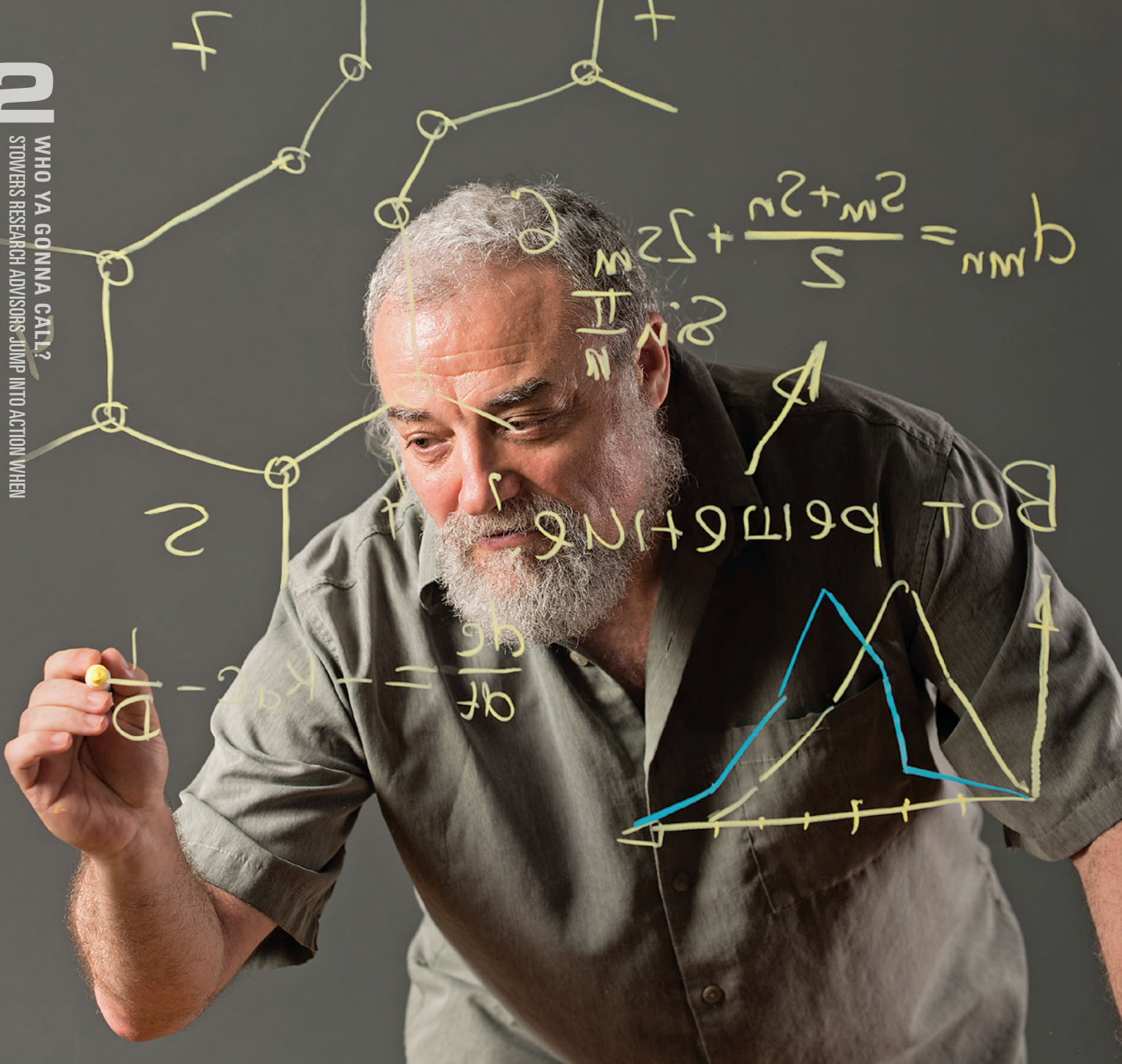




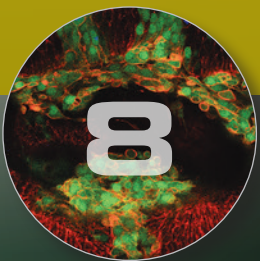
WHO YA GONNA CALL?
STOWERS RESEARCH ADVISORS JUMP INTO ACTION WHEN
COMPLEX PROBLEMS REQUIRE HIGHLY SPECIALIZED EXPERTISE



STOWERS REPORT

NEWS AND INSIGHT FROM THE STOWERS INSTITUTE FOR MEDICAL RESEARCH

FALL 2013



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PUBLISHED BY THE STOWERS INSTITUTE FOR MEDICAL RESEARCH
FALL 2013



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CONTRIBUTORS:

Gina Kirchweger
Editor

Kristin Kessler
Assistant editor

Elise Lamar
Alissa Poh
Contributing writers

Juan Carlos Grover
Web editor

Linda Flynn
Copy editor

Miller Medical Art
Scientific Illustration

Mark McDonald
Don Ipock
Photography

Kuhn & Wittenborn
Design and production

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In perspective



BY DAVID CHAO, PHD
PRESIDENT AND CEO

In modern biological research, new technologies and methods are growing ever more important as scientists ask increasingly probing and comprehensive questions.

From the beginning, Jim and Virginia Stowers recognized that surrounding researchers with sophisticated, cutting-edge technology would be a necessary condition for building a world-class research institution. Rapid, convenient, and well supported access to technology has remained a critical cornerstone of the institute's operating philosophy. Today, the institute dedicates about a third of its annual scientific budget to its technology centers and core facilities. This heavy investment in technology provides members with ready access to some of the world's most advanced instrumentation, some of which is custom-built and not yet commercially available.

Hundreds of years ago, science was often a solitary pursuit. Individuals might need to grind their own lenses for a handheld microscope and record observations with their own pen and ink drawings. The institute's most recently purchased million-dollar super-resolution microscope is a good example of how much things have changed. For centuries, microscopes could not resolve features closer together than the wavelength of light, the so-called "diffraction limit." When viewed with a standard microscope, features below the diffraction limit blur together and cannot be visually separated. With some clever optical tricks, the institute's new super-resolution microscope enables observations well beyond the diffraction limit. Unlike the classic image of a scientist alone in the laboratory, breaking through the diffraction limit requires coordinated

contributions from biologists, physicists, IT experts, and software engineers.

In addition to investing heavily in technology, Jim and Virginia Stowers were equally committed to following an enterprising approach. In their vision for the institute, innovation and initiative apply just as much to its culture and organization as they do to its technological infrastructure. For instance, in response to the need for individuals with the skills and personality to work across different disciplines, the institute created research advisor positions. Unique to Stowers, these highly trained specialists act as internal consultants to help scientists develop and apply novel methods to solve biological problems. Positioned at the intersection of research labs, technology centers, and core centers, research advisors share expert perspectives, offer specialized skills, and facilitate interactions among groups with expertise in different disciplines.

Articles in the following pages introduce some of our resident research advisors and highlight the many ways their knowledge has proved indispensable for different research projects' success. In this issue, we also celebrate Peter Baumann's selection as a Howard Hughes Medical Institute Investigator and Jerry Workman's election to the American Academy of Arts and Sciences. I hope you will enjoy reading about the institute's enterprising approach, its focus on teamwork and technology, and some of our recent individual and collective accomplishments.

By Elise Lamar, PhD

WHO YA GONNNA CALL?

TECHNOLOGY SPEEDS DISCOVERY, BUT ONLY IF YOU KNOW HOW TO USE IT. THREE HIGHLY SKILLED STOWERS SCIENTISTS OFFER UNIQUE SOLUTIONS TO RESEARCHERS' TECHNICAL DILEMMAS. AND YES, THEY MAKE LAB CALLS.



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Boris Rubinstein
"The Modeler"
MS in nuclear physics
PhD in optics

Brian Slaughter
"The Experimentalist"
BA in chemistry
and mathematics
PhD in chemistry

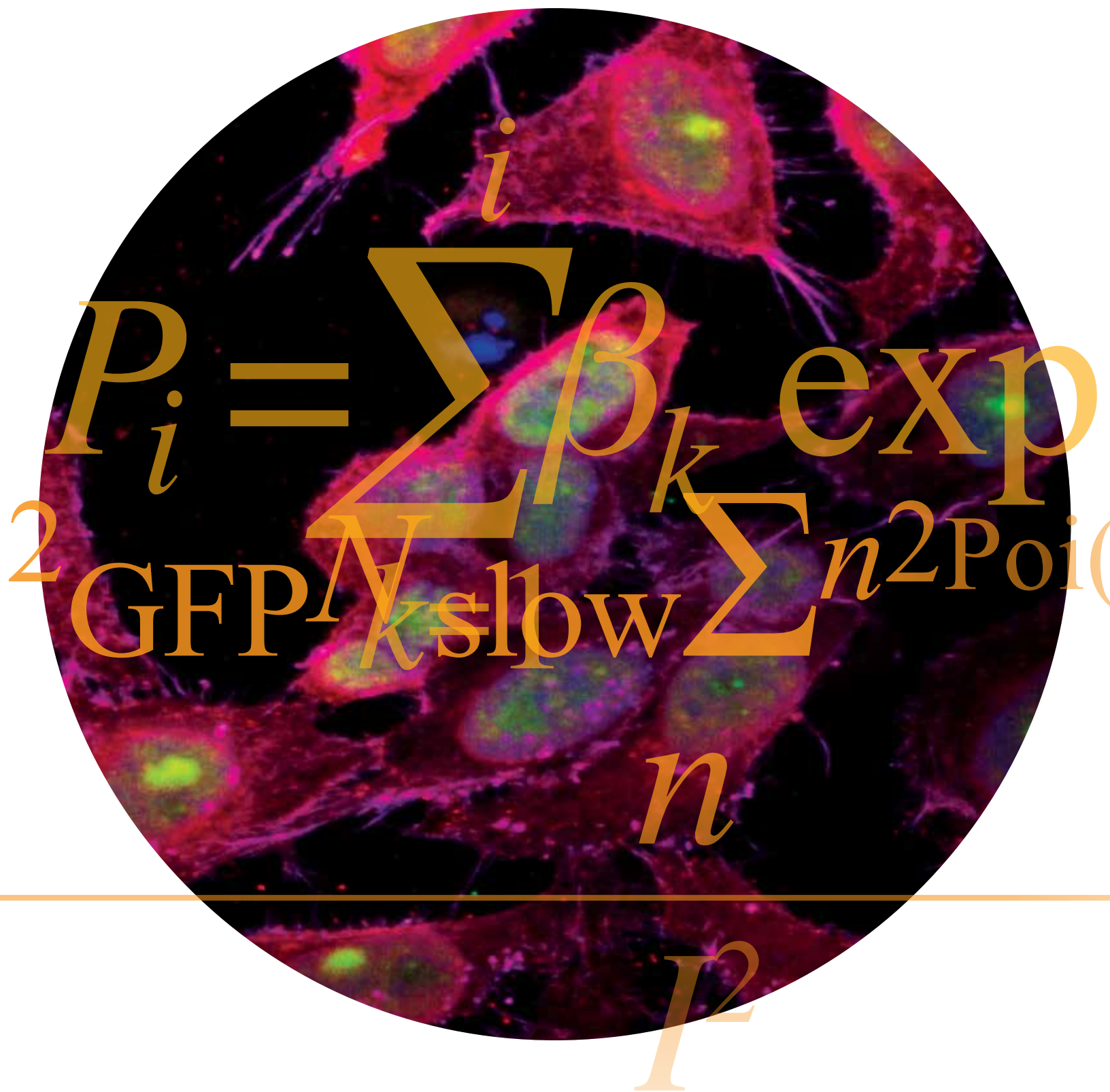


Jay Unruh
“The Programmer”
BS in biochemistry
PhD in chemistry

Associate Investigator Kausik Si, PhD, was on the cusp of a major discovery but at his wits' end. His lab had mountains of data showing that a self-aggregating protein in the fruit fly brain formed the very basis of long-term memory. Si was poised to report this ground-breaking story. But there was a problem.

Biochemical evidence indicated the memory protein had to be present on nerve cells, but Si's team couldn't detect it microscopically. This was no small matter—submitting a paper without this crucial evidence would be tantamount to announcing you've discovered a new planet that nobody can see. Unbelievable.

Si mentioned the problem to Brian Slaughter, PhD, and Jay Unruh, PhD, who work on his floor and act as in-house consultants known as research advisors. They sat down with members of his lab and applied a microscopy technique called spectral imaging to image fly nerve cells while filtering out noise created by the sea of other proteins. The effort paid off, and the study, including an image showing dots of the memory protein peppering the connection points between nerve cells in a fly brain, was published in *Cell* in early 2012.



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The architects

Almost four years ago, Stowers Scientific Director Robb Krumlauf and President and CEO Dave Chao came up with the concept of research advisors. Their goal was to attract PhD-level scientists with specialized skills as full-time consultants to faculty on highly technical matters, something unusual at an academic institution.

“Other institutions had difficulty defining positions like this,” says Krumlauf, explaining that most PhD-level scientists in academia either teach or do independent research. “But we wanted to provide hands-on advice on the application of cutting-edge technology in-house to Stowers faculty and at the same time find ways to acknowledge and reward these people for their talents.”

Stowers now employs three research advisors: Slaughter and Unruh, whose expertise is in microscopy, and mathematician Boris Rubinstein. “We want research advisors to help faculty in ways they haven’t even imagined,” says Krumlauf. “If you think of faculty members as homeowners, then the research advisor could be the architect who translates their dream into a design.”

Wanted: multitaskers

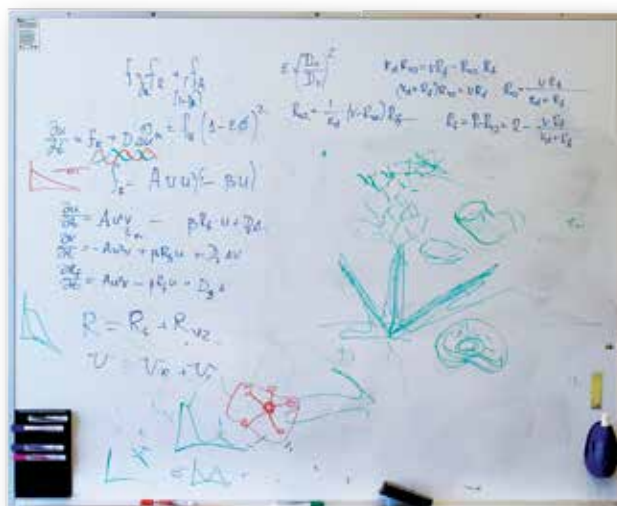
Keeping a diverse faculty of twenty “homeowners” happy demands tremendous intellectual flexibility. Rubinstein, Slaughter, and Unruh routinely consult with faculty working in model organisms as diverse as yeast and zebrafish. They also simultaneously ponder questions as seemingly unrelated as how *Drosophila* cell shape guides cell division to how yeast nuclear proteins pull chromosomes apart.

Slaughter says his average day could include teaching a postdoc to use a new technique on a microscope, attending an investigator’s lab meeting, analyzing data by himself, and then kicking back to stay up with scientific literature. Unruh is more specific: “I spent half of today writing chromosome-counting software for Rong Li’s lab and the other half counting centromere spots for the Hawley lab. But I usually do about five things at a time.”

Research advisors also spend a lot of time informally educating faculty and students about ways to address a problem. “All these guys are just great teachers,” says Stowers Investigator Rong Li, PhD, who works frequently with all three. “I have a white board in my office that Boris occupies. He writes out his equations for my students and postdocs in the nicest handwriting. What he puts there, stays there.”

Brian and Jay

Slaughter and Unruh became microscopy research advisors in 2010 and now often work together, so much so that most Stowers faculty refer to them as a unit. Both earned chemistry PhDs from the University of Kansas, but their skills span very different areas of expertise. Unruh was a postdoc at the University of California, Irvine, where he applied fluorescence microscopy to mammalian cells, while Slaughter studied yeast cell asymmetry as a postdoc with Li before moving into the research advisor position.



The whiteboard in Rong Li’s office bears witness to Boris Rubinstein’s frequent visits.

"Jay is an incredibly talented programmer. He writes all our software, while I struggle to program my alarm clock," says Slaughter. Unruh calls Slaughter the "experimentalist." "I consider Brian one of the world's experts on advanced microscopy in budding yeast, which comes in quite handy around here."

Currently, about a third of the labs at Stowers use yeast as a model system, among them the lab of Associate Investigator Jennifer Gerton, who studies cell division. She focuses on a chromosomal structure called the centromere, which in yeast and vertebrates is part of a complex that pulls chromosomes into daughter cells during cell division. A year ago researchers in her field still argued about how many molecules of the yeast protein resided in each chromosome twisted into a centromeric knot and if that number could vary.

Gerton, who relies primarily on biochemistry and genetics, asked Unruh and Slaughter if microscopy could resolve the question. They suggested combining two approaches—brightness measurements and a method known as fluorescence correlation spectroscopy—to come up with what they called calibrated imaging. That technology enabled the Gerton team to literally count how many Cse4 molecules hooked to a fluorescent tag glowed in a dot marking a centromere in living cells, a daunting task since the centromere moves.

In the end, the highly technical approach solved the problem: this year the Gerton lab used advanced microscopy in part to report in *Cell* that the centromere of each chromosome contained just one copy of Cse4 up until the very end of cell division, a stage called anaphase. Then it added one more, which changed the overall architecture of the centromere.

"This question has been a matter of intense debate," says Gerton, noting that forming a centromere correctly dictates whether a cell will drag the right number of chromosomes into daughter cells. "Brian and Jay combined two methods to come up with a way to answer this question. That approach is not something my lab would have developed on our own."

Biology grows up

If you are of a certain age, you may wonder why you didn't learn about this kind of biology in high school. The answer is, it only emerged in the last two decades from the onslaught of genomic/proteomic data, the capability to image living cells, and the upsurge in computer power available to make sense of this information.

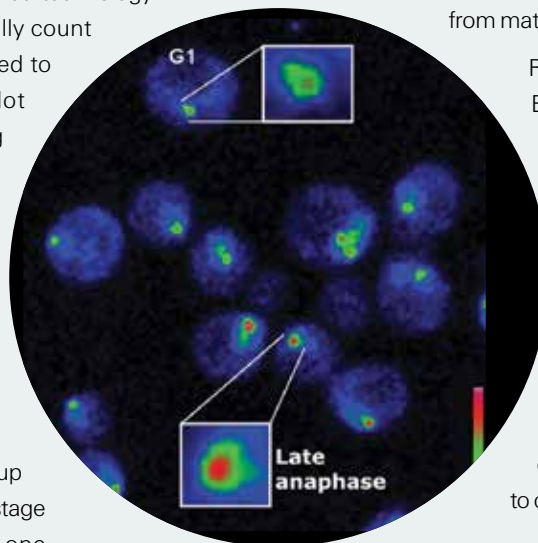
Seen from mathematician Rubinstein's perspective, this means that biology is finally becoming a quantitative science. "For a long time, biology was considered a purely descriptive science," he says. "But that's not enough. The goal is to be able to make predictions."

Born in Russia, Rubinstein earned a PhD in optics at Irkutsk State University in Siberia and worked as an engineer and mathematician in Israel and the US. When he started postdoctoral studies at the University of California, Davis, in 2002, he encountered biologists for the first time and advised them on mathematical models of cell motility. Recruited to Stowers in 2007, he became a research advisor three years ago with a mission to counsel faculty on issues ranging from mathematical modeling to biophysics.

Rubinstein speaks Russian, Hebrew, and English. He also uses scientific language different from most biologists. For example, in 2011 he published papers with Associate Investigator Matt Gibson on what he calls "a question of geometry" (translation: how epithelial cells pack into a sheet) and in 2012 and 2013 with Rong Li on two mechanical problems related to cell division in different organisms. Plus he also occasionally refers to cells as "elastic bags filled with water."

A matter of survival

According to Li, collaborating with technology-savvy advisors isn't a luxury—it's how a scientist survives today's biology revolution. "If you aren't working in an interdisciplinary way, you won't be at the cutting edge," she says. Li should know. Over the last three years, she has frequently teamed with one or more of the research advisors to produce a string of coauthored publications, many reported in high-impact journals.



A novel microscopic approach developed by Unruh and Slaughter allowed researchers to count for the first time the number of individual fluorescing molecules in a cluster of proteins. Cell, July 2012.

One, published early this year in *Nature Communications*, addresses how cells achieve sidedness, or polarity. Working with Slaughter, Unruh, and Rubinstein, Li and her students used microscopy and mathematics to expand her previous model of how yeast cells concentrate a cap of Cdc42 protein in a discrete region of the cell membrane that buds off to form a daughter cell.

In 2009, she, Slaughter, and Rubinstein had reported in *Developmental Cell* that the membrane distribution of Cdc42, which is trucked around cells on vesicles or chaperoned by a protein called Rdi 1, is mathematically described via a balance of exocytosis, which carted Cdc42 to a target area in the cell membrane, endocytosis, which grabbed it back inside cells when it wandered off into adjacent regions, and Rdi 1-based recycling.

The new work addresses questions others raised about their model. Combining imaging conducted by Slaughter, computer simulations run by Unruh, and mathematical modeling done by Rubinstein, Li shows that the model works only when one posits that membranes in the bud area are stickier than regions beyond it. "This analysis suggested that there are membrane regions with high and low diffusion rates," says Rubinstein. "Once you consider this imbalance, you can predict where there will be regions of increased protein in a membrane."


These predictions are not simply a "game for mathematicians," as Rubinstein recalls old-guard biologists once saying. A computational framework for how cells create polarity explains why animal cells, like neurons or gut epithelial cells, don't look like bags of water but instead exhibit wildly variant shapes critical to their functionality. Plus, loss of polarity is a hallmark of cancer cells.

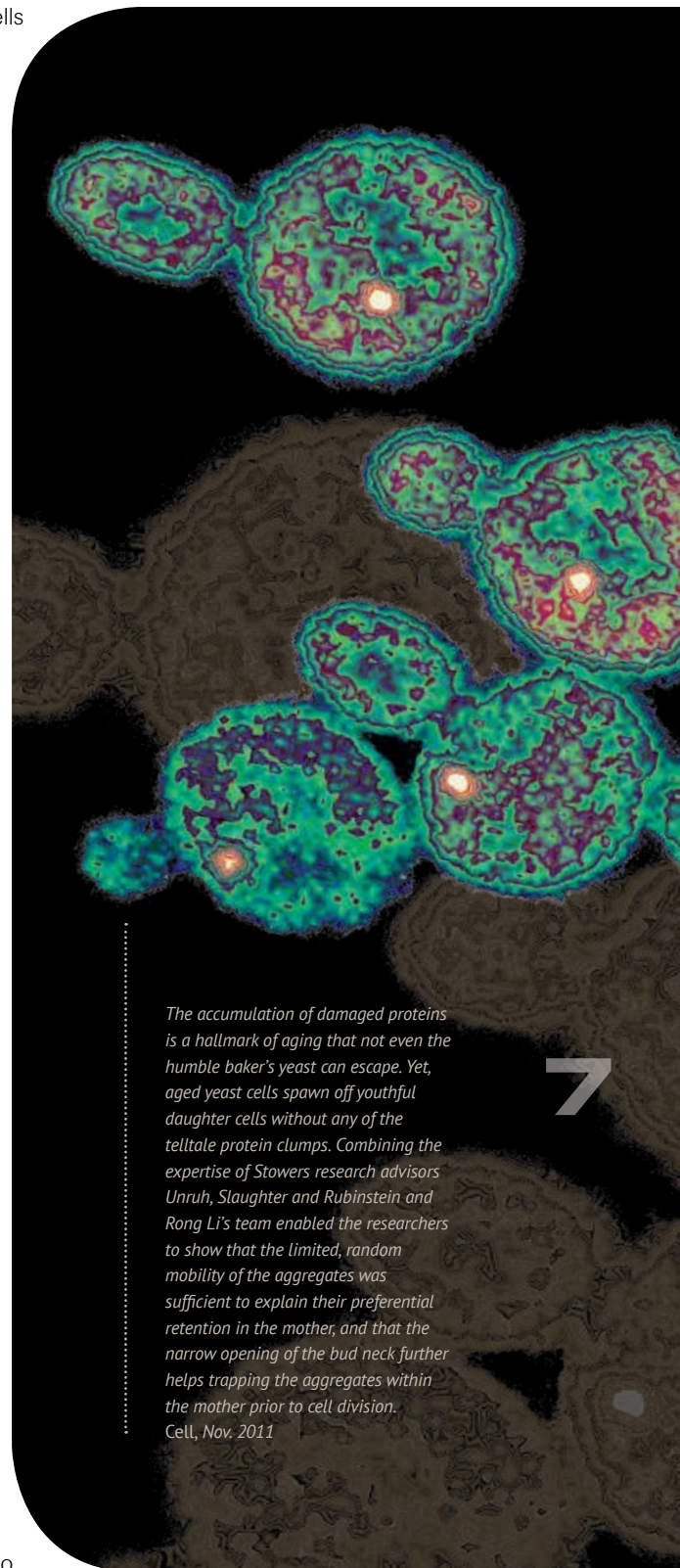
Defeatists: Look elsewhere

Unruh says the *Nature Communications* study emerged not only from hard work but from brainstorming sessions among people with unique skill sets—often for long hours in Li's office. "Stowers is one of the few places in the world where that problem was solvable," Unruh says, adding that Stowers' advanced instrumentation played no small part.

Not all stories have such a happy ending, but research advisors have a high tolerance for failure. "When one project isn't working we usually have two others that are," says Unruh. Slaughter has the same can't-win-if-you-don't-bet spirit: "If we pitch an idea to a researcher and discover it isn't going to work, we come back to our office and think of another."

Stowers investigators appreciate research advisors' willingness to jump into complex problems as much as their expertise. "I really like working with these guys," says Kausik Si. "They are some of the few people I know in science that when you suggest doing an experiment, they say, 'Hey! Let's try it!' rather than coming up with a hundred reasons not to."

That's because advising folks not to move forward is likely absent from the research advisor job description. Or as Unruh says, "This is the first time in my life where I can actually sit down in a meeting and say, 'Let's figure out the best way to answer this question' as opposed to saying, 'This is the best essay we have right now.'" 



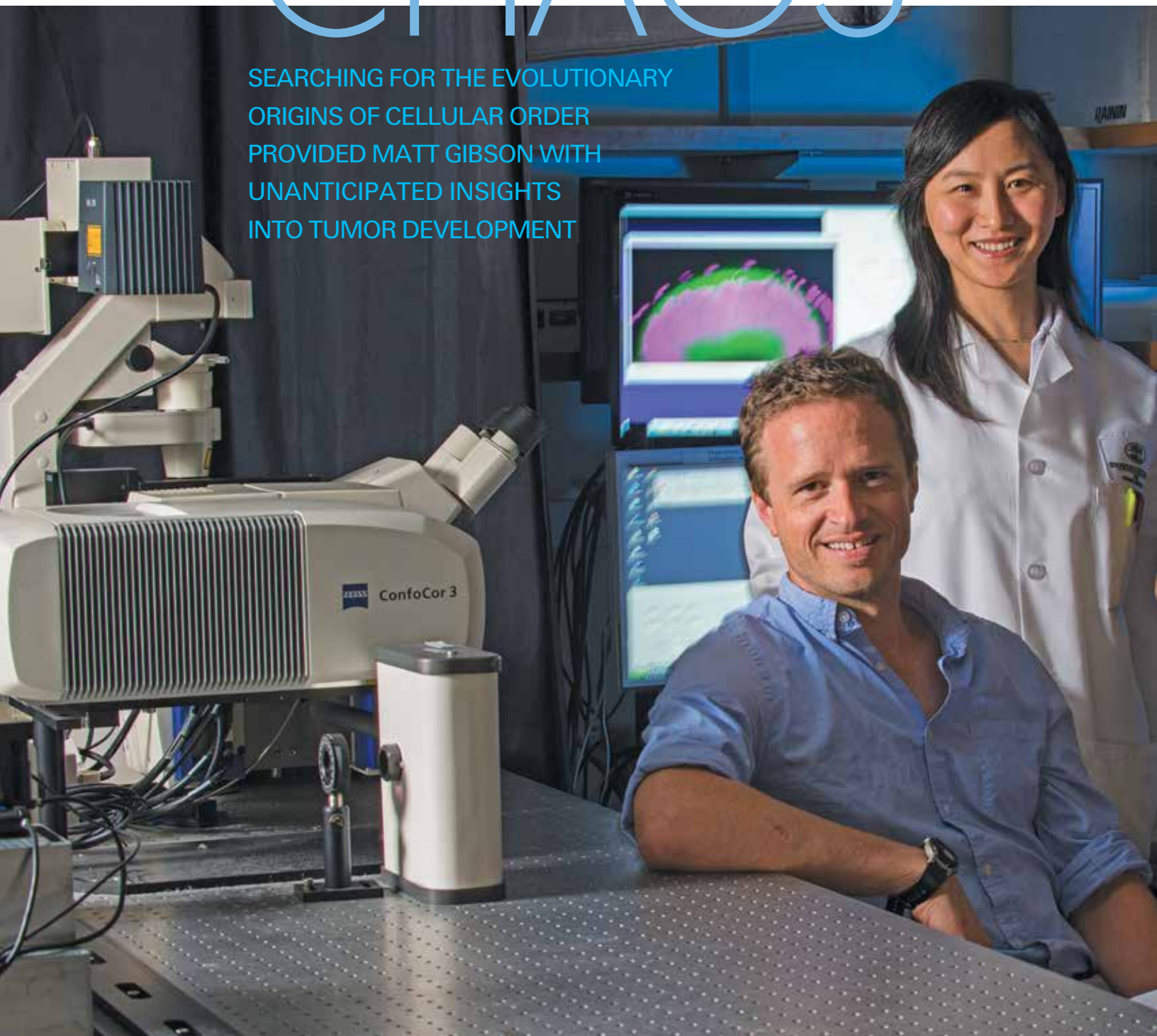
The accumulation of damaged proteins is a hallmark of aging that not even the humble baker's yeast can escape. Yet, aged yeast cells spawn off youthful daughter cells without any of the telltale protein clumps. Combining the expertise of Stowers research advisors Unruh, Slaughter and Rubinstein and Rong Li's team enabled the researchers to show that the limited, random mobility of the aggregates was sufficient to explain their preferential retention in the mother, and that the narrow opening of the bud neck further helps trapping the aggregates within the mother prior to cell division. *Cell*, Nov. 2011



By Elise Lamar, PhD

AVERTING CHAOS

SEARCHING FOR THE EVOLUTIONARY
ORIGINS OF CELLULAR ORDER
PROVIDED MATT GIBSON WITH
UNANTICIPATED INSIGHTS
INTO TUMOR DEVELOPMENT



From left to right: Matt Gibson, PhD, Liang Liang, Yu-ichiro Nakajima, PhD



In the animal kingdom, epithelia—layers of tightly packed cells—are ubiquitous. They stretch over every external and internal surface of animals' bodies forming protective barriers; channeling liquids; secreting milk, enzymes, and hormones; and constructing structures as diverse as insect wings, fish gills and the human spinal cord.

Not surprisingly, most human tumors originate in epithelia. Collectively known as carcinomas, they emerge when something goes terribly wrong and the highly organized structure of epithelia starts to melt down. "When cells are confined in an epithelial layer, things stay nicely organized," says Stowers Associate Investigator Matt Gibson, PhD, who uses simple model organisms to reveal the universal mechanisms animals rely on to construct tissues. But recently, he and his team discovered that if dividing cells fail to align properly within the orderly array of the existing epithelium, rogue cells can break free—bringing them a step closer to initiating cancer.

Gibson hadn't set out to study tumorigenesis. Rather, the work—which bridges basic and translational science—originated in evolutionary and cell biological studies the Gibson lab began two years ago.

An unanticipated discovery

Epithelial cells are polarized; that is, their upper (apical) end differs from their bottom (basal) side. In a 2011 *Current Biology* paper, the Gibson lab's *Drosophila* team used imaging to show that fly cells round up at the apical epithelial surface during cell division to allow the nucleus to move into that region of the cell.

Prior to those studies, Gibson had recruited postdocs to help pioneer a novel experimental system in his lab: the sea anemone, which builds tentacles (not wings) from embryonic epithelia. One member of that team was Aissam Ikmi, PhD, who was trained at the University of Paris-Sud in Orsay as a *Drosophila* geneticist, but had decided to tackle a new challenge.

Pioneering sounds glamorous but, in fact, it means that one might spend tedious months creating a molecular tool kit from scratch, while colleagues working in established systems like *Drosophila* publish papers. Ikmi might have found himself in that position, but instead got an unforeseen reward.

While testing reagents he made from scratch, he discovered that nuclei in dividing sea anemone epithelial cells moved into the apical end, which ballooned out just like *Drosophila* cells did. “I knew I would face challenges in establishing tools needed to study biological problems in an emerging model organism,” Ikmi says. “But this work brought important insight to the history of life by elucidating how ancient multicellular animals are constructed at the cellular and molecular levels.”

Emily Meyer, a Gibson lab technician who was co-first author with Ikmi on the study, did the *Drosophila* work. “We had planned experiments in flies to gather this data,” she says, explaining that sea anemone work was initially viewed as a side project. “But these important findings gave evolutionary direction to the story.”

Gibson agrees that side-by-side comparisons of insect and sea anemone epithelial cells led to a much broader perspective on this biological problem. “Previously, the nuclear movement we describe here was thought to occur primarily in cells of the vertebrate neural tube,” he says. “But we showed that a fundamentally similar type of epithelial cell division occurs in organisms as distantly related as fruit flies and sea anemones.”

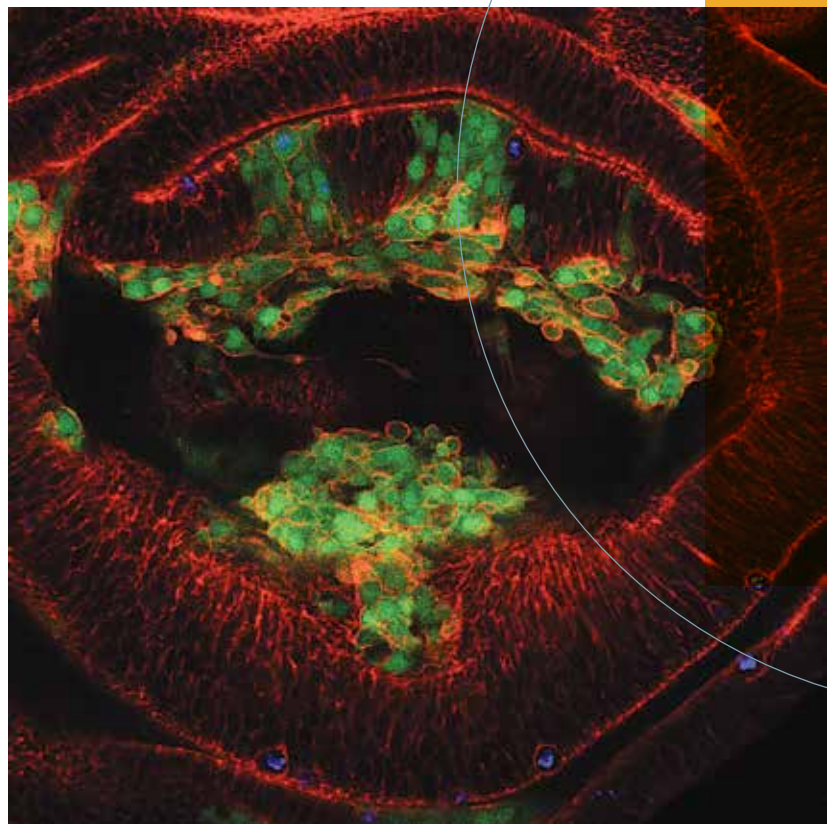
Discovering why

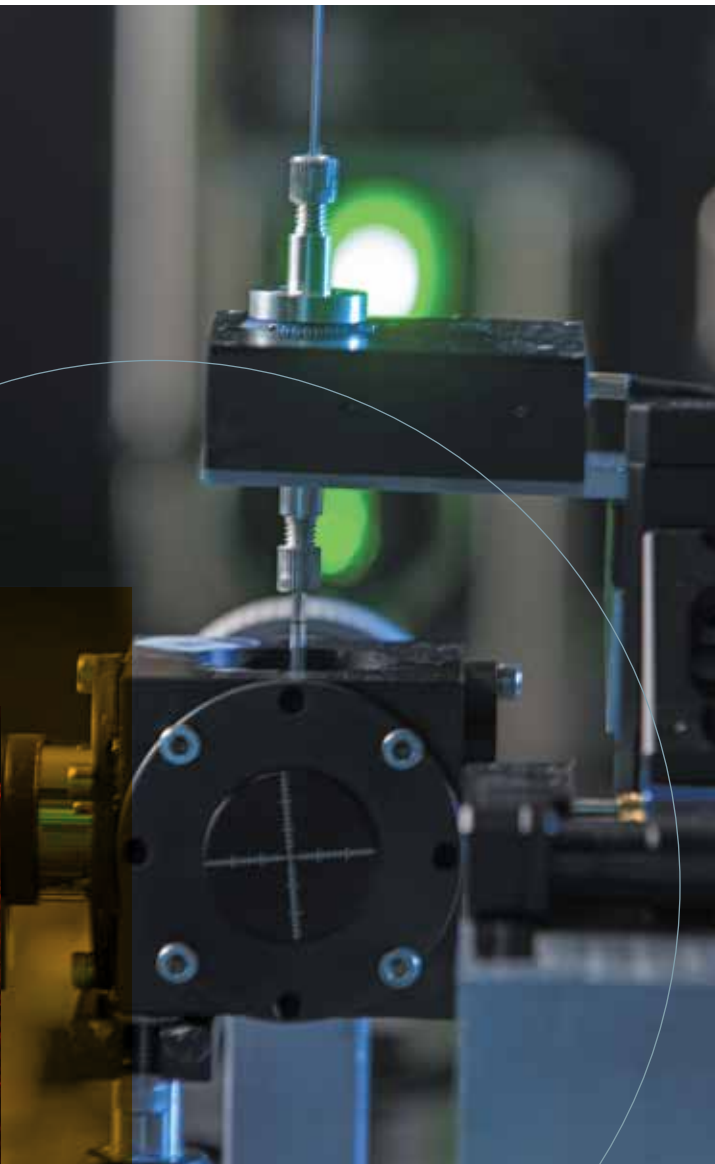
Biology 101 students know that if an organism more primitive than a fruit fly, like a sea anemone, does something resembling what human embryonic brain cells do, that something must be important, with a capital “I.” The *Current Biology* paper established that flaring out at one end before cell division was important. The question remained why.

Earlier work provided a hint: The group had observed that a dividing cell’s mitotic spindle—the web-like machinery that separates chromosomes into daughter cells—invariably orients itself parallel to the apical surface of the cell layer, suggesting that apical rounding might play a key role in setting the stage for proper alignment of the mitotic spindle.

To determine what holds the spindle in the correct position, Gibson lab postdoc Yu-ichiro Nakajima, PhD, the first author of a 2013 *Nature* study, used high resolution imaging to look inside epithelial cells developing into a fly wing. He observed that the two ends, or poles, of the mitotic spindle always sat near the septate junctions, regions of close contact between neighboring cells. There, two proteins called Discs Large and Scribble were juxtaposed to the spindle.

“The spindle in mitotic cells seemed to know the right position and direction to orient,” says Nakajima. “That suggested that Discs Large and Scribble might provide the cue to orient at this position.” Given the Gibson lab’s dual expertise in genetics and cellular imaging the next step was clear—namely, to genetically delete Scribble and Discs Large in *Drosophila* embryos and watch what happens.





A custom-built microscope (above) allowed Yu-ichiro Nakajima to follow individual cells as they failed to find their proper place within the epithelium and started to form tumor-like masses (left).

Viewing “misorientation”

Conventional microscopy revealed that Nakajima was right. Deleting Scribble caused the mitotic spindle to flop over at a random angle, as did loss of Discs Large. The group then perturbed the spindle with other reagents and video-captured outcomes using a microscope custom-built by Sean McKinney, PhD, and Amanda Kroesen of the Stowers Microscopy Center. Using methods pioneered by Gibson lab graduate student Liang Liang, that microscope allowed the team to embed living fly tissue in a gel and then spin it around while filming what happened for more than an hour.

Analysis of the resulting videos revealed that during division, misoriented cells peel away, or delaminate, from the epithelium. By contrast, videos of normal tissue show epithelial cells dividing, jostling their neighbors, and then settling in an orderly block.

Gibson says that when potentially harmful cells “fall out of the epithelium” they are generally killed by apoptosis, a self-policing mechanism that eradicates damaged cells. Nakajima, in fact, had studied apoptosis in *Drosophila* as a PhD student at the University of Tokyo. At his suggestion, the group experimentally blocked apoptosis and observed what happened in cells once spindle orientation was disrupted.

That manipulation produced the paper’s critical result: Misoriented cells that got an experimental reprieve from protective cell death produced tumor-like growths. Even worse, cells in those masses lost all semblance of normal polarity, or shape, and switched on fruit fly homologues of human carcinoma markers.

The answer to basic questions

As Gibson and Nakajima observed, the good news for flies, sea anemones, and humans is that tissues usually succeed in killing off cellular miscreants via apoptosis. But their lab’s work suggests that if apoptosis were short-circuited by mutations in genes required for good cell death—mutations common to almost all human cancers—cells ejected from an epithelium could switch on cancer genes and flee to a different tissue. The clinical term for that phenomenon is metastasis.

“If you disrupt mitotic spindle orientation, abnormal cells should typically die because epithelia have an intrinsic mechanism to protect themselves,” says Gibson. “But if this mechanism is compromised in a given individual, they would be vulnerable to potentially tumorigenic events.”

Overall, these studies prove that answering the most basic questions—such as what cellular mechanisms are conserved across millions of years of animal evolution—is the very basis of meeting translational goals of knowing what goes wrong in a cancer cell. **S**

By Alissa Poh

A DISCUSSION WITH

PETER BAUMANN

Investigator Peter Baumann, PhD, fondly recalls portraying the lovelorn poet Eugene Marchbanks in the George Bernard Shaw play *Candida* during high school. "Being the same age as my character made it even more interesting," says Baumann, who grew up in Germany. He even considered a stage career, changing his mind after learning from professionals that acting was much more fun when it wasn't a job.


He decided instead to indulge his passion for creativity through science. "I wanted work that would leave me with a sense of accomplishment," he says, "so I settled on exploring the interface between biology and chemistry." And Baumann hasn't looked back. After defining the protein Rad51's role in DNA repair, his postdoctoral studies shifted to chromosome ends. Pot1, the protein Baumann discovered to be vital for protecting telomeres, jump-started his career and landed him his first faculty position at the Stowers Institute in 2002.

Where Baumann's innate curiosity leads, animals inevitably follow. When he was eight and trawling the Danube for larvae one afternoon, he rescued two orphaned mallard ducklings. They domesticated well, quickly wising up to the fact that young Baumann armed with a shovel in the garden meant a windfall of worms. "If I paused too long at digging, they'd nip at my trousers," he says. "Ducks are quite capable of learning—at least in exploiting food from humans." He's had opportunities aplenty to make other anecdotal observations about poultry. A handful of backyard tomato plants became, in Baumann and his wife, Diana's, hands, five acres of suburban homesteading, which more recently burgeoned into forty acres of sustainable farming—with chickens and ducks galore—southeast of Missouri's Smithville Lake.

Then there are the whiptail lizards Baumann's investigating. He's long been intrigued by the molecular basis of parthenogenesis, or asexual reproduction among certain all-female reptile populations. "It's a stretch, studying this alongside telomeres and RNA processing," he admits. "But to me, it's all chromosome biology."

For his prowess in both fields, Baumann was appointed one of just twenty seven new Howard Hughes Medical Institute (HHMI) investigators—from more than 1,200 applicants—in May 2013.





WHAT FUELS YOUR CURIOSITY, AND IS THERE A METHOD TO YOUR MADNESS OF SIMULTANEOUSLY TACKLING MULTIPLE SCIENTIFIC MYSTERIES?

I've always been more interested in testing the boundaries of what we know and never got out of the "Why?" phase all kids go through. But I don't find multitasking productive; it's better to be really focused for a limited time—for instance, spending several hours thinking only about telomere biology. That's when the best ideas come to me.

I also enjoy letting my mind run along a specific topic while something else is going on; I can watch a movie and not even remember that I did. Some research seminars are harder to get into and I'm inclined to give up trying if, a third of the way through, I still haven't grasped the main point. But I walk away thinking the time was incredibly productive anyway because I've come up with new ideas.

WHY HAVE WE MADE SO LITTLE HEADWAY IN THE HUNT FOR TELOMERASE INHIBITORS THAT MIGHT PROVE THERAPEUTIC IN CANCER AND AGING-RELATED DISORDERS?

In my opinion, by trying to measure telomerase activity we have been barking up the wrong tree. Less effort has been put into cell-based assays, because it's much harder. Over forty eight hours, the enzyme lengthens a few telomeres by just one to two percent resulting in a tiny signal-to-noise ratio. My ideal assay, which we're working on at Stowers, would measure the effect on telomere length, not telomerase activity.

We can keep looking for something that jams telomerase's active site, but the history of HIV research should remind us that it's difficult to suppress a reverse transcriptase in a cellular context without multiple side effects. That's why I'm more interested in the complex machinery required to make a functional ribonucleoprotein (RNP), so we might have other avenues to exploit in preventing telomerase from ever becoming active.

WHAT MADE YOU DECIDE TO TAKE A SHOT THIS YEAR AT FULL HHMI INVESTIGATOR STATUS?

It's really through my HHMI Early Career Scientist appointment [awarded in 2008] that I've been able to study parthenogenesis in whiptail lizards. Having since published in this field, I realized that I could no longer regard my lizards as a side project. But neither did I want to abandon telomere research. Knowing HHMI's nonconservative nature in selecting investigators, I decided to stick my neck out and show them who I really am: someone investigating RNA processing in telomerase biogenesis, who would also like to bring this other field, still mostly unexplored, to the same level of mechanistic detail. Apparently, this charmed the review committee.

From front to back: Chloe, Peter Baumann, PhD, and Dakota



SPEAKING OF PARTHENOGENESIS, WHAT GOT YOU HOOKED IN THE FIRST PLACE?

The notion of long-term sperm storage, which was postulated when zoos housing only females of reptiles like Komodo dragons and Burmese pythons found themselves dealing, inexplicably, with offspring. Perhaps, like some amphibians, there were compartments in these female reptiles where sperm could hang out at the right ambient temperature. If so, did the females release some factor to help keep the sperm viable, and could one adapt that for, say, overcoming the loss of viability associated with freezing sperm?

In retrospect, we were probably looking parthenogenesis dead in the eye, but it was the nineties and techniques like genotyping or deep sequencing had yet to emerge. Then Diana and I had dinner with Bill Neaves [president emeritus of the Stowers Institute] and his wife and learned about his seminal studies, back in the sixties, identifying the sexual hybridization that resulted in all-female whiptail lizards.

My question to Bill was, “So what happens to meiosis?” [Meiosis halves the number of chromosomes in sperm and eggs in preparation for fertilization.] And he answered, “We still don’t know.” I was sure that somebody had to have figured out an answer. But after first discovering that PubMed is not a good source for papers on herpetology, then spending a long time in the library, I concluded that Bill was right. That’s how I got started. It’s a fascinating difference that makes reptiles stand out among vertebrates: They’re the only group that can be truly independent of males.

SO DINOSAURS REPRODUCED ASEXUALLY?

Michael Crichton employed the idea in *Jurassic Park*, a story that involved a hefty dose of artistic license. But while I am not aware of any scientific evidence in support of unisexual dinosaurs, I don’t know of any data that rules out such a scenario either. It’s an intriguing possibility, though, that there may have been periods in evolution’s history where parthenogenesis played a more pivotal role than we currently assume.

AS YOU’VE SAID, THIS IS ALL A LARGELY UNCHARTED AREA OF BIOLOGY WHICH YOU’LL KEEP EXPLORING, MAINLY THROUGH YOUR HHMI RESOURCES.

Absolutely. To me, it’s forensics – using comparative genomics to piece together a story from ancient records to current vertebrates. During hybridization, it’s not that changes accumulate at a constant velocity over the next ten million years. There are very rapid changes initially, providing the adaptations necessary for a particular hybrid to work. There’s scant research on this, but now that we have the tools to change an

organism’s ploidy and analyze the immediate consequences and effects over a few generations, it’s an exciting endeavor.

LATELY, SCIENTIFIC MISCONDUCT HAS BEEN INCREASINGLY ON PEOPLE’S RADAR. HOW DO YOU PERSONALLY DEFINE SCIENTIFIC INTEGRITY?

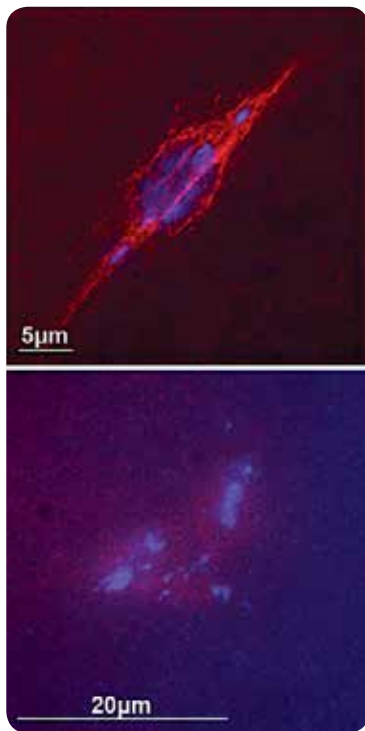
I grew up in a scientific culture that emphasized getting it right, rather than being first. That’s no longer the norm, which I think is terrible. With every paper published, countless hours of people’s lives go into trying to repeat that work and build on it. Too often, they can’t. Instead of providing an integrity compass and encouraging creativity, today’s investigators have to publish, almost recklessly, just to hang on to their funding.

WHAT’S ONE PIECE OF ADVICE YOU’D GIVE TO THOSE JUST STARTING OUT IN ACADEMIC SCIENCE?

Don’t burn bridges. You’ve heard of Sayre’s law: “Academic politics are so vicious because the stakes are so low.” We get into squabbles and break off contact with each other over really trivial things. The longer I am in science, the more I realize how this behavior does everyone involved a great disservice.

IF YOU HAD A TIME MACHINE, WHERE MIGHT YOU GO AND WHY?

If I could go to any point in time, I’d like to go all the way back to the origin of life, to see the earliest hints of what we now consider a cell. It’s a fascinating topic, given all the initial obstacles that had to be overcome to make a functional organism. Hopefully, conditions wouldn’t be such that I’d burn up immediately upon arrival. **SI**



POLO TAKES THE BAIT

Matrimony (Mtrm), a seemingly obscure gene in the female fruit fly that is only active in cells that will become eggs, led Investigator R. Scott Hawley's team to the discovery of an atypical protein that lures, traps, and inactivates the powerful Polo kinase. Polo is widely considered the master regulator of cell division, and its human homolog, Polo-like kinase-1 (Plk1), is misregulated in many types of cancer.

The Hawley lab discovered the Matrimony gene in 2003 and over time learned that Mtrm was a critical player in the cell divisions that occur as an egg is being made. In their latest study, Matrimony emerged as a rare example of a protein that can stably bind (and turn off) Polo kinase. It attracts the Polo kinase with three phosphorylated amino acids that resemble Polo's favored binding sites. As soon as Polo

takes the bait, the other end of Matrimony wraps around Polo and represses its function.

Hawley hopes that this highly selective kinase trap might give drug developers, who are working to inhibit Polo's crucial role in driving the multiplication of cancer cells, a new method to inactivate Polo without blocking other vital kinases in normal cells. "It provides some real therapeutic possibilities because Polo is misregulated in so many types of cancer," says the study's lead author Amanda Bonner, a former research technician in Hawley's lab. "To find something small and specific to Polo that doesn't interact with anything else is pretty exciting." **SI**

The study was published in the March 23, 2013, edition of the *Proceedings of the National Academy of Science* and picked as an "Editor's choice" in the April 5 issue of *Science*.

HIT BY TWO HAMMERS: HIRSCHSPRUNG DISEASE

Mutations in at least twelve individual genes are associated with the congenital defect Hirschsprung Disease (HSCR), in which children are born lacking nerves that innervate the gastrointestinal tract. As a result, the affected portion of intestine or bowel cannot undergo peristaltic movements and affected individuals are left with lasting complications including constipation, dehydration and poor nutrient absorption.

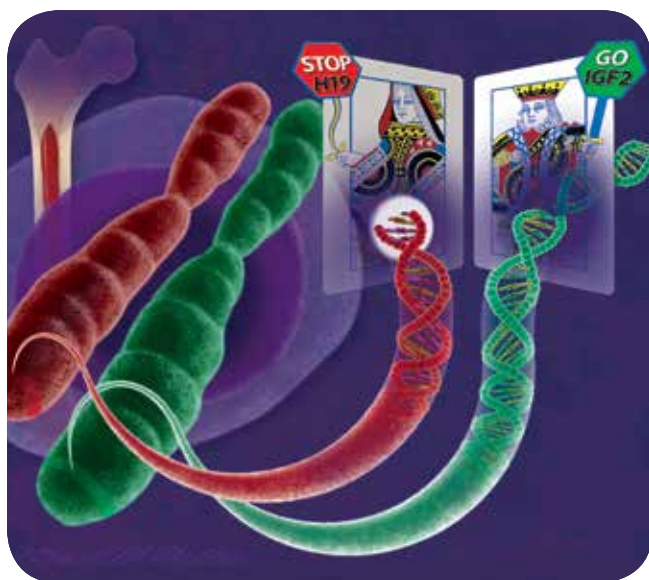
Investigator Paul Trainor, PhD, and Amanda Barlow, PhD, a former postdoctoral scientist in the lab, identified new genetic interactions associated with HSCR and showed how the migration of cells that form the gut nervous system is impeded when the combined doses of two candidate genes, known as *Toof1* and *Pax3*, are low. The cells that go awry in HSCR are a subset of neural crest cells, embryonic cells that spring from the developing brain and spinal cord in mice or humans and then travel long distances to form, among other things, bone and cartilage structures in the face, smooth muscle in the heart, and neurons of the peripheral nervous system, including those that innervate the gut.

Trainor has been interested in neural crest cells since he was a graduate student, often focusing on developmental defects caused by their malfunction. "Neural crest cells have to be born in the right place, migrate incredibly long distances, survive, multiply, and then differentiate into many different mature cell types," says Trainor, who until recently was primarily interested in neural crest-related craniofacial anomalies. "In Hirschsprung Disease neural crest cells don't make it to the end of the gastrointestinal tract, and we need to better understand why in the hope of eventually minimizing or preventing this from happening in newborn babies."

Understanding the genetic basis of HSCR offers hope for better diagnostics and treatment for this and other developmental defects caused by the failure of neural crest cell development. **SI**

The study was published in the January 2013 issue of *Human Molecular Genetics* and a review of the etiology and pathogenesis of HSCR by Naomi Butler Tjaden (a predoctoral student in the Trainor lab) was published in the March 2013 issue of *Translational Research*.





KEEPING THE RESERVE FORCE HOME

HEMATOPOIETIC STEM CELLS—BONE MARROW-DERIVED ADULT STEM CELLS THAT GIVE RISE TO THE WIDE VARIETY OF SPECIALIZED BLOOD CELLS—COME IN TWO FLAVORS: THE RESERVE FORCE THAT SITS QUIETLY WAITING TO BE CALLED UPON AND THE ACTIVE ARM THAT CONTINUALLY PROLIFERATES, SPAWNING BILLIONS OF BLOOD CELLS EVERY DAY. IN THEIR LATEST STUDY, STOWERS INVESTIGATOR LINHENG LI, PHD AND HIS TEAM REVEALED THAT GENOMIC IMPRINTING, A PROCESS THAT SPECIFICALLY SHUTS DOWN ONE OF THE TWO GENE COPIES FOUND IN EACH MAMMALIAN CELL, PREVENTS THE RESERVISTS FROM BEING CALLED UP PREMATURELY.

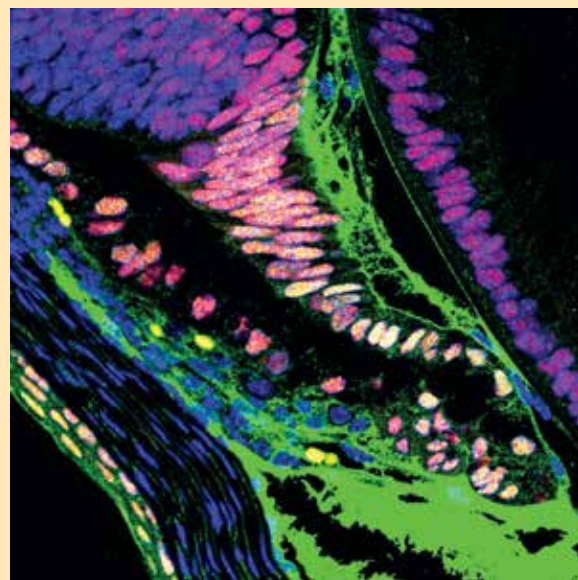
Sexual reproduction yields progeny with two copies, or alleles, for each gene, one from the mother and one from the father. Most genes are expressed from both copies, but in mammals and marsupials a small subset of genes receives a mark, or imprint during the development of egg or sperm cells. These genomic imprints not only differentiate between genes of maternal and paternal origin, but they specifically shut down one copy of those genes in the offspring.

“Active HSCs (hematopoietic stem cells) form the daily supply line that continually replenishes worn-out blood and immune cells while the reserve pool serves as a backup system that replaces damaged active HSCs and steps in during times of increased need,” explains Li. “In order to maintain a long-term strategic reserve of hematopoietic stem cells that lasts a lifetime, it is very important to ensure that the backup crew isn’t mobilized all at once. Genomic imprinting provides an additional layer of regulation that does just that.” **SI**

The study was published in the August 15, 2013, issue of the journal *Nature*.

Same musicians: brand new tune

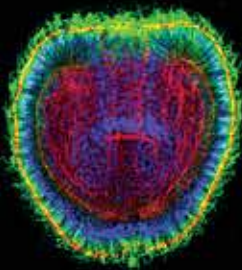
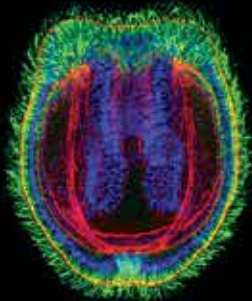
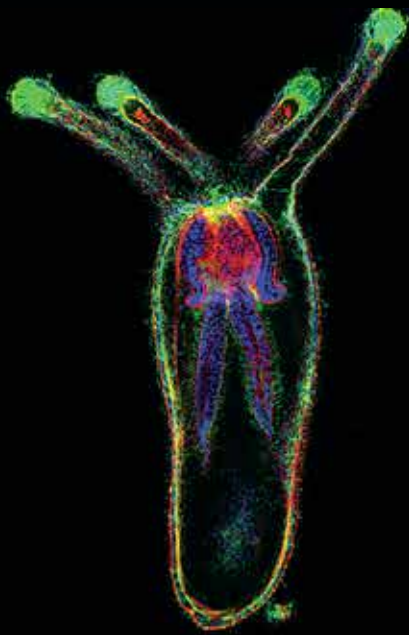
A small ensemble of musicians can produce an infinite number of melodies, harmonies, and rhythms. So, too, do a handful of workhorse-signaling pathways that interact to build multiple structures that comprise the vertebrate body. In fact, cross talk between two of those pathways—those governed by proteins known as Notch and BMP (bone morphogenetic protein) receptors—occurs over and over in processes as diverse as forming a tooth, sculpting a heart valve, and building a brain.



A new study by Investigator Ting Xie, PhD, and his team reveals yet another duet played by Notch and BMP signals, this time with Notch calling the tune. Using mouse genetics, the researchers demonstrated how one Notch family protein, Notch2, shapes an eye structure known as the ciliary body (CB), most likely by ensuring that BMP signals remain loud and clear.

In vertebrates, the CB encircles the lens and performs two tasks essential for normal vision. First, it contains a tiny muscle that reshapes the lens when you change focus, or “accommodate.” And it also secretes aqueous humor into the front compartment of the eye where it helps maintain correct eye pressure. Understanding CB construction is critical, as excessive pressure is one risk factor for glaucoma. **SI**

The study was published in the May 15, 2013, issue of the *Proceedings of the National Academy of Sciences*.



FINDING *NEMATOSTELLA*

Lacking even left-right symmetry, sea anemones are evolutionarily ancient. But during embryogenesis, their larvae compensate for an uninspiring torso by sprouting tentacles from thickened epithelial buds surrounding their mouths.

And there's no time to lose. Freshly hatched sea anemone larvae are under intense pressure to get their tentacles up and running to be able to feed themselves. Associate Investigator Matt Gibson, PhD, and his team wanted to know which kind of cellular reshuffling drives these survival-dependent changes in morphology? The Gibson lab has historically used fruit flies to investigate the control of epithelial cell shape and proliferation during wing, leg and eye development. Breaking with tradition, the lab's latest study focuses on the starlet sea anemone *Nematostella vectensis*.

"We thought tentacle outgrowth might be driven by cell proliferation," says the paper's first author Ashleigh Fritz, a graduate student at the University of Kansas School of Medicine working in the Gibson lab, who notes that some of *Nematostella*'s freshwater cousins sprout appendages by constant cell division. "Instead, we observed that cells begin thickened and then thin out as tentacles elongate." In other words, the process was driven not by cell duplication along a tentacle axis but rather by stretching a stockpile of cells.

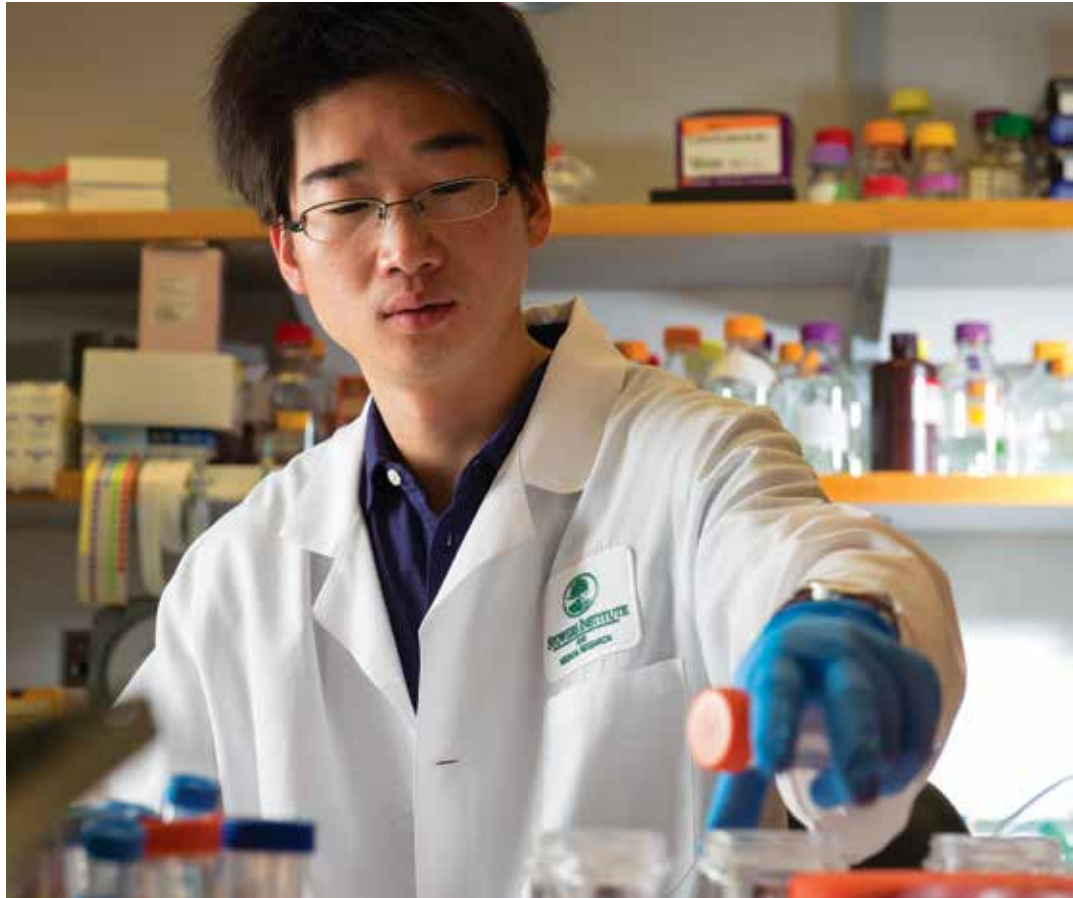
In addition to charting how epithelial cell shape changes drive tentacle development, the study is also the first to identify candidate genes driving those changes. Most of all, by putting center stage a new model organism representing one of the simplest animals, it illuminates some of the most fundamental principles animals use to construct a body. **SI**

The study was published in the May 1, 2013, issue of *Development*.

By Alissa Poh

THE THRILL OF THE SCIENTIFIC CHASE: CHENGQI LIN, PHD

Chengqi Lin was already halfway through the five-year medical program at Nanjing's Southeast University in China when the siren of science sounded its call. Realizing he was far more attracted by the prospect of unraveling disease pathologies than diagnosing a steady stream of patients, Lin delved into *Drosophila* genetics in the laboratory of Wei Xie, PhD, in the university's Institute of Life Sciences, where he quickly became enamored with basic research.



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"All I had heard from my father was that medical school would be tough and I'd need to stick it out," says Lin, who grew up in the Fujian Province. "It's one of his principles: 'If you start something, make sure you finish it.' Otherwise, he and the rest of my family were very supportive."

So Lin juggled lab experiments alongside just enough of the program's final-year hospital internship requirements to complete his bachelor's degree in clinical medicine. Then, while his classmates scattered to medical centers large and small, Lin settled back down at the bench.

Using the fruit fly *Drosophila* as his model, Lin spent the next three years pursuing a novel transcription factor thought to interact with and

influence p53, a protein byword in cancer research. After he completed the coursework for a master's degree in genetics, he headed to Singapore with his wife, Zhuojuan Luo.

While Luo toiled over her PhD thesis at the National University of Singapore, Lin worked as a structural biologist at Temasek Life Sciences Laboratory. But he hankered for more graduate training, too, and after exploring assorted possibilities, Lin eventually connected with Stowers Investigator Ali Shilatifard.

"I'd become interested in how histone acetyltransferases [HATs] regulate gene expression," Lin explains, "and exploring the structure of one HAT in particular, Rtt109 [a histone acetyltransferase that was discovered in Shilatifard's laboratory], led me to Dr. Shilatifard. He is interested in leukemias at the molecular level, and I had a medical background, so it was a good fit." In more ways than one: Gaining ground on cancer's underpinnings is personal for Chengqi because during his adolescence his grandmother succumbed to the disease—a loss he describes as profoundly sad.

Lin was recruited to the Stowers Institute in 2008 as a predoctoral research student in Shilatifard's laboratory through the Open University, a relationship that links to the institute as an affiliated research center. For much of the last five years, he collected evidence for the hypothesis proposed by Shilatifard fifteen years ago that certain leukemias can occur if transcription elongation, a key event in the multistep process comprising gene expression, goes awry.

Since then, Lin and his fellow researchers have identified and named a whole host of transcription elongation factors in the Super Elongation Complex. Lin has been hard on the heels of a particular SEC member: Ell3, neglected for years because of its notable presence in sperm, long regarded as nothing more than a paternal DNA contributor. Last December, he and Shilatifard published a paper in *Cell* showing that

Ell3, far from being negligible because of its location, primes the activation of multiple genes that control stem cell specification.

When not at the bench, Lin sometimes dabbles in Chinese calligraphy. Snippets of philosophical sayings come to mind, he says, prompting him to put brush to paper. He's fond of listening to traditional Chinese music—performed on the likes of the pipa, guzheng, and other plucked string instruments—as a way to unwind; the classical piece Gao Shan Liu Shui ("High Mountains, Flowing Water") is a favorite. Lin daydreams of traveling the world someday, although his first destination choice might surprise some: He'd like to visit the Gobi Desert or the Sahara.

Later this year, Lin will leave the US for Singapore. Having successfully defended his PhD thesis, he's been offered a position as a junior investigator at the Institute of Molecular and Cell Biology, with start-up funds to run his own lab. As happened when he first moved to Kansas City, he and his wife will be a long-distance couple while she wraps up her postdoctoral fellowship at Stowers, albeit with an added wrinkle—shuttling their not-quite-two-year-old daughter, Sarah, between both parents until the young family can be reunited.

"I think I'm ready to be an independent researcher," Lin says. "While totally supportive, Dr. Shilatifard has always given me lots of space to figure things out on my own, which is outstanding training for someone who wants to become an independent scientist." He's well aware that stateside opportunities to leap from newly minted PhD to full-fledged faculty are few and far between. Countries like Singapore and China, he notes, are investing far more in outfitting a whole new generation for the thrill of the scientific chase—which, for Lin, remains the juiciest carrot of all along his career path.

"With so many unanswered questions," he says, "why wouldn't you want to be able to test all the ideas you might come up with?" **SI**

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Five new predoctoral researchers join Stowers Graduate School

THE SECOND-EVER COHORT OF PREDOCTORAL RESEARCHERS ARRIVED IN AUGUST TO START THEIR GRADUATE RESEARCH PROGRAM AT THE STOWERS INSTITUTE. THE SMALL BUT DIVERSE GROUP HAILS FROM LOCALES ALL OVER THE WESTERN HEMISPHERE WITH INTERESTS AS DIVERSE AS THEIR ORIGINS.

Elisabeth Bauerly successfully tried her hand at research as a research technician in Stowers Investigator R. Scott Hawley's lab before taking the plunge into Graduate School.

Zachary Lee, who received his BA in biochemistry from Rockhurst University in Kansas City, is drawn to proteins and hopes to apply advanced proteomic analysis to fields such as transcription.

Joaquín Navajas Acedo, who hails from Spain, studied developmental neurobiology and neuronal cell biology at the Autonomous University of Madrid.

Diego Páez-Moscoso studied at the Pontificia Universidad Católica del Ecuador in Quito and is one of the world's foremost experts on *Osornophryne*, a genus of Andean plump toads.

Adrienne Van Antwerp, a native of Reno, Nevada, was captivated by Stowers Associate Investigator Kausik Sī's work on the molecular basis of memory when she spent the summer in his lab as a summer scholar last year.

To learn more about the newest predoctoral researchers, visit stowers.org/stowers-report/fall-2013 and listen to a podcast describing why they came to Stowers and what they hope to accomplish as scientists. 



left to right-Diego Páez-Moscoso, Zachary Lee, Adrienne Van Antwerp, Joaquín Navajas Acedo, and Elisabeth Bauerly.

Summer Scholars:

HOOKED ON SCIENCE

When, as a young toddler, Kelsey Kaeding became mesmerized by a live surgery channel on TV, her future path seemed set: She wanted to become a doctor. As part of a high school vocational immersion program, she shadowed a physician. In college, she was squarely on the premed track until she had an opportunity to explore hands-on bench research. And that was all it took...she was hooked on science.




Working with one of her professors (developmental biologist Patrick Ferree, PhD, at Claremont McKenna College in Claremont, California), Kaeding is pursuing an independent research project geared to finding out what factors in female heterochromatin interact and influence ring-X chromosome lethality.

During her summer breaks, when many undergrads like to while away the dog days of summer poolside, Kaeding dove headlong into even more research. In 2012, Kaeding spent the summer in a genome science program at the University of Washington in her hometown of Seattle and this summer participated in the Stowers Institute's Summer Scholars Program.

Under the mentorship of Hawley Lab Research Specialist Stacie Hughes, PhD, Kaeding worked to narrow the location of a genetic mutation found somewhere on the third chromosome of the fruit fly *Drosophila melanogaster*. Being able to tease out the specific location is no small feat. The third chromosome is huge and contains many individual genes. To narrow down the location

possibilities requires multiple two-generation genetic crosses that can take up to four weeks each—too long for a ten-week program. Still Hughes believes that Kaeding's summer scholar work added great value to the larger project: "Kaeding was incredibly productive in analyzing the effects of the mutation on female meiosis."

But more important to Hughes than characterizing a genetic mutation is Kaeding's opportunity to determine if she wants to pursue science as a vocation. "The purpose of the scholars program is to help undergraduates learn if they like lab work. It is a chance to see what real science is all about," says Hughes, who is optimistic that Kaeding will pursue bench science. "Kelsey came into the lab well-prepared. She was enthusiastic and inquisitive not just about her project, but about all the projects in the lab."

From Kaeding's perspective, science is looking promising and she is planning to apply to graduate school. "The Stowers Summer Scholars Program was a very positive experience. It definitely reinforced my decision to pursue science," she says. 

By Elise Lamar, PhD

Preparing the next generation

Stowers partners with University of Oregon to train computational biologists

Some students may gravitate to the coasts to get tech-savvy. But this year three University of Oregon (UO) graduate students headed to Stowers to learn how to apply computer analysis to molecular genetics, a booming discipline known as bioinformatics.

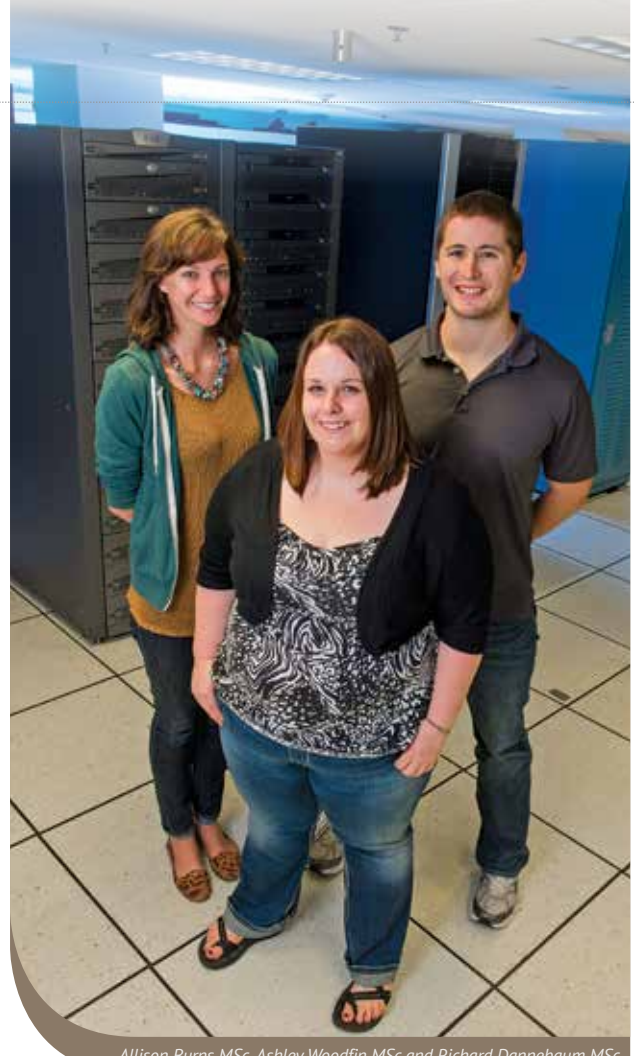
To earn a master's degree in that field, UO students first take statistics and programming courses on the Eugene campus, then intern for eight months in academia or industry. For the class of 2013, Stowers was a popular option: of six students, half interned here. They included Allison Burns and Richard Dannebaum, who worked in Peter Baumann's lab, and Ashley Woodfin, who worked with Rong Li.

Stowers genomics scientist Marco Blanchette, PhD, who interviewed the interns in Eugene, says the demand for biologists proficient in data analysis has skyrocketed due to next-generation sequencing technology, which allows analyses of entire genomes. "Once biologists evaluated a thousand nucleotides a week," he says, referring to DNA's building blocks. "Now we generate billions of nucleotides of sequencing data a week. We need people who can translate questions asked by biologists into software."

If Woodfin's experience is typical, the need is acute. As a UO molecular biology undergrad she realized that interpreting masses of sequencing data might soon form the basis of a majority of biological assays. "But I hadn't met many PhD students who knew how to analyze their own data," she says. "If I were to pursue a PhD or a career in biology, I would want to know how to analyze my own data."

The Stowers interns seem to have accomplished that goal. Burns, who majored in biology at UO, admits she was a complete novice in bioinformatics when she started the program. "But now I can hold my own in the field," she says.

Nonetheless, some hesitated to leave a campus described on its website as, "Oceans, Mountains, and Everything In Between." Dannebaum, a snowboarder and hiker, initially balked at moving to the Midwest but changed his mind after researching Stowers online. Mentored by both Baumann and Blanchette, Dannebaum has refined his programming skills as he compared global RNA



Allison Burns MSc, Ashley Woodfin MSc and Richard Dannebaum MSc

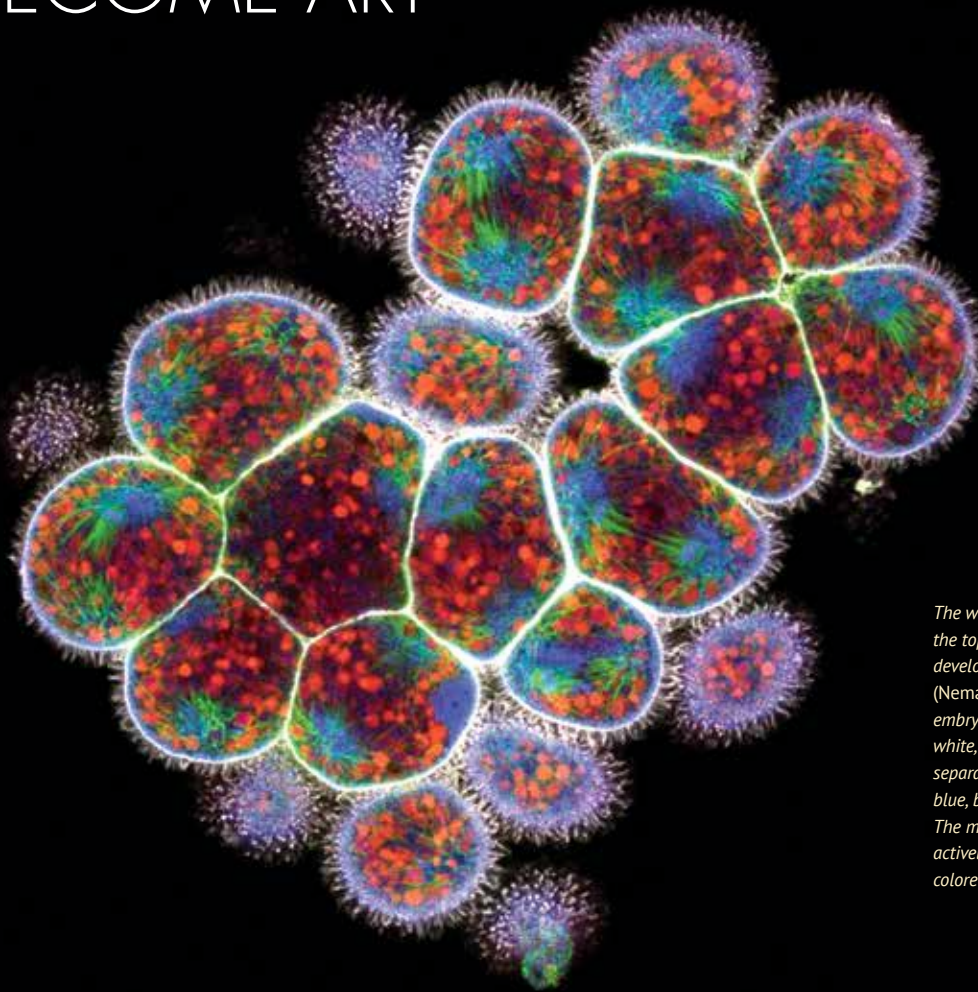
expression patterns in yeast mutants. And he is impressed by Stowers' collegiality. "Every door is open here," he says. "You don't have to stay at your level of the totem pole."

Friendship between the program's co-creator UO biochemist Andy Berglund, PhD, and Baumann initiated the Stowers/UO collaboration. Both were postdocs in the same lab at the University of Colorado, and after visiting Kansas City, Berglund came away impressed by Stowers' technical prowess and philosophy. When he approached Baumann about participating in the traineeship, Baumann knew it was a plus for both.

"The UO students have the opportunity to work on diverse computational problems, while Stowers gets a group of motivated entry-level analysts who are eager to learn more," says Baumann, noting that some students may consider the Stowers PhD program or apply for full-time jobs at the institute.

He may be right: Woodfin, Burns, and Dannebaum officially received master's degrees in biology with an emphasis in bioinformatics this September, and each will remain at Stowers for a while as analysts. Meanwhile, Blanchette and Baumann traveled to Eugene in August to chat with ten new members of the UO bioinformatics class of 2014. "We had a thoroughly positive experience with students in the first class," says Baumann. "We are very enthusiastic about continuing this partnership." **S**

WHEN EXPERIMENTS BECOME ART




The winning entry displayed the top surface of a developing sea anemone (Nematostella vectensis) embryo. Each cell, outlined in white, is in the process of separating its DNA, colored in blue, before it divides in two. The molecular machinery that actively pulls the DNA apart is colored in green.

Every day, scientists train the lenses of their high-powered microscopes onto cells and capture the world that unfolds before them in stunning displays. And once a year, Crossroads, the Stowers postdoc and student organization, calls on them to enter their most dazzling photographs into a scientific image competition, held as part of the Young Investigators Research Days (YIRD).

Although they blur the line between art and science, these amazing images are not art for art's sake. Instead, they provide Stowers scientists with valuable insights and important confirmation of processes that occur hidden from the naked eye.

This year's winning image, submitted by postdoctoral researcher Katerina Ragkousi, PhD, helped answer the question of how epithelial sheets—single layers of tightly packed cells that line every body cavity from the gut to mammary glands—hold together and maintain order as they make room for new cells during cell division (*for more details see page 8*).

But for many, they are simply beautiful art. 

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WEB SPECIAL:

To view more entries, please visit our online gallery at www.stowers.org/YIRD2013

A LASTING LEGACY

*President Emeritus Bill Neaves establishes
The Priscilla Wood Neaves Endowed Chair
in the Biomedical Sciences*




More than sixty years ago, as first and second graders in their small west Texas town of Spur, Bill Neaves and Priscilla Wood began building their life together. During grade school, they often scoured the shelves at the local library for books to feed their curiosities. At thirteen, when Bill reached legal driving age, he and Priscilla shared a first date at the bookmobile's monthly visit.

From the beginning, the couple developed a passion for scholarly pursuits. Each earned baccalaureate and advanced degrees at research-intensive academic institutions: Bill in biology and anatomy and Priscilla in sociology and theology.

Immersed in academics, they experienced firsthand the importance and value of endowed chairs. In the 1990s, Bill held the Doris and Bryan Wildenthal Distinguished Chair in Biomedical Science at the University of Texas Southwestern Medical School, and Priscilla led a fundraising campaign to establish the William Joseph Ambrose Power Chair at the Perkins School of Theology at Southern Methodist University.

As an expression of their shared appreciation for the scholarly endeavors assisted by a named endowment, Bill established the Priscilla Wood Neaves Endowed Chair in the Biomedical Sciences at the Stowers Institute for Medical Research in honor of his wife, who has battled a degenerative brain disease for nearly ten years. "I hope this gift will perpetuate Priscilla's memory in the context of scholarship and research that can benefit humankind," says Neaves.

Fellow researcher and colleague Peter Baumann was appointed the inaugural holder of the Priscilla Wood Neaves Endowed Chair in the Biomedical Sciences. For Bill Neaves, Baumann's appointment holds special significance because Priscilla felt great respect and affection for Peter. "I know Peter will ask and answer questions of fundamental biological importance in the coming years as he has done in the past," says Neaves. "It is a great privilege to see Peter's work associated with Priscilla's name." 

*Bill Neaves, PhD (standing), Peter Baumann, PhD, Inaugural Holder of
the Priscilla Wood Neaves Endowed Chair in the Biomedical Sciences*

JERRY WORKMAN ELECTED TO AMERICAN ACADEMY OF ARTS AND SCIENCES

This October, Stowers Institute Investigator Jerry Workman, PhD, was inducted into the American Academy of Arts and Sciences at the Academy's headquarters in Cambridge, Massachusetts.


Workman was one of the first scientists to discover that histones, proteins that keep the genomic DNA neatly organized inside the cell nucleus, are both important for the exquisite packaging of DNA into chromatin and crucial players in the regulation of gene expression. He has identified and characterized several giant protein complexes that modify histones, causing them to either loosen or tighten their grips on DNA, leaving it open to enzymes that can read its code and turn on genes.



Jerry Workman, PhD

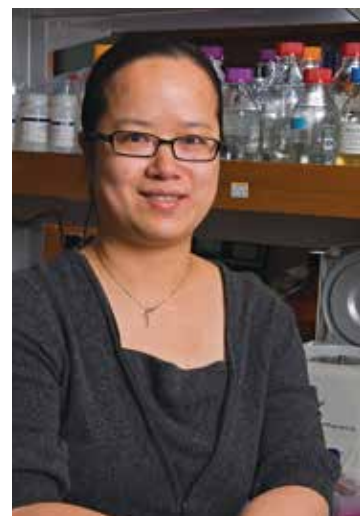
"This is a highly prestigious—and very fitting—recognition of Jerry's pioneering contributions to the field of chromatin biology and gene expression," says Scientific Director Robb Krumlauf, PhD. "With boundless creative and intellectual energy, he changed our fundamental understanding of how genes are turned on and off, and as a result has had a profound impact on a wide range of other fields, such as developmental biology and cancer research."

Since 1780, the American Academy of Arts and Sciences has recognized thinkers and doers from each generation; past members include George Washington, Benjamin Franklin, Winston Churchill, and Albert Einstein. Among this year's fellows are the recipient of the 2011 Nobel Prize in Physiology or Medicine Bruce A. Beutler; the director and actor Robert De Niro; singer-songwriter Bruce Springsteen; Pulitzer Prize-winning poet Annie Dillard; and astronaut, former Senator, and Presidential Medal of Freedom winner John Glenn.

Workman is the sixth person from the Stowers Institute to be inducted into the American Academy of Arts and Sciences. 

ZHUOJUAN LUO WINS THREE-YEAR FELLOWSHIP GRANT

Zhuojuan Luo, PhD, a postdoctoral research fellow in the lab of Stowers Investigator Ali Shilatifard, PhD, has been awarded a prestigious Fellow Award from the Leukemia & Lymphoma Society. She will receive \$165,000 over a three-year period to study the molecular biology of Mixed Lineage Leukemia (MLL) and identify potential anti-leukemic preclinical drug candidates.




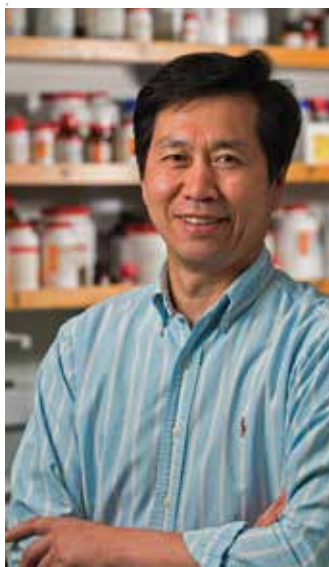
Zhuojuan Luo, PhD

MLL, a particularly aggressive childhood cancer, is caused by chromosomal rearrangements that misplace a copy of the MLL gene. The resulting fusion proteins stimulate aberrant gene expression ultimately leading to leukemia.

Luo will use the funds to determine which genes are activated by MLL fusion proteins and how they contribute to the development of leukemia. In collaboration with Children's Mercy Hospital in Kansas City, Missouri, and Saint Jude Children's Research Hospital in Memphis, Tennessee, she will analyze leukemic cells from human patients to identify additional factors that accelerate disease progression.

"Once we have a better understanding of the molecular mechanisms contributing to the pathogenesis of MLL we can start searching for small molecules that interrupt the process," says Luo.

The Leukemia & Lymphoma Society is the world's largest voluntary health agency dedicated to blood cancer. In addition to funding lifesaving blood cancer research, the agency provides free information and support services. 



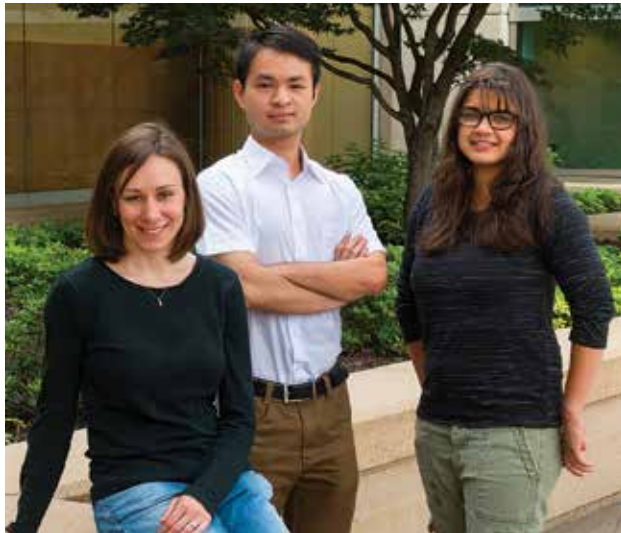
Linheng Li, PhD

LINHENG LI ELECTED AGA FELLOW

Stowers Investigator Linheng Li, PhD, has been inducted as a fellow of the American Gastroenterological Association (AGA), the nation's oldest medical society dedicated to disorders of the gastrointestinal tract. AGA fellowship is an honor bestowed on members who have been recognized by their peers and community for superior professional achievement in basic research and/or practice in the field of gastroenterology.

Li is an internationally recognized authority on the biology of stem cell niches, specialized microenvironments that nurture and direct the behavior of adult stem cells. His pioneering efforts highlighted a mechanistic link between the maintenance of intestinal stem cells and early stages of colorectal cancer. **SI**

STOWERS RESEARCHERS SHINE AT STUDENT COMPETITION



From left to right: Kristin Watt, Yi Zhou and Shachi Bhatt.

Three University of Kansas Medical Center (KUMC) graduate students performing research in Stowers laboratories were recognized for their outstanding presentations at the 2013 Student Research Forum. The two-day event, hosted by the Graduate Student Council at KUMC, included poster presentations and formal talks by students in the schools of medicine, nursing, health professions, and graduate studies.

Kristin Watt, a graduate student conducting her research in Investigator Paul Trainor's lab, was awarded first place in the Basic Science I competition. Watt's winning presentation highlighted her research on two genes that may play a pivotal role in the pathogenesis of Treacher Collins syndrome, a craniofacial disorder characterized by severe deformities of the eyes, ears, and facial bones in humans.

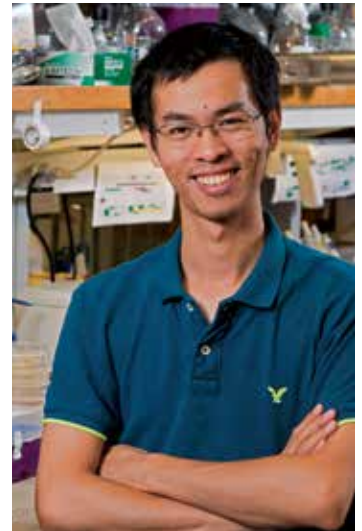
Another student researcher in the Trainor Lab, Shachi Bhatt tied for second place in the Basic Science IV division. Her studies focus on a novel gene called med23. Bhatt discovered that mutations in med23 are responsible for defects in cranial-sensory neurons and derail vascular development. Bhatt hopes further investigations will lead to a better understanding of med23's contributions to craniofacial disorders.

Yi Zhou from Stowers Investigator Ting Xie's lab placed first overall in the poster competition. His poster described work recently

published in *Proceedings of the National Academy of Sciences* (PNAS) that provides a better understanding of the signaling pathways involved in development of the ciliary body structures of the eye that may play an integral role in glaucoma. **SI**

PREDOCTORAL RESEARCH SCHOLAR WINS AMERICAN HEART ASSOCIATION FELLOWSHIP

Chuankai Zhou, a predoctoral researcher in the lab of Stowers Investigator Rong Li, PhD, has been awarded a highly competitive predoctoral fellowship by the American Heart Association (AHA). The AHA predoctoral fellowship will provide Zhou with \$52,000 of support toward the study of misfolded proteins and their contribution to cardiovascular disease.



Chuankai Zhou

Protein misfolding and the resulting aggregates are observed in various human illnesses including cardiovascular diseases. Known as protein aggregate these disorders are characterized by clumps of abnormally folded proteins that interfere with normal cell function.

Specifically, Zhou will use baker's yeast to study the interactions of protein aggregates with mitochondria, which generate the chemical energy necessary to power cells' biochemical reactions. Heart muscle cells, in particular, require a tremendous amount of energy to keep the heart beating, and mitochondrial dysfunction causes many heart failures.

"Cells can rid themselves of protein aggregates by either degrading them or refolding them with the help of chaperones," explains Zhou. "My long-term goal is to decipher the cross talk between chaperone-mediated refolding and mitochondria and to apply the resulting knowledge to the treatment of cardiovascular disease."


The American Heart Association is the nation's oldest and largest voluntary organization dedicated to fighting heart disease and stroke – America's number one and number four killers, respectively. **SI**

NIH AWARDS PREDOCTORAL FELLOWSHIP TO KRISTIN WATT

Kristin Watt, a graduate student in Stowers Investigator Paul Trainor's lab successfully competed for a Ruth L. Kirschstein National Research Service Award (NRSA), which is awarded by the National Institutes of Health to outstanding predoctoral fellows. Watt will receive \$62,800 over three years for her studies into the causes of Treacher Collins syndrome, a severe birth defect that leads to malformation of the eyes, ears, and facial bones.

Treacher Collins syndrome (TCS) affects approximately one in fifty thousand live births and is associated with mutations in TCOF1, POLR1C, and POLR1D. Mutations in TCOF1 disrupt the development of neural crest cells, a population of cells which generate most of the cartilage, bone, and connective tissue in the head and face. The mutations explain the link between disrupted neural crest cell development and craniofacial malformations.

Less is known about the role of mutations in POLR1C and POLR1D, and Watt plans to use zebrafish as a model system to investigate their contribution to the pathogenesis of the disease. "We already found that mutations in the fish versions

of these genes mimic the characteristic cranioskeletal abnormalities seen in human patients," says Watt. "We are hoping that a better understanding of their function during development will highlight important avenues for the potential prevention of TCS." 



Kristin Watt

ONCE AGAIN, STOWERS INSTITUTE RANKS AMONG THE TOP THREE PLACES TO WORK

For the second year running, *The Scientist* magazine placed the Stowers Institute for Medical Research among the top three "Best Places to Work in Academia."

In the magazine's tenth and final annual survey, on newsstands in August, Stowers scientists cited the institute's infrastructure and environment—as well as available research resources—as key factors that give Stowers the "core strength" that lifted the institute into the number three spot.

Providing a first-rate scientific infrastructure ranks high on the institute's list of priorities and, as a result, about a third of its scientific budget is earmarked for technology centers and core facilities.

"Our funding structure gives us the flexibility to invest heavily into new technologies but also to come up with organizational innovations to provide the kind of expertise that allows Stowers scientists to dream big," says Scientific Director Robb Krumlauf, PhD. "We are very pleased that our consistent ranking as a great place to work for scientists supports our emphasis on providing the best possible resources for talented people to flourish."

In addition, research advisors, highly trained specialists who act as internal consultants, work closely with investigators on projects that break new technological ground. "What's unique about Stowers is that we are committed to providing the expertise to apply technology in novel ways," says Jay Unruh, PhD, a research advisor who specializes in molecular imaging. "This has repeatedly proven to be a critical step in helping our investigators unravel the mysteries of complex biological phenomena."

But it is the Stowers famously collaborative atmosphere—a commonly cited quality of organizations that place highly in Best Places to Work, according to *The Scientist*—that encourages the kind of chance encounters and casual conversations that often spark new ideas.

The rankings were based on surveys that gathered 1,249 responses from scientists across the country. Participants were asked to rate their institutions on thirty seven criteria in eight categories: job satisfaction, peers, infrastructure and environment, resources, compensation, management and policies, teaching and mentoring, and tenure and promotion.



ROBB KRUMLAUF

Renewed as investigator

Robb Krumlauf, PhD, has a long-term interest in the molecular signals and regulatory networks that pattern both the nervous system and overall body plan of vertebrate embryos. He is renowned for his work showing that the family of conserved DNA-binding proteins encoded by Hox genes function as master regulators that govern the formation of the hindbrain and face during mouse development. Those pioneering studies illustrate unifying principles that shape organisms as diverse as fruit flies and mammals during development, disease, and evolution.

His current research uses genomic technologies to identify downstream target genes of Hox proteins and to understand how combinations of Hox proteins specify the unique properties of tissues. Krumlauf is also investigating the origins of vertebrate head diversity by studying the sea lamprey, a jawless fish at the base of the vertebrate family tree.

In recent collaborative work with Stowers colleagues, Krumlauf surveyed how factors that change DNA structure switch Hox genes off and on in a tissue-specific manner. These studies also revealed that the SEC protein complex, which elongates RNA transcripts, is recruited to specific Hox genes to facilitate their rapid expression in response to developmental cues.

In addition to leading a research group, Krumlauf serves as Stowers' scientific director, a position he has held since the institute was founded in 2000. During that time Stowers has recruited twenty eight faculty members and three leaders of technology centers integral to the institute's activities.

JENNIFER GERTON

Promoted to investigator

Jennifer Gerton, PhD, analyzes cell division focusing on factors that maintain proper chromosome number. Working primarily in yeast as a model system, Gerton studies two classes of proteins regulating the process.

One includes centromeric proteins residing at the knot of duplicated DNA strands. Last year her lab used microscopy to track a yeast protein unique to the centromeric protein core, and quantified how that protein, known as Cse4, is reshuffled during cell division. Understanding this rearrangement could suggest how cells occasionally acquire the wrong number of chromosomes, a disastrous condition associated with birth defects and cancer.

Gerton's other focus is cohesins, proteins that encircle and connect duplicated chromosomes prior to their segregation during cell division. Cohesin mutations cause human birth defects known as cohesinopathies, which are marked by head and limb anomalies and mental retardation. Interestingly, Gerton recently reported that yeast cohesin mutants also make fewer ribosomes, the machinery used to manufacture proteins, as do cells from patients with the cohesinopathy Roberts syndrome. This unanticipated finding suggests that reduced translation may underlie the disease.

R. SCOTT HAWLEY

Renewed as investigator

Scott Hawley, PhD, studies events occurring in meiosis, the specialized cell division that allows sexual reproduction by halving chromosome number. Historically, he has focused on the myriad factors required for egg generation in the fruit fly *Drosophila*.

Recently, Hawley has defined signaling factors that choreograph the process, among them the protein Matrimony, which he showed blocks a major driver of cell division, the Polo kinase. As Polo is frequently hyperactive in human cancer, the work provides a novel tool to potentially antagonize cancer growth. Hawley's lab also recently proposed a mechanism through which the highly conserved Shaggy kinase terminates female meiosis.

At the other end of the meiosis timeline, Hawley discovered that chromosome structures called centromeres cluster as maternal and paternal chromosomes line up and swap genetic information at the beginning of the process. Most recently, Hawley launched comparative studies of meiosis in planaria worms, which are better known for their remarkable regenerative capacity.

Inducted into the National Academy of Sciences in 2011, this year Hawley received the George W. Beadle Award for outstanding contributions to genetics research. Also known for his love of teaching, Hawley was instrumental in establishing the institute's Graduate School, which welcomed its first class a year ago led by Hawley as dean.

ALI SHILATIFARD

Renewed as investigator

Ali Shilatifard, PhD, has been studying protein complexes that regulate gene expression during normal development and mutations associated with human cancer. His interest lies in how these complexes function and how information about their catalytic properties can be used for the treatment of human malignancies.

Shilatifard's laboratory made history when its scientists identified the first histone H3K4 methylase in yeast. Known as Set1/COMPASS, it regulates gene expression through the methylation of histone H3, one of several DNA packaging proteins. Mammalian cells contain an extended set of six COMPASS-like complexes including Set1A/B, MLL1/2, and MLL3/4. Mutations and translocations involving MLL family members play a role in different forms of human cancer.

MLL translocations, which fuse MLL to seemingly unrelated genes, in particular, are associated with childhood leukemia, but it was unclear why. Shilatifard's lab discovered that many of the MLL translocation partners belong to the Super Elongation Complex (SEC) and demonstrated that the translocation of MLL into SEC leads to the misrecruitment of the SEC to MLL target genes. As a result, the transcription elongation checkpoint control at these loci is perturbed, ultimately leading to leukemia.

From left to right: Scientific Director and Investigator Robb Krumlauf, PhD, Investigator Jennifer Gerton, PhD, Dean of The Graduate School and Investigator R. Scott Hawley, PhD, Investigator Ali Shilatifard, PhD, Associate Investigator Julia Zeitlinger, PhD, Investigators Joan Conaway, PhD, and Ron Conaway, PhD.

JULIA ZEITLINGER

Promoted to associate investigator

Julia Zeitlinger, PhD, investigates global changes in gene expression, or transcription, that occur as an organism develops. Using the fruit fly as a model system, her long-term goal is to detect genomic patterns predictive of human disease.

In one approach, she compared DNA regions recognized by the site-specific regulator of transcription Twist among fruit fly species. That study reported evolutionary conservation of DNA regions recognized by Twist and its interacting partners despite significant cross-species differences in DNA sequence.

Zeitlinger is also extending paradigm-shifting discoveries she made as a postdoc showing that the enzyme pol II, which copies DNA into RNA, can reside at a DNA site in an idling, or poised state prior to gene activation. She now reports that recruitment of poised pol II to genes in maturing muscle cells changes over time. That study further showed that expression of polycomb proteins, which likely restrain pol II by creating a repressive DNA structure, is tissue-specific. The work reveals an exciting cross talk between temporal and tissue-specific mechanisms to control gene expression as an organism develops.

RON and JOAN CONAWAY

Renewed as investigators

Ron and Joan Conaway, PhDs, study how the enzyme pol II copies, or transcribes, DNA into RNA to activate gene expression. During their twenty nine-year scientific partnership they have characterized numerous components of the basic pol II transcription machinery and defined how other protein complexes control its function.

One frequent interactor with pol II is called the Mediator, which allows pol II to either stop or go. Recently, the Conaway lab showed how one Mediator subunit, MED26, sets pol II in motion from an idling state. That work illustrated that occupancy of DNA by pol II is not sufficient for proper gene expression but that pol II must be kicked into RNA-elongating mode by the Mediator.

In other work, the Conaways showed how a membrane-bound factor ATF6, which moves into the nucleus in response to cellular stress, recruits partners, including the Mediator and other enzymes that alter chromatin structure, to numerous gene targets to alleviate that stress. More recently they identified factors that switch on a different chromatin remodeler, ALC1. Since ALC1 is overactive in many liver cancers, the work could suggest new ways to dampen its activity. [SI](#)



FIRST NORTH AMERICAN PLANARIA MEETING HELD AT STOWERS

In May, more than seventy planaria researchers gathered at the Stowers Institute to present their latest findings and discuss future directions for their work at the first North American planaria meeting. For the meeting's organizer, Alejandro Sánchez Alvarado, PhD, a Howard Hughes Medical Institute and Stowers investigator, it was also a scientific family reunion.

Four generations of planaria researchers can trace their scientific pedigree to the day in 1997 when Phillip Newmark, PhD arrived from Spain with a thermos full of *Schmidtea mediterranea* to start his postdoctoral research in Sánchez Alvarado's lab at the Carnegie Institution of Washington.

Planarians, tiny freshwater flatworms, had been known for centuries for their remarkable regenerative abilities. Yet they didn't emerge as a recognized model system for the study of regeneration until Newmark and Sánchez Alvarado developed tools for studying gene function and visualizing stem cells in planarians.

"Failure was not something Alejandro ever considered," says Newmark, now a professor who heads a lab at the University of Illinois at Urbana-Champaign. "He was always confident that it was a worthwhile endeavor and that we would make it work."

Even when their whole planaria colony perished due to water quality problems Newmark and Sánchez Alvarado didn't quit. Instead, they got on the next plane to Spain to collect new specimens in a little-known fountain in one of Barcelona's public parks—a trip that over time not only took on an almost mythical aura, but also yielded all current lab strains of *Schmidtea mediterranea*.


"Back in the lab, this disaster provided the motivation to buckle down and spend nearly a year establishing a new colony derived from clonal lines," remembers Newmark, also a Howard Hughes Medical Institute investigator.

A few years later, while a postdoc with Sánchez Alvarado, Peter Reddien, PhD, conducted the first RNA interference screen in planaria research. The method, which relies on small RNA molecules to suppress the activity of specific genes, allowed him to turn off the activity of hundreds of genes one by one. This effort is among the first unbiased regeneration genetic screens performed, which allowed investigators to zero in on the molecular mechanisms driving regeneration.

Reddien, a member of the Whitehead Institute for Biomedical Research in Cambridge, Massachusetts, and a newly selected Howard Hughes Medical

investigator, describes those early days as a series of scientific and intellectual adventures driven by Sánchez Alvarado's unceasing curiosity about the natural world. "We took a risk by studying planaria, but if you ask challenging biological questions, it is inevitable that something of impact will arise."

Since these first pioneers started to poke and prod planarians with molecular tools, the field of planaria research has grown by leaps and bounds. Young scientists who trained with Newmark and Reddien have established their own labs and started to mentor the latest generation of students and postdoctoral students captivated by planaria's regenerative powers.

"As a scientist, the way I see it, I'd rather be engaged in the discovery of new continents, rather than mapping those that have already been discovered," says Sánchez Alvarado. "Planarians and regeneration offer vast, unexplored biological frontiers, fertile territories for discovery, and therefore for the expansion of human knowledge and understanding. Given the high caliber of the science discussed by the conference participants, it is clear to me that this group is meeting the challenge of discovery head on, and that the mysteries of regeneration will ultimately yield to their efforts." 



From left to right: Phillip Newmark, PhD, Christian Petersen, PhD, Alejandro Sánchez Alvarado, PhD, Jochen Rink, PhD, Nestor Oviedo, PhD, Erica Smith, PhD, Peter Reddien, PhD, Ricardo Zayas, PhD, Amy Hubert, PhD, Jason Pellettieri, PhD, James Sikes, PhD, Labib Rouhana, PhD



2002-2012 CELEBRANTS:
Members who have attained ten years of employment at Stowers celebrate with President and CEO Dave Chao and Scientific Director Robb Krumlauf.

Front row left to right: Dave Chao, Paul Kulesa, Debbie Baker, Michael Boyer, Jennifer Gerton, Robb Krumlauf.

Back row left to right: Donna Hartman, Rose Owens, Mike Elmore, Tari Parmely, Jamie Peterson, Malcolm Cook, Youbin Xiang, Rory Fender.

Not pictured: George Hewitt and Peter Baumann

Fourteen members were honored for ten years of loyal service to the Stowers Institute at an anniversary tea last spring. These extraordinary individuals have shared not only their time and talents but also their hearts to turn into reality the founders' vision of creating the world's most innovative research institute.

Together their experiences create a kaleidoscope of memories that paint a vivid picture of the uniquely collaborative culture that lies at the core of the Stowers Institute.

Lead Maintenance Engineer Jamie Peterson notes that no good job goes unrecognized. "I was proud of the work I did on the reptile facility a few years ago. But to get a letter of appreciation from the president of the company for all the hard work I had done made it seem even more worthwhile."

Benefits Specialist Debbie Baker says she most values the opportunity she has to meet and work with people from all over the world. "It feels good to be able to help our members understand all of the insurance and benefits we

offer. And what's even more gratifying is that everyone is so appreciative of those efforts."

Tari Parmely, head of Tissue Culture, Media Prep, Histology, and Electron Microscopy, continues to be inspired by her smart and dedicated co-workers. "Even after ten years, I still am happy to turn into the lot here at Stowers and take my small part in something great," she says. **SI**

BRENT KREIDER JOINS STOWERS AS CHIEF OPERATING OFFICER

This past summer, Brent Kreider, PhD, joined the Stowers Institute as chief operating officer (COO). In his role, he will oversee all aspects of Stowers' research support services and operational functions, including technology cores, operations and services, research regulations, environmental health and safety, information management, and security. He will also serve as COO of BioMed Valley Discoveries.

Kreider has an extensive track record of helping small and large biomedical research organizations develop and streamline the scientific support functions needed to operate efficiently.

"Brent loves working with people and gets great satisfaction from energizing and enabling them to move forward and be successful," says President and CEO Dave Chao, PhD. "He comes with tremendous experience in scientific operations and is a great fit for the collaborative

culture here at the institute. I look forward to working with him on providing our scientists with the most supportive environment we can."

Kreider joins Stowers after serving as vice president and global head of scientific operations at Novartis Institutes for Biomedical Research (NIBR) in Cambridge, Massachusetts, where he provided senior management oversight to scientific support functions at NIBR sites spread over North America, Europe, and Asia.

A native of Philadelphia, Kreider received a BS in microbiology from Penn State University and a PhD in molecular microbiology from the University of Pennsylvania. After completing postdoctoral studies at St. Jude Children's Research Hospital in Memphis, Tennessee, he held several positions at biotech companies, before joining NIBR as director of program operations in the cardiovascular disease area, in 2004.



Chief Operating Officer Brent Kreider, PhD

"I am honored to be included in the mission of the Stowers Institute as well as contribute to BVD's efforts of addressing unmet patient needs across the globe," says Kreider. "The progress of both organizations has been tremendous to date and I am excited to be a part of the continued success for years to come." **SI**



BACKSTAGE PASS

Erlenmeyer and Büchner flasks, measuring cylinders, test tubes, bottles, and beakers: Even in the era of high-tech plastics and nano materials, scientific glassware has retained its place as a science lab staple. It is specially designed to resist corrosive chemical attack, endure high temperatures, and maintain a constant measurement. The four-person team running the Stowers glass wash facility is in charge of decontaminating, cleaning, drying, and sterilizing or heat-treating all the glassware at the institute.

GLASS WASH BY THE NUMBERS

50,000

pieces of glassware

9,680

identifying tattoos applied to
new glassware annually

3,000

gallons of water used daily

900

pieces of glassware washed and sterilized daily

150

square feet of aluminum foil used to cap bottles
each day

20

volume in liters of the largest item washed
and sterilized

10

volume in milliliters of the smallest item washed
and sterilized

4

number of commercial size dishwashers

2.25

gallons of detergent used per day



STOWERS INSTITUTE®
FOR MEDICAL RESEARCH

1000 E. 50th Street
Kansas City, Missouri 64110
Tel: (816) 926-4000
Fax: (816) 926-2000
www.stowers.org



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OUR MISSION:

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



PLANARIA ARE FAMOUS FOR THEIR CAPACITY TO REGROW COMPLETE ANIMALS FROM MINUSCULE FLECKS OF TISSUE. HOWARD HUGHES MEDICAL INSTITUTE AND STOWERS INVESTIGATOR ALEJANDRO SÁNCHEZ ALVARADO, PHD, ESTABLISHED THEM AS A VALUABLE LABORATORY TOOL TO STUDY STEM CELLS, TISSUE MAINTENANCE AND ORGAN REGENERATION.

IMAGE: *Schmidtea mediterranea*.
The nervous system is shown in green, the intestinal cavity in red and the eyes in yellow.

Courtesy of Sarah Elliott (Stowers Institute for Medical Research) and Lisandro Maya-Ramos (UCSF)