotrowski Lab)
RUNNER-UP – Wanqing Shao (Zeitlinger Lab)
HONORABLE MENTION – Kristi Jensen (Baumann Lab)

Oral Session I:
WINNER – John Perry (Linheng Li Lab)
RUNNER-UP – Elizabeth Duncan (Sánchez Alvarado Lab)

Oral Session II:
WINNER – Liying Li (Si Lab)
RUNNER-UP – Longhua Guo (Sánchez Alvarado Lab)

Image competition:
1st place: Sarah Elliott (Sánchez Alvarado Lab)
2nd place: Ryan Mohan (Workman Lab)
3rd place: Praveen Suraneni (Rong Li Lab)

Data visualization:
1st place: Kobe Yuen (Gerton Lab)
2nd place: Rushi Trivedi (Conway Lab)
3rd place: Mihaela Sardiu (Proteomics)

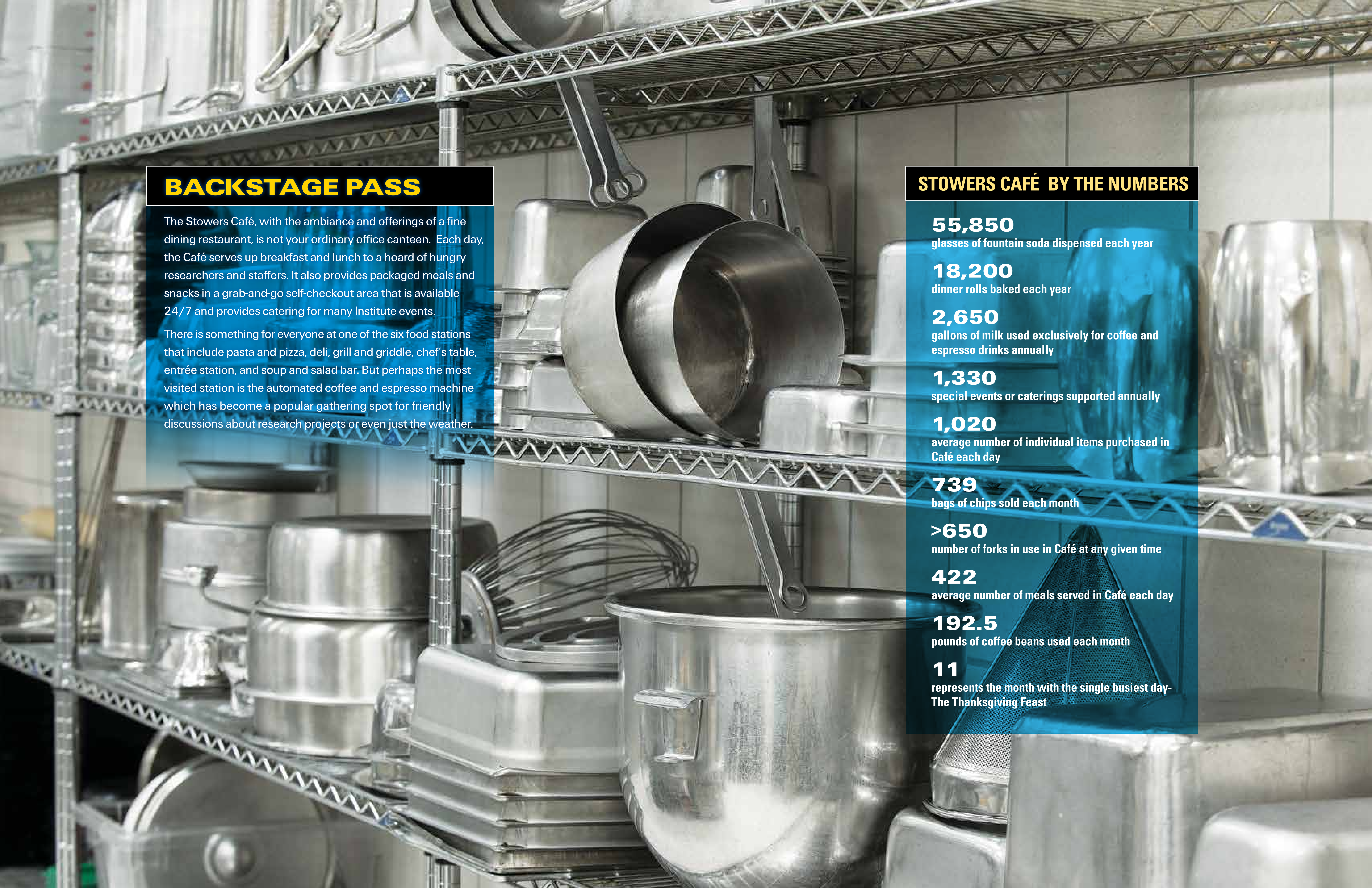
Most Popular Oral Session I selected by members
Tamara Potapova (Rong Li Lab)

Most Popular Oral Session II selected by members
Rushi Trivedi (Conaway Lab)

Most Popular Poster Session I selected by members
Juston Weems (Conaway Lab)

Most Popular Poster Session II selected by members
Parama Paul (Rong Li Lab)

YIRD Award for Highest Scientific Representation by a Lab
Rong Li Lab



BACKSTAGE PASS

The Stowers Café, with the ambiance and offerings of a fine dining restaurant, is not your ordinary office canteen. Each day, the Café serves up breakfast and lunch to a hoard of hungry researchers and staffers. It also provides packaged meals and snacks in a grab-and-go self-checkout area that is available 24/7 and provides catering for many Institute events.

There is something for everyone at one of the six food stations that include pasta and pizza, deli, grill and griddle, chef's table, entrée station, and soup and salad bar. But perhaps the most visited station is the automated coffee and espresso machine which has become a popular gathering spot for friendly discussions about research projects or even just the weather.

STOWERS CAFÉ BY THE NUMBERS

55,850
glasses of fountain soda dispensed each year

18,200
dinner rolls baked each year

2,650
gallons of milk used exclusively for coffee and espresso drinks annually

1,330
special events or caterings supported annually

1,020
average number of individual items purchased in Café each day

739
bags of chips sold each month

>650
number of forks in use in Café at any given time

422
average number of meals served in Café each day

192.5
pounds of coffee beans used each month

11
represents the month with the single busiest day-The Thanksgiving Feast