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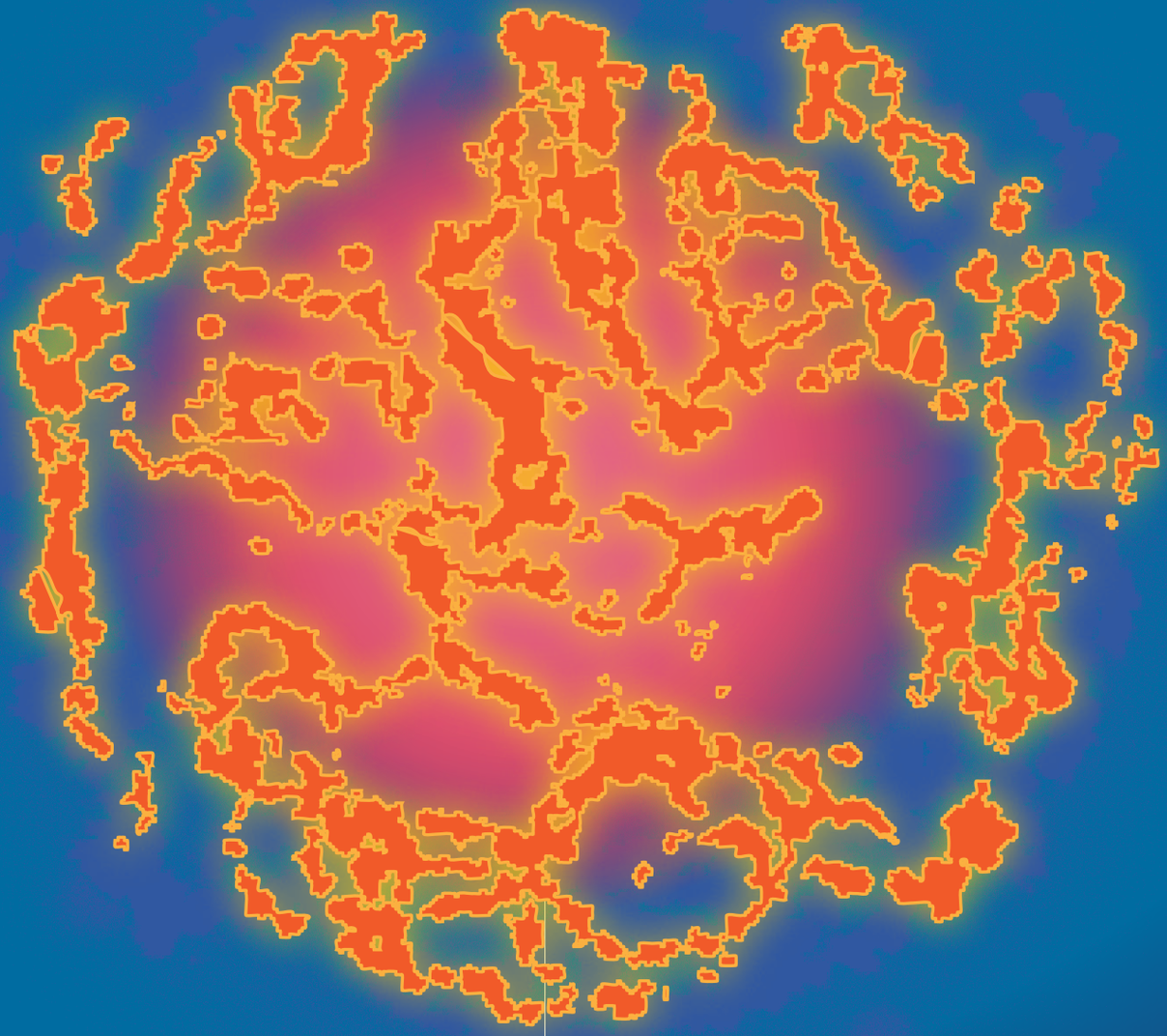

REPRODUCTION IN AN ALL-FEMALE SPECIES OF LIZARD. Page 5

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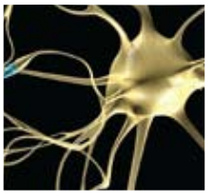

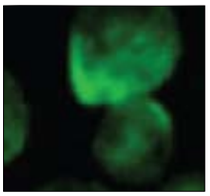

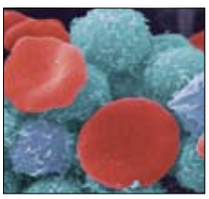

ALSO IN THIS ISSUE

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PUBLISHED BY THE STOWERS INSTITUTE FOR MEDICAL RESEARCH

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PRESIDENT'S LETTER

BY DAVID CHAO, PH.D., PRESIDENT

"Every great advance in science has issued from a new audacity of imagination." Philosopher John Dewey's observation, made eight decades ago, is an apt description of the Stowers Institute's approach to supporting research today. The Institute's approach, simply put, is to create an environment that fosters the audacity of imagination in our scientists. The Institute seeks to enable and inspire researchers to ask the audacious questions – those challenging questions whose pursuit may be marked by recurring failure but whose successful resolution will provide a leap forward in our understanding of biology and human health.

In part, the Institute encourages this kind of research by providing its investigators with generous endowment-based funding. Committed funding from the Institute is ideally suited for the support of high-risk or long-term projects that are harder to fund through granting agencies. Since its inception, the Institute has spent over $800 million to support bold research. On an ongoing basis, approximately 90% of the research at the Institute is funded from the endowment and 10% from grants, a proportion typically reversed at most research organizations. The Institute's commitment to endowment-based funding allows researchers to stretch their imaginations and focus on science rather than the distraction of constant applications for grant funding.

The Institute also provides its researchers with access to cutting-edge technology and, more importantly, to specialists with expertise in maximizing the impact of this technology. As technologies for observing and measuring biological phenomena improve rapidly and dramatically, the frontier of questions that can feasibly be addressed continuously expands. Experts in cutting-edge technologies are essential guides to exploring this frontier. Coordinating the application of different technologies requires a team-based approach, an approach that is a key part of the Institute's culture and strategy. Today, over 175 members of the Institute are dedicated to providing technological expertise to members of investigator-led laboratories. These experts are organized in over a dozen core laboratories and support facilities, with over 40% of the Institute's scientific operating budget committed to funding these services.

One of the Institute's core beliefs is that imagination thrives in an environment where ideas and information are exchanged freely and productively. Cultivating such an environment requires a careful blend of research programs and a commitment to a collegial culture. By choosing a scientific focus of developmental genetics, the Institute has built a critical mass of colleagues with a common interest in an important area of biology. At the same time, within this subject area, the Institute's investigators study a wide variety of research problems with a broad range of different approaches. The combination of a common interest with a diversity of perspectives provides the optimal constituency to maximize the likelihood for productive exchanges. Many of the Institute's policies and programs are aimed at further enhancing informal exchanges among members across labs, disciplines, and tenures.

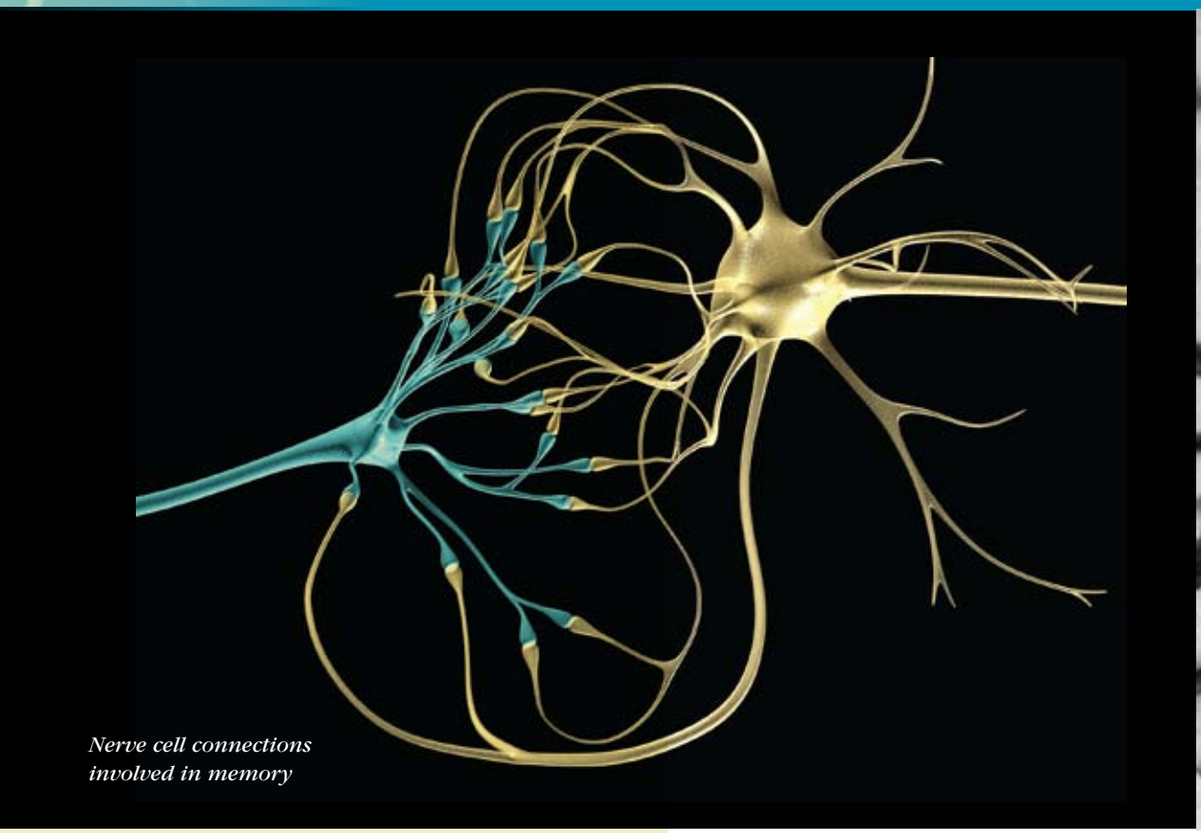
In this issue of the *Stowers Report*, you will read about some of the researchers who ask and answer bold questions that would have been challenging to pursue at any place other than the Stowers Institute. The approaches used to answer these questions drew heavily upon expertise resident in Bioinformatics, Microscopy, Proteomics, and Reptile and Aquatics.

The distinctive benefits of technological support are highlighted in an article describing the Institute's first "Technology Day" that brought together experts from the technology support facilities and investigator-led laboratories to imagine solutions to complex biological problems.

I hope you will enjoy the stories of "an audacity of imagination" in the pages that follow.

By Eugenia A. Park, Ph.D.

A PRION A DAY KEEPS THE DOCTOR AWAY:



Nerve cell connections involved in memory

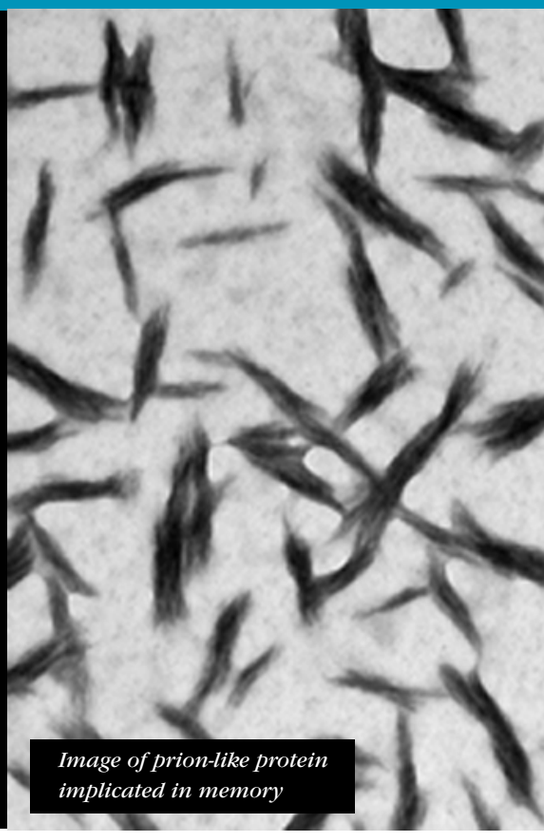


Image of prion-like protein implicated in memory

Laguna Design/Photo Researchers, Inc.

When you think "prion proteins" you might think "bad for the brain." You might think of mad cow disease, or the outbreak of Kuru in the Fore tribe of Papua New Guinea in the 1960s. Indeed, prions were originally described as infectious agents that are composed primarily of protein.

However, as the molecular basis for prion infections has become clearer, the term "prion" has been extended to describe non-infectious prion-like proteins. Like prions, these prion-like proteins have the potential to exist in two stable forms, one of which has the ability to convert molecules with the opposite form to its own. In a surprising twist, researchers in Kausik Si's Lab found that a prion-like protein plays a key role in memory.

The human brain contains roughly 100 billion neurons. Each of these neurons makes connections with potentially thousands of other neurons in a vast network. Each experience or thought causes an electric current to race through the network finding a path unique to that experience or thought. If the experience or thought is repeated, the electric current races down the same neural pathway and strengthens it. With repeated use, the neural pathway grows stronger and stronger, and a long-lasting memory forms.

How Prion-like Proteins may be Good for Your Health

Si Lab

Imagine life without memories.

Work from Kausik Si's Lab has uncovered an exciting new mechanism by which memories are maintained.

The synapse is a structure that connects neurons in a neural pathway. Synapses act as gatekeepers. They regulate the passage of a signal from one neuron to another. When a synapse is strong, the gatekeeper readily sees the signal and lets it pass. When a synapse is weak, the gatekeeper may not see the signal to let it through. Because synapses act as gatekeepers, neural pathways are only as strong as their synapses. If a neural pathway is to persist for days, weeks, or years, as many memories do, increases in synapse strength must last as long. A classic example of this occurs in the gill-withdrawal reflex of the sea snail.

The sea snail withdraws its gill in response to a perceived threat. When the siphon is gently stimulated, the siphon sensory neuron transmits a signal to the gill motor neuron and the snail withdraws its gill. With repeated siphon stimulation, this reflex disappears because the snail learns that stimulation does not present a threat. A shock to the tail restores the reflex for several minutes to an hour because the shock presents a threat. With repeated tail shocks, the reflex lasts longer, from days to weeks.

The lasting sensitization of the gill-withdrawal reflex with repeated tail shocks is a form of long-term memory. It is an example where the strength of the synapse joining the siphon sensory neuron and the gill motor neuron (the sensory/motor neuron synapse) *is* the memory. The period for which the sensory/motor neuron synapse stays strong coincides with how long the memory lasts. This sustained increase in the synapse's strength is known as long-term facilitation.

Mechanistically, a single tail shock causes the tail sensory neuron to signal a second neuron, the interneuron, to release the neurotransmitter serotonin at the interneuron's synapse with a third neuron, the siphon sensory neuron, which also connects to the gill motor neuron at the sensory/motor neuron synapse. The interneuron's release of serotonin at its synapse with the sensory neuron enhances the strength of the sensory/motor neuron synapse temporarily. Multiple shocks trigger the interneuron to release serotonin repeatedly. The serotonin binds to receptors on the siphon sensory neuron and activates cellular processes that ultimately alter the levels of different proteins. The changes in protein levels drive long-term structural and functional changes at the sensory/motor neuron synapse that establish and maintain long-term facilitation.

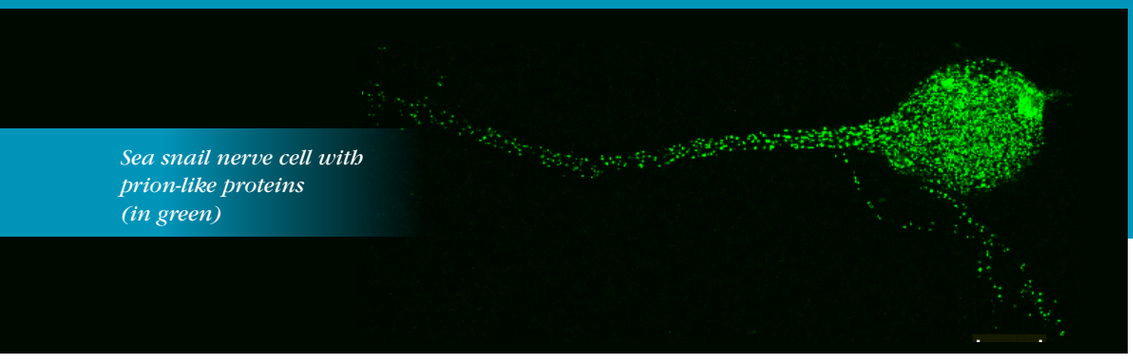
How does a neuron maintain long-term facilitation at one synapse (out of many) for hundreds of hours? In the case of the gill-withdrawal reflex, neuroscientists postulated that the molecular events that initiate long-term facilitation create a synapse-specific mark, or a molecular flag that designates a select synapse for sustained increase in the synapse's strength. However, many of the molecular determinants of long-term facilitation are proteins, and proteins degrade. If the mark were a protein, it might last only as long as the protein does.

Previously, Kausik Si and his colleagues proposed that a prion-like protein, ApCPEB, acts as the synapse-specific mark in sea snail sensory neurons. They made the observation that prion proteins exhibit characteristics that might enable a synapse-specific mark to endure and that ApCPEB displays prion-like characteristics in the unicellular fungus, baker's yeast.

Recently, Si Lab members made the critical observation that ApCPEB displays prion-like characteristics in sea snail sensory neurons. Prion proteins exist in two conformations, a normal cellular conformation and a misfolded conformation that causes disease. Misfolded prion protein binds to other misfolded prion proteins to create complexes called multimers. These multimers recruit normally folded prion proteins in order to grow. Since prion protein is a cellular protein, the cell synthesizes it and supplies multimers with building material. In the example of prion proteins, multimerization accounts for the spread of disease and also wreaks havoc on the nervous system. In contrast, for a synapse-specific mark that maintains long-term facilitation at certain synapses, this process may enable the mark to replenish itself and last for a long time.

Si Lab researchers, in collaboration with Eric Kandel's laboratory at Columbia University, found ApCPEB multimers in sea snail sensory neurons. They observed fluorescently labeled ApCPEB multimers in sensory neurons, and, in an experiment where they saw pre-existing ApCPEB multimers incorporate newly synthesized ApCPEB over two days, they concluded that ApCPEB multimers are self-sustaining in sensory neurons. In the course of the experiment, they found that ApCPEB multimers are immobile. This characteristic is also desirable in a synapse-specific mark since a mobile mark might travel to the wrong synapse.

These results are consistent with a prion-like multimeric ApCPEB having the characteristics necessary to act as a synapse-specific mark. The multimer makes more of itself so it lasts even if its protein components don't, and it doesn't seem to move so it won't wander to a different synapse. Si Lab researchers recognized



Sea snail nerve cell with prion-like proteins (in green)

Si Lab

that if ApCPEB multimers act as a synapse-specific mark that maintains long-term facilitation, ApCPEB multimers might be regulated by the neurotransmitter serotonin. They found this to be the case when they treated sensory neurons with the same course of serotonin that initiates long-term facilitation and observed increased amounts of multimeric ApCPEB in cells.

But how does ApCPEB actually maintain long-term facilitation, or a sustained increase in synapse strength, at certain synapses and not others? Kausik Si and his colleagues proposed an explanatory mechanism. ApCPEB regulates translation, or the synthesis of proteins, by binding to mRNAs. Previous work indicated that multimeric ApCPEB is more active than monomeric ApCPEB. This suggested that multimeric ApCPEB, present only at activated synapses, stimulates local protein synthesis using dormant mRNAs available at all synapses. Thus, multimeric ApCPEB ensures that the proteins needed to maintain long-term facilitation are made only at activated synapses.

If ApCPEB multimers are needed to maintain long-term facilitation, then disrupting multimer function should disrupt long-term facilitation. Si Lab researchers tested this possibility by using an antibody which specifically binds ApCPEB multimers. Sometimes when an antibody binds a protein, it disrupts the protein's function. By injecting an antibody that binds ApCPEB multimers into a sensory neuron, Si Lab members blocked the neuron's ability to maintain long-term facilitation.

ApCPEB is the first example of a prion-like protein that multimerizes in response to a physiological signal. In all other examples known to date, the conversion occurs spontaneously.

It is possible that the prion-like propagation of multimers in response to a physiological signal is an evolutionarily conserved mechanism by which organisms regulate the activity of cellular proteins. Si Lab researchers found that when expressed in sea snail sensory neurons, the fruit fly version of ApCPEB forms multimers in response to the neurotransmitter serotonin, which initiates long-term facilitation. This suggests that physiologically regulated multimerization of ApCPEB is evolutionarily conserved and may contribute to memory maintenance in other organisms, including humans.

The Si Lab's recent work provides insight into the molecular mechanisms underlying memory persistence. According to Kausik Si, Ph.D., Assistant Investigator, their work "provides a completely unexpected view about the potential physiological role of prion-like proteins in higher eukaryotes that contrasts with the pathological function of known prions."

Also surprising, a cell may induce a protein to adopt a prion-like state as a way to regulate the protein's activity after it is synthesized. "A regulatable conformational switch via prion-like conversion provides a novel paradigm for conferring post-translational changes in protein activity," says Kausik Si. "The idea that prion-like molecules could have normal physiological function has challenged our perception about prions, memory, and protein as a heritable factor."

PAPER: Aplysia CPEB Can Form Prion-like Multimers in Sensory Neurons that Contribute to Long-term Facilitation

JOURNAL: *Cell*

ISSUE: February 5, 2010

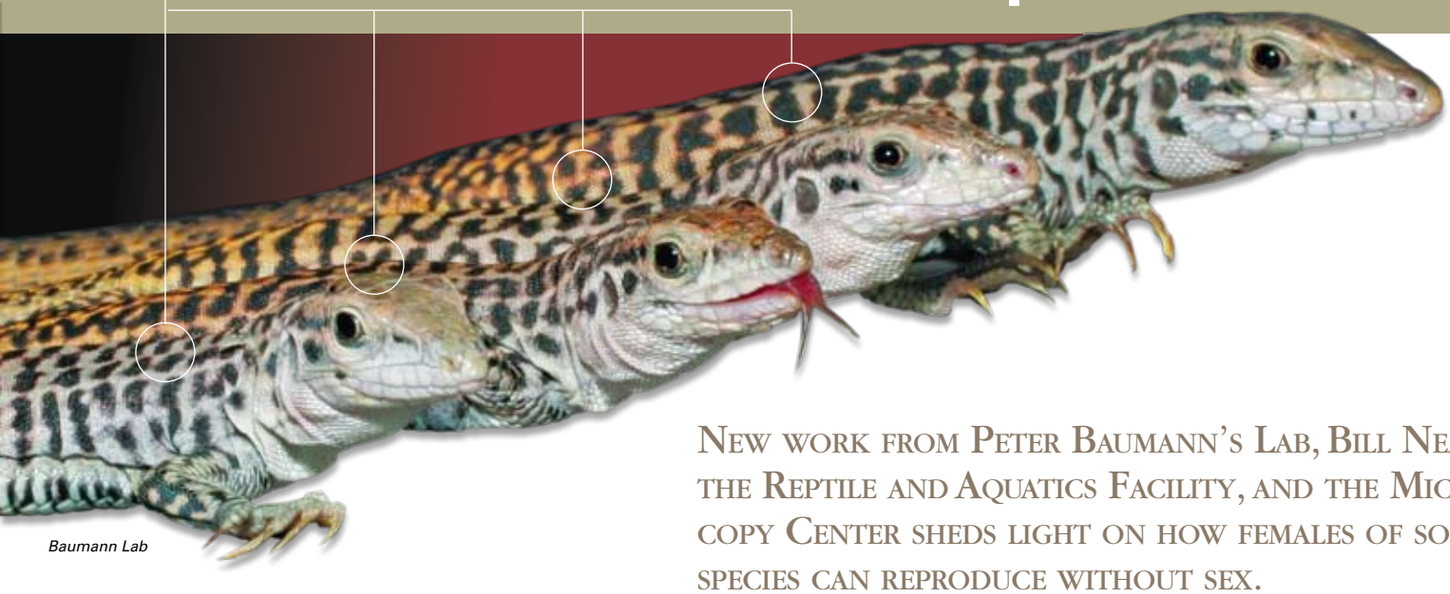
AUTHORS*: **Kausik Si, Ph.D.**, Assistant Investigator; **Yun-Beom Choi, M.D., Ph.D.**, Columbia University; **Erica White-Grindley, Ph.D.**, Postdoctoral Research Associate; **Amitabha Majumdar, Ph.D.**, Postdoctoral Research Associate; **Eric R. Kandel, Ph.D.**, Howard Hughes Medical Institute, Columbia University

**Authors' primary appointments are with the Stowers Institute for Medical Research unless otherwise noted.*

Kausik Si, Ph.D., Assistant Investigator, also is a Searle Scholar and an Assistant Professor in the Department of Molecular and Integrative Physiology at The University of Kansas Medical Center. Learn more about his work at www.stowers.org/labs/SiLab.asp.

By Eugenia A. Park, Ph.D.

Reproduction in an All-female Species of Lizard



Baumann Lab

Four generations of all-female (parthenogenetic) lizards reared in the Institute's Reptile Facility

New work from Peter Baumann's Lab, Bill Neaves, the Reptile and Aquatics Facility, and the Microscopy Center sheds light on how females of some species can reproduce without sex.

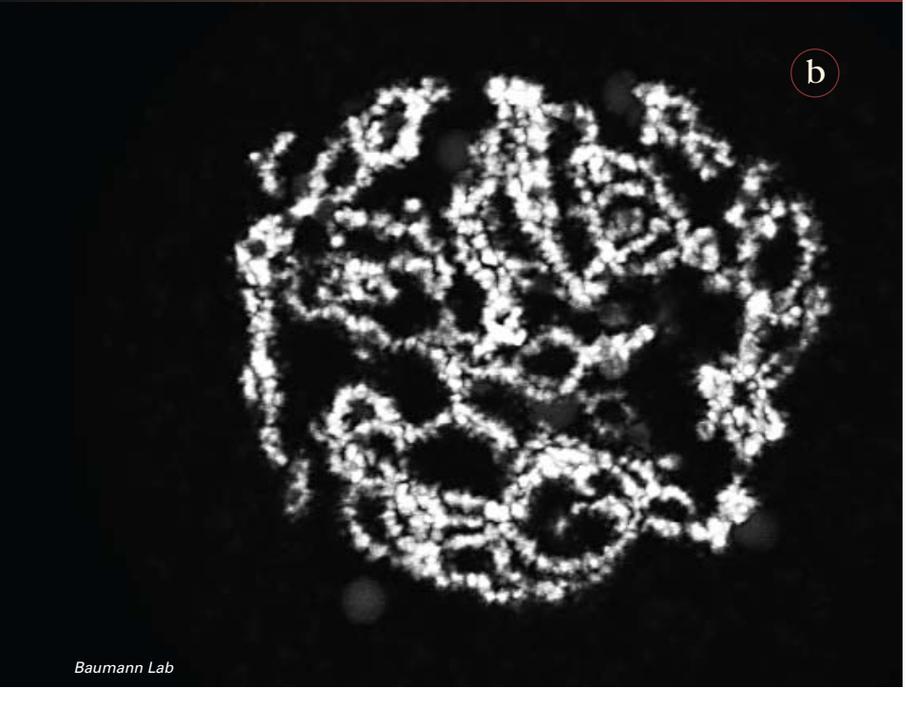
Sexually reproducing organisms use a process called meiosis to halve the number of chromosomes found in somatic cells (which make up the body) to generate sex cells (eggs and sperm). An organism made up of somatic cells with two copies of each chromosome uses meiosis to produce sex cells carrying one copy of each chromosome. When a sperm containing one copy of each chromosome from the father fertilizes an egg containing one copy of each chromosome from the mother, the resulting embryo contains two copies of each chromosome in its somatic cells: one from the father and one from the mother.

Over 70 vertebrate species reproduce by parthenogenesis, in which females produce offspring without mating with males, but the way in which many of these species accomplish this remained unknown. Recently, Diana Baumann and the Reptile and Aquatics Facility established reproducing colonies of parthenogenetic lizards at the Stowers Institute. This allowed the team to show that some parthenogenetic lizards use meiosis as sexually reproducing organisms do. However, instead of starting with oocytes, or egg precursor cells, containing *four* copies of each chromosome and generating eggs with one copy of each chromosome, these parthenogenetic lizards start with oocytes containing *eight* copies of each chromosome and generate parthenogenetic eggs containing two copies of each chromosome. These eggs give rise to offspring that are clones of the mother without being fertilized by sperm.

Graduate student Aracely Lutes isolated the nuclei, or chromosome-containing compartments, of oocytes about to enter meiosis and stained them with a DNA dye which stains chromosomes. With help from Winfried Wiegraebe of the Microscopy Center, she collected images of the nuclei at different depths and assembled three-dimensional reconstructions of the chromosomes contained within them. They found that oocyte nuclei from parthenogenetic species contain more chromosomes than those from sexually reproducing species. "We looked just before meiotic division when the chromosomes are highly condensed," says Peter

Baumann Lab

Chromosomes in egg-forming cells from sexual (a) and parthenogenetic (b) lizards.



Baumann Lab

Baumann, Ph.D., Associate Investigator. "This really conclusively showed us that oocytes from parthenogenetic lizards went into meiosis with twice the number of chromosomes than oocytes from sexually reproducing lizards do."

These results suggest that whether a female reproduces sexually or by parthenogenesis depends on the chromosome content of oocytes entering meiosis. "It raises the intriguing possibility that females of some species may switch from sexual reproduction to parthenogenesis by regulating the chromosome content of oocytes entering meiosis," says Bill Neaves, Ph.D., Chief Executive Officer. "There are cases where females from sexually reproducing species, such as Komodo dragons, sharks, and snakes, reproduce parthenogenetically when mating options are limited. Switching from sexual reproduction to parthenogenesis may allow a female to pass her genes on to another generation in case a male comes along later."

Stowers scientists also shed light on how parthenogenetic species stay heterozygous over many generations. Previous work by Bill Neaves indicated that parthenogenetic females arose from the mating of two sexual species. Founder females received one copy of each chromosome from a father of one species and the other copy from a mother of another species.

What exactly does heterozygous mean? It means that an individual carries two different versions, or alleles, of a gene. Both alleles encode the same kind of protein – for instance, an enzyme required for breaking down dietary sugar – but the alleles and very often the proteins they encode are slightly different. It's like having two Phillips screwdrivers with different-size handles in a toolbox. They're both screwdrivers, but they're different and can be used in different situations. Being heterozygous for a gene is generally good because if one allele doesn't work in a situation, then the other might. If the screwdriver with the long handle doesn't fit into a tight space, the one with the short handle does. On the other hand, if an individual carries two identical alleles of a gene, then that individual might not have a tool necessary for survival. The individual carries two long-handled screwdrivers, and neither fits into a tight space.

In the case of the first parthenogenetic females that arose from mating between two sexual species, females received one allele of a gene from a mother of one species and a second allele of the same gene from a father of another species. Stowers scientists found that parthenogenetic lizards alive

today use meiosis to transmit both alleles to succeeding generations by regulating how chromosomes interact.

Before meiosis, the cell's machinery replicates each chromosome to make an identical copy which attaches along its length to the original. In sexually reproducing species, one copy of each maternal chromosome swaps segments with one copy of the corresponding paternal chromosome. This process of crossing-over is important for the chromosomes to divide correctly during meiosis, but it also means that the maternal and paternal chromosomes swap alleles, which are carried on the swapped chromosome segments.

If crossing-over occurred in founder females between a maternal chromosome from one species and a paternal chromosome from another species, they would not have transmitted alleles from both species to present-day lizards. To illustrate, if the maternal chromosome from one species carries an allele for a short-handled screwdriver and the paternal chromosome from the other species carries an allele for a long-handled screwdriver, and the two chromosomes swap alleles, the maternal chromosome ends up with the long-handled screwdriver allele. At the end of meiosis, a parthenogenetic egg with an intact paternal chromosome (which carries the long-handled screwdriver allele) and a maternal chromosome (onto which the long-handled screwdriver allele was transferred) carries two identical alleles of the gene. A lizard generated from this egg would carry two long-handled screwdriver alleles originating from the same species and could not access a screw in a tight space.

Stowers scientists showed that parthenogenetic species maintain heterozygosity over many generations by ensuring that only identical chromosomes cross over. Thus, the crossing-over necessary for accurate meiosis occurs, but identical chromosomes pair and exchange identical alleles, or versions, of a gene: a "maternal" chromosome pairs with another "maternal" chromosome and exchanges the short-handled screwdriver allele for another short-handled screwdriver allele. When the "maternal" chromosome transmits with a "paternal" chromosome carrying a long-handled screwdriver allele, the resulting parthenogenetic egg carries two different alleles from two different ancestral species. The lizard generated from this egg carries a short-handled screwdriver allele and a long-handled screwdriver allele and can access a screw in a tight space. If that screw needs tightening in order for the lizard to survive, the lizard will live.

Sexual reproduction allows different combinations of alleles to assemble on the same chromosome. For example, if a maternal chromosome carries alleles for long-handled flathead screwdriver and short-handled Phillips screwdriver and a paternal chromosome carries alleles for short-handled flathead and long-handled Phillips, crossing-over between these chromosomes can generate two new chromosomes: one carrying long-handled flathead and long-handled Phillips alleles and a second carrying short-handled flathead and short-handled Phillips alleles.

This does not happen in parthenogenetic lizard species because crossing-over occurs between identical chromosomes carrying identical alleles. However, parthenogenesis provides other advantages. It allows females with limited mating opportunities to safeguard genetic material in a daughter. Also, since each parthenogenetic female produces only females which produce only females, parthenogenesis rapidly expands a species' population, and this may enable parthenogenetic species to outcompete sexually reproducing species in a habitat.

Stowers scientists' work shows that sexually reproducing and parthenogenetic females produce eggs in remarkably similar ways. They employ meiosis. Notably, the chromosome content of oocytes entering meiosis differs. The work raises the possibility that a female could switch from sexual reproduction to parthenogenesis and back again by regulating the chromosome content of oocytes. Switching between sexual reproduction and parthenogenesis may equip a species to survive conditions that an exclusively sexually reproducing species or an exclusively parthenogenetic species could not.

PAPER: Sister Chromosome Pairing Maintains Heterozygosity in Parthenogenetic Lizards

JOURNAL: *Nature*

ISSUE: March 11, 2010

AUTHORS*: **Aracely A. Lutes**, Graduate Student; **William B. Neaves, Ph.D.**, Chief Executive Officer; **Diana P. Baumann**, Managing Director, Reptile and Aquatics Facility; **Winfried Wiegraebe, Ph.D.**, Director of Microscopy; **Peter Baumann, Ph.D.**, Associate Investigator

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William B. Neaves, Ph.D., Chief Executive Officer, also is a Professor in the School of Medicine at the University of Missouri at Kansas City.

By Stephanie C.W. Huang, Ph.D.

The Party Never Stops: PROTEIN DYNAMICS UNDERLYING

THE HUMAN BODY CONTAINS HUNDREDS OF DIFFERENT CELL TYPES, MANY TAKING ON VASTLY DIFFERENT SHAPES, OR MORPHOLOGIES, IN ORDER TO PERFORM SPECIALIZED FUNCTIONS.

For example, neuronal cells typically extend numerous protrusions from their central cell bodies with which to receive and send electrochemical signals. Epithelial cells, by contrast, do not have protrusions and are tightly adhered to their neighboring cells in order to form a solid layer of tissue that lines the cavities and structures in our bodies.

How do these different cell shapes arise? One important component is cell polarity – this refers to one end of a cell being distinguished from the other. These two ends are often very different in function. In a neuronal cell, the protrusions that receive signals are different from the protrusions that send signals. Similarly, in an epithelial cell, the side that faces the inside of the structure (the intestine, for example) is different from the side that faces the outside. Without polarity, such functional specialization would not occur.

At the Stowers Institute, the Rong Li Lab strives to understand the general mechanisms by which cells establish and maintain polarity by studying the mechanisms in the versatile model organism, budding yeast.

The Block Party

Budding yeast are so-called because they form a single bud on the cell surface during each round of cell division. The growing bud eventually breaks off to become a new cell.

Just before the bud emerges, a number of proteins can be observed at the site of this future bud, or the presumptive bud site. These proteins play an active role in establishing and maintaining this polarized site and in the protrusion and growth of the bud.

The presumptive bud site was initially postulated to be a static structure – one in which proteins would arrive, bind to each other, and stick in place. However, work from the Rong Li Lab and others in the field have put to rest this notion. This polarized site is in fact extremely dynamic, with proteins rapidly coming in and, just as rapidly, detaching and going back out.

"It's like a big block party," explains Rong Li, Ph.D., Investigator. "If you're looking down at the party from an airplane, it looks like people are stuck. But in reality, people are moving around and dancing. There is a balance between the number of people leaving the party and coming to the party."

The Master Regulator

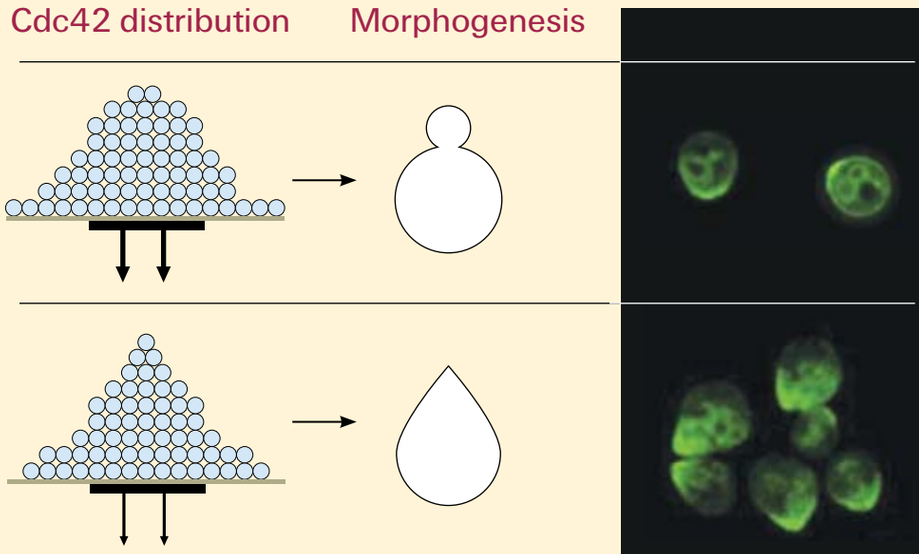
For the past several years, the Rong Li Lab has worked hard to understand the regulation of this dynamic polarized site. They primarily have focused on understanding the dynamic behavior of a protein called Cdc42. Cdc42 is important because it is the master regulator of polarity in many eukaryotic cell types, including yeast. Cdc42 activates a large number of other proteins to set into action all the cellular processes necessary for polarization.

Work from the Rong Li Lab has demonstrated that there are two delivery systems, or feedback loops, working together to deliver molecules of Cdc42 to establish the polarized site. In one loop, Cdc42 binds to vesicles, which are tiny hollow spheres of membrane, and travels along microscopic filaments called actin cables, which serve as transport highways in the yeast cell. In the other loop, three proteins form a complex with Cdc42 and help it to accumulate in order to form the polarized site.

But delivery of Cdc42 is only one part of the picture. Because the polarized site is dynamic, that means there is nothing keeping Cdc42 and other proteins attached to the site. Cdc42 molecules can quickly diffuse away from the polarized site along the plasma membrane, the membrane that forms the periphery of the cell. In order to maintain Cdc42 accumulation, molecules that diffuse away must be continuously brought back. This can be accomplished by capturing Cdc42 molecules and bringing them back to the same delivery tracks for return to the polarized site. This process is referred to as recycling.

In other words, if partygoers are free to leave the block party, there must be a way to bring them back – otherwise, the party is over.

YEAST CELL POLARIZATION



The distribution of Cdc42 on the plasma membrane of a yeast cell is influenced by the rate of internalization. A faster rate results in a relatively broad distribution of Cdc42 (top left). A slower rate results in a high concentration of Cdc42 in the center (bottom left). These are predicted to form, respectively, a round bud or pointed shmoo. On the right are microscopic images of live yeast cells containing a form of Cdc42 fused to a fluorescent protein.

Adapted from Slaughter et al. Dev Cell. *2009;17:823-35.*

Back to the Party

In a preliminary effort to address this question, the Rong Li Lab and collaborators published a study in *Cell* in 2007, reporting a simplified mathematical model that examined only one form of Cdc42, one that cannot detach from cell membranes. The model demonstrated that endocytosis plays a key role in the recycling of Cdc42. Endocytosis is the process by which small vesicles are formed from the plasma membrane, carrying any proteins contained within that portion of the membrane, and by which these vesicles and proteins are sent back into the cell. In the case of Cdc42 recycling, these vesicles can be sent right back to the actin cables for transport back to the polarized site.

Building on this earlier study, Brian Slaughter, Arupratan Das, and Rong Li, in collaboration with Joel Schwartz of the Imaging Center and Boris Rubinstein of the Bioinformatics Center, have now considered recycling in a more physiological context. Their findings, including an unexpected insight into the malleability of the polarity state, are published in the December 15, 2009 issue of *Developmental Cell*.

The simplified model had examined only membrane-bound Cdc42. In live yeast cells, however, much of Cdc42 is diffusing through the cell, unattached to membranes. In this new study, the team demonstrated that recycling of Cdc42 in live cells occurs via two distinct mechanisms. Endocytosis mediates recycling of membrane-bound Cdc42. In addition, a protein called Rdi1, which can pluck or extract Cdc42 from membranes, mediates the recycling of Cdc42 through a non-membrane route.

Next, the team built a complete mathematical model describing Cdc42 recycling, incorporating the Rdi1 component into the earlier model. They found that the dynamic behavior of Cdc42, as observed in live yeast cells, can be adequately described both experimentally and mathematically as a sum of the Rdi1-mediated and endocytosis pathways.

An Unexpected Finding

Analysis of the simplified mathematical model had indicated that the rate of endocytosis was optimized in order to maximize the concentration of Cdc42 at the polarized site. However, analysis of the new model indicated that internalization rates (now taking into account both endocytosis and Rdi1-mediated mechanisms) were faster than expected and that polarity was not maximized.

Upon further investigation, the team found that varying the rate of internalization affects the Cdc42 distribution on the membrane and likely affects the subsequent shape or morphology of the bud. A faster rate of internalization results in a relatively broad distribution of Cdc42. This is observed in dividing yeast cells and is consistent with the formation of a round bud. A slower rate of internalization results in a higher concentration of Cdc42 in the center. This would be predicted to form a pointed cell tip, not a round bud.

In fact, this is an alternative morphology that is actually observed in yeast cells. Cells exposed to mating pheromone form pointed extensions, or shmoos, which help them locate and fuse with cells of the opposite mating type. The team examined mating yeast cells and confirmed that the internalization rates of Cdc42 in these cells were in fact slower compared to rates in dividing yeast cells.

Future Implications

This study illustrates an elegant combination of experimental work and mathematical modeling. Through quantitative microscopy methods, the team was able to generate numerical parameters with which to build and refine the mathematical model. The mathematical model, in turn, allowed the team to identify key processes, predict behaviors, and then return to the experimental system to confirm these predictions. Together, the different approaches identified the rate of internalization as a key parameter in cell shape determination. Varying this one parameter can lead to very different morphological responses in yeast, i.e., either a round bud for cell division or a pointed shmoo for mating.

The findings by the team have implications for understanding polarization in other types of cells, especially our own. Epithelial cells, for example, are highly polarized. One of the hallmarks of tumor development is loss of cell polarity. Cancerous epithelial cells can detach from their neighbors, hyperproliferate, and migrate or metastasize to other sites. Given that the vast majority of human cancers are epithelial in origin, being able to understand how an epithelial cell establishes polarity and what can go wrong would help us to figure out how to prevent that process from ever happening or how to fix it when it does go wrong.

The uniqueness of the Rong Li Lab's study is their emphasis on dynamics, as opposed to genetic pathways. "Most disease research takes a gene-centric approach," says Dr. Li. "There has been very little attempt to incorporate models or dynamics into the morphogenesis and assembly of cellular structures. In explaining dynamics, we are also showing that dynamics are important. In this case, dynamics underlie the different morphologies. Just looking at the genetic pathway, you'll never get to this level of understanding."

PAPER: Dual Modes of Cdc42 Recycling Fine-Tune Polarized Morphogenesis

JOURNAL: *Developmental Cell*

ISSUE: December 15, 2009

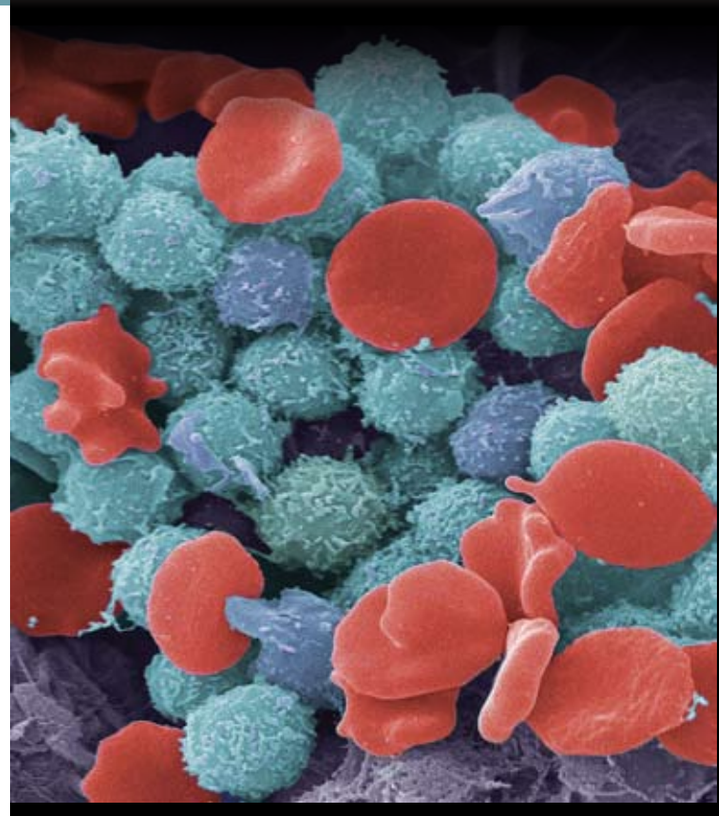
AUTHORS*: **Brian D. Slaughter, Ph.D.**, Postdoctoral Research Associate; **Arupratan Das**, Predoctoral Researcher; **Joel W. Schwartz, Ph.D.**, formerly Managing Director, Imaging; **Boris Rubinstein, Ph.D.**, Biomathematician; **Rong Li, Ph.D.**, Investigator.

**Authors' primary appointments are with the Stowers Institute for Medical Research.*

Rong Li, Ph.D., Investigator, also is a Professor in the Department of Molecular and Integrative Physiology at The University of Kansas Medical Center. Learn more about her work at www.stowers.org/labs/RongLiLab.asp.

By Stephanie C.W. Huang, Ph.D.

Towards a Better Understanding of a DEADLY LEUKEMIA



Colored image of leukemia blood cells taken with electron microscope (red blood cells are colored red, leukemia cells are colored in blue).

SPL/Photo Researchers, Inc.

Blood cancers, such as leukemia and lymphoma, are highly prevalent. Last year in the United States, blood cancers accounted for nearly 10% of newly diagnosed cancer cases, as well as nearly 10% of cancer-related deaths. Leukemia, in particular, is the most common type of cancer and the leading cause of cancer-related death in children and young adults under the age of 20.

Modern medicine has made great strides towards understanding and treating various forms of leukemia. For example, treatment of acute lymphoblastic leukemia in infants is generally highly effective, with 90% of patients achieving complete remission.

In contrast, infants with a particular subtype of leukemia called mixed lineage leukemia have a poor prognosis, with a mere 40% 5-year survival rate. Mixed lineage leukemia can be identified by examining cancer cells under the microscope and pinpointing a specific abnormality on chromosome 11, at a gene called MLL.

At the Stowers Institute, the Shilatifard Lab studies on a molecular level how leukemia arises, and through their studies, identifies potential targets for cancer therapy. Their previous work has helped to establish the normal cellular function of the MLL gene and contributed to our basic understanding of the processes involved in the development of leukemia.

Multiple Fusion Partners, One Disease

Many types of leukemia are caused by chromosomal rearrangements, particularly chromosomal translocations. A chromosomal translocation is an event where pieces of two different chromosomes break off and switch places. If the breakpoint occurs inside a gene, this can result in the formation of a fusion gene, one that contains a part of two different genes from different chromosomes.

In mixed lineage leukemia, the translocation event occurs in the middle of the MLL gene. This results in a fusion gene that contains the first half of the MLL gene and the second half of a variety of fusion partners. To date, over 50 different fusion partners for MLL have been identified. Despite this large number of fusion partners for the MLL gene, the cells from patients with mixed lineage leukemia show the same molecular changes. How is it that MLL fuses with so many different genes, yet these fusions result in the same symptoms and disease?

Turning Genes On and Off

In order to understand this, we need to first understand gene expression and how it can be regulated. Genes are encoded in our DNA-based genome contained within the nucleus of our cells. Gene expression refers to the process of "reading" the information encoded in our DNA, which is known as transcription. The information is transcribed into a strand of RNA, which is then brought out into the cytoplasm for translation into a gene product, often a protein.

James King-Holmes/Photo Researchers, Inc.

Example of chromosome translocation that can cause cancer. Chromosomes are stained blue. The pink and aqua chromosomes represent chromosomes in which the pink and aqua portions have switched chromosomes.

Not all of our genes are "on" all of the time. In fact, depending on the specific cell type or stage of development, certain subsets of genes will be "on" and others "off." The turning on and off of specific genes is how gene expression is regulated. When this on-off switch is broken, cells can exhibit aberrant cell behavior and turn into cancer cells.

There are numerous ways of regulating gene expression. One way is through modifying histone proteins. Histones help to package and organize DNA within the nucleus. There are enzymes in the nucleus dedicated to chemically modifying histone proteins so that DNA can be pulled away from the histones and "read" by the transcription machinery.

Another way of regulating gene expression is through regulating the RNA polymerase, the enzyme that "reads" DNA and transcribes it into an RNA strand. There are numerous proteins that promote transcription elongation – keeping the RNA polymerase moving along DNA and preventing it from stalling – and these are appropriately called elongation factors.

Dot1, A Questionable Suspect

Previous work has shown that many of the common MLL fusion partners interact with each other in a multiprotein complex. This complex is called EAP (for ENL-associated proteins) and is thought to assist in transcription elongation.

This EAP complex contains two key proteins that may help explain its role in the development of mixed lineage leukemia. One of these proteins is an enzyme called P-TEFb. P-TEFb chemically modifies the tail region of RNA polymerase, kick starting the polymerase if it has stalled.

But many studies have instead focused on the role of another protein, Dot1, which has been identified as a potential target for cancer therapy. Dot1 chemically modifies histones. It was proposed that Dot1 might turn "on" genes inappropriately, leading to the development of mixed lineage leukemia. However, it is poorly understood how the chemical modification by Dot1 might lead to transcription elongation.

AFF4, Always Present at the Scene of the Crime

In a paper published in the February 12, 2010 issue of *Molecular Cell*, the Shilatifard Lab presents the findings of a study that questions the role of Dot1 in mixed lineage leukemia and instead introduces a stronger candidate, a protein called AFF4.

The Shilatifard Lab asked what common factors might bind to MLL fusion proteins. They introduced into cells four of the most common MLL fusions and purified the protein complexes that bind to these fusion proteins. In close collaboration with the Proteomics Facility at the Stowers Institute, they analyzed the components of these protein complexes. Notably, two of the complexes do not contain Dot1, suggesting that Dot1 may not play a direct role in the development of mixed lineage leukemia. What they did find is that the protein AFF4 is present in all of these complexes.

This was fairly unexpected as AFF4 is not a well-characterized protein. Upon further investigation, the Shilatifard Lab discovered that AFF4 forms a complex with multiple elongation factors, many of which are MLL fusion partners. They named this assembly of proteins super elongation complex (SEC). SEC also contains P-TEFb, like the previously studied EAP complex, and SEC is able to modify the tail region of RNA

polymerase, and thus kick start the polymerase into action. More importantly, the stability and integrity of the SEC complex requires AFF4 – without AFF4, the protein complex falls apart and cannot function.

AFF4 is a Key Player

One of the key molecular changes that occurs in cells with MLL translocations is the turning "on" of the HOX genes, which are involved in development. Using a cell line from a patient with an MLL translocation, the Shilatifard Lab confirmed that two of these HOX genes, *HOXA9* and *HOXA10*, are turned "on" and additionally show that AFF4 is present at these genes, suggesting that it plays an active role in turning them "on." Removing AFF4 protein from these cells appears to turn "off" these HOX genes and results in a decrease in the levels of their gene products.

This final result highlights the therapeutic potential of AFF4. A drug that inactivates AFF4 or decreases its levels in the cell could prevent the turning "on" of the HOX genes, eliminating a key event in the development of mixed lineage leukemia.

Looking to the Future

It is important to note that further studies are necessary to flesh out the contribution of AFF4 to the development of mixed lineage leukemia and thus determine potential therapeutic routes. However, this study represents an important turning point. It moves us closer to an understanding of mixed lineage leukemia on a molecular level and provides a way forward in treating this aggressive disease.

"This study questions whether there is a direct role for Dot1 in the pathogenesis of leukemia, as previously proposed," explains Ali Shilatifard, Ph.D., Investigator. "What has been published in the literature is the tagging of ENL, a common component of both the Dot1 complex and the SEC, resulting in the purification of both complexes in one step and assuming that they are one. What we have shown in our study is that the real McCoy is the SEC, and that AFF4 is central to the SEC and its role in transcriptional elongation control and leukemogenesis."

Dr. Shilatifard credits his team for the success of this study. "On the one hand, we had a hard-working graduate student (first author Chengqi Lin), and on the other hand, we had a wonderful collaboration with the fabulous Proteomics Facility run by Mike Washburn and Laurence Florens. It was like the stars and sun aligned."

For more information, please visit the website of The Leukemia and Lymphoma Society: http://www.leukemia-lymphoma.org/hm_lls

PAPER: AFF4, a Component of the ELL/P-TEFb Elongation Complex and a Shared Subunit of MLL Chimeras, Can Link Transcription Elongation to Leukemia

JOURNAL: *Molecular Cell*

ISSUE: February 12, 2010

AUTHORS*: **Chengqi Lin**, Research Technician I; **Edwin R. Smith, Ph.D.**, Research Scientist; **Hidehisa Takahashi**, Senior Research Associate; **Ka Chun Lai**, Research Technician III; **Skylar Martin-Brown**, Research Technician III; **Laurence Florens, Ph.D.**, Managing Director of Proteomics; **Michael P. Washburn, Ph.D.**, Director of Proteomics; **Joan W. Conaway, Ph.D.**, Investigator; **Ronald C. Conaway, Ph.D.**, Investigator; **Ali Shilatifard, Ph.D.**, Investigator

**Authors' primary appointments are with the Stowers Institute for Medical Research.*

Joan Conaway, Ph.D., Investigator, holds the Helen Nelson Distinguished Chair. She also is a Professor in the Department of Biochemistry and Molecular Biology at The University of Kansas Medical Center. Learn more about her work at www.stowers.org/labs/ConawayLab.asp.

Ronald Conaway, Ph.D., Investigator, also is a Professor in the Department of Biochemistry and Molecular Biology at The University of Kansas Medical Center. Learn more about his work at www.stowers.org/labs/ConawayLab.asp.

Ali Shilatifard, Ph.D., Investigator, joined the Stowers Institute in 2007 from the Saint Louis University School of Medicine. Learn more about his work at www.stowers.org/labs/ShilatifardLab.asp.

Michael Washburn, Ph.D., Director of Proteomics Center, also is an Associate Professor in the Department of Pathology and Laboratory Medicine at The University of Kansas Medical Center. Learn more about his work at www.stowers.org/labs/WashburnLab.asp.

OLIVIER POURQUIÉ BECOMES DIRECTOR OF THE INSTITUTE OF GENETICS AND MOLECULAR AND CELLULAR BIOLOGY

Investigator Olivier Pourquié, Ph.D., resigned his Howard Hughes Medical Institute appointment at the Stowers Institute on September 30, 2009 to become Director of the Institute of Genetics and Molecular and Cellular Biology (IGBMC) in Strasbourg, France.

The IGBMC was founded in 1994 and has become one of the leading European centers of biomedical research. It is devoted to the study of higher eukaryotic genomes and to the control of genetic expression as well as the analysis of the function of genes and proteins.

Dr. Pourquié joined the Stowers Institute in June 2002 after serving as an independent research group leader in the Developmental Biology Institute of Marseille, France. At the Stowers Institute, Dr. Pourquié quickly established a highly productive research program based on his earlier discovery of the rhythmic gene regulation underlying formation of periodic structures of the vertebrate body such as the vertebrae. While at the Stowers Institute, he published numerous high-profile papers in leading scientific journals that firmly established his leadership in the field of vertebrate developmental biology. His research at the Institute revealed the detailed mechanisms governing the segmental organization of muscle and vertebral precursors, a field of research with significant relevance to developmental disorders and human birth defects.

Dr. Pourquié's research accomplishments at the Institute led to numerous prestigious awards and honors. They include:

1. In 2004, the American Association of Anatomists honored Dr. Pourquié with the Harland Winfield Mossman Award in Developmental Biology in recognition of his pioneering research on mechanisms governing temporal control of patterning in spinal segmentation.

2. Also in 2004, the editors of the Nature Publishing Group released their *Milestones in Development* which credited Dr. Pourquié with the most recent of 24 notable discoveries in developmental biology over the past 100 years: his discovery of the segmentation clock that controls somite formation during spinal development.

3. In 2005, the Howard Hughes Medical Institute selected Dr. Pourquié as one of only 43 researchers to receive coveted Investigator appointments from among more than 300 invited nominees.

4. Later in 2005, Dr. Pourquié received the Victor Noury Award from the Institut de France on the recommendation of the French Academy of Sciences in recognition of his research discoveries regarding the molecular processes responsible for spine development in vertebrates.

"During his seven years here, Olivier Pourquié's collaboration with our research support facilities and technology centers brought cutting-edge technologies to bear on important questions in the field of spinal development," said David Chao, Ph.D., President of the Stowers Institute. "We are proud of Olivier's significant contributions in this area and pleased that his notable productivity has accelerated international recognition of the Institute as a sponsor of superlative biomedical research."

"We are gratified that France has recognized Olivier Pourquié as the best-qualified successor of Pierre Chambon to lead the Institute of Genetics and Molecular and Cellular Biology in Strasbourg," said Bill Neaves, Ph.D., Chief Executive Officer of the Stowers Institute. "Olivier will do an outstanding job in his new position, and the Stowers Institute is pleased to have played a role in preparing him for it."

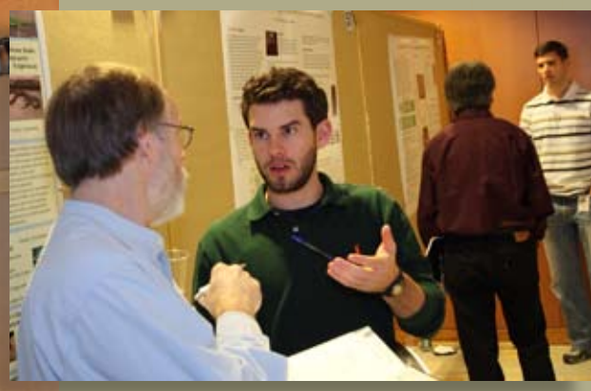
"It was an incredibly exciting experience to participate in the success of the Stowers Institute and see it grow so rapidly to become an international leader in basic biomedical research," said Olivier Pourquié, Ph.D. "It was wonderful to hold a Howard Hughes investigatorship at the Stowers Institute and focus entirely on science in the most supportive environment I have ever experienced while surrounded by outstanding colleagues. Returning to France was not an easy decision, but the opportunity to lead such a prestigious institute as the IGBMC constituted a unique opportunity. This, together with family ties in France, eventually led me to decide to come back home."

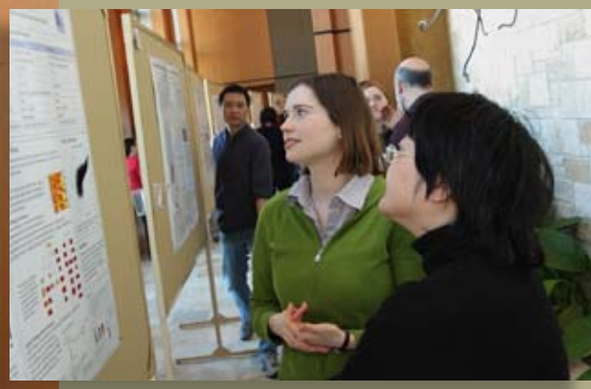
By Traci Angel

CULTIVATING COLLABORATION

Pictured are representatives from the following groups who participated in Technology Day:
Technology Facilities – Bioinformatics, Cytometry, Histology, Imaging, Microscopy, Molecular Biology, Proteomics, Reptile and Aquatics, Research Advisor, Tissue Culture

Other Support Services Teams – Glasswash, Information Technology, Lab Animal Services, Lab Support, Library Services, Media Prep, Research Regulations and Environmental Health and Safety, Technical Services





All photos this page—J. Casillas

Stowers scientists use cutting-edge technology provided on site to enhance experiments they publish in leading scientific journals. This technological expertise ranges from DNA sequencing to cell sorting to statistical analysis of results.

Technology Day on January 26 showcased technological support teams and what they offer principal investigators and their laboratories. The day allowed the mixing of approximately 350 members from the Institute's technology centers and research laboratories. Members of the technology support groups presented over 70 posters.

The event was an example of "the Institute's support of science through extraordinary commitment to world-class technology," said Jeff Haug, Managing Director of the Cytometry Facility and co-organizer of Technology Day. "This particular event provided just one more venue for scientists to exchange ideas and build collaborations," he said.

Over the lunch period, technology representatives answered questions about their posters, which highlighted their team's work and discussed possible techniques that scientists might utilize in future projects.

"We wanted to give them a forum to show off with technologies they love and are experts in," said Winfried Wiegraebe, Ph.D., Director of Microscopy and the event's co-organizer.

The day was also an opportunity for technology groups to receive feedback from scientists. "What we learned when presenting the posters helps us to plan for the future," Dr. Wiegraebe said. "It guides our decisions when committing new resources and starting to develop new technologies."

"Recent discussions with scientists at the Stowers Institute show that the seeds we planted at Technology Day are germinating," continued Dr. Wiegraebe. "We soon expect to see some new and exciting science to bloom."

2009 Year in Review

Taking Stock

At the close of 2009, 487 people worked at the Stowers Institute each day. 348 people were members of the scientific staff, including:

- 22 Principal Investigators
- 3 Technology Center Directors
- 88 Postdoctoral Research Associates and Fellows
- 41 Predoctoral Research Associates

By Eugenia A. Park, Ph.D.

J. Casillas

Making a Mark

In 2009, Stowers Institute research teams made discoveries meriting publication in leading peer-reviewed scientific journals – 57 papers in all. Add to that 35 reviews, commentaries and chapters, and one book, it makes for another impressive year. Highlights among 2009's published primary papers include:

- **Linheng Li's Lab**, in collaboration with the **Cytometry, Histology,** and **Imaging Facilities**, determined that inner bone surface stimulates blood stem cell proliferation in response to bone marrow damage by radiation (January 1 issue of *Nature*).
- The **Blanchette Lab** elucidated how cellular machinery cuts and pastes protein-encoding RNAs in different ways to generate protein variants (February issue of *Molecular Cell*).
- The **Mak Lab** elucidated how worm pheromones are made (February 10 issue of *Proceedings of the National Academy of Sciences*).
- The **Bioinformatics Center** discovered that co-transmission of genes from one species to another during evolution predict that they belong to the same biochemical pathway (published online by *PLoS One* on April 24).
- The **Washburn Lab** and **Proteomics Center** discovered that the protein Rtr1 modifies and regulates RNA polymerase II, which transcribes DNA into RNA (April 24 issue of *Molecular Cell*).
- The **Hawley Lab** and **Molecular Biology Facility** identified a mutated gene by sequencing the entire genome of a mutant and pioneered a new way to use whole genome sequencing to determine gene function (May issue of *Genetics*).
- The **Gibson Lab** found that different organisms use different patterns of cell division to make and maintain the linings of their organs and outer surface (published online by *PLoS Computational Biology* on June 12).
- The **Abmayr Lab** reported on fruit fly proteins that function similarly to the human proteins Neph1 and Nephrin that detoxify blood. Their work sheds light on congenital nephrotic syndrome in which infants develop protein in urine and swelling of the body (July issue of *Development*).
- The **Trainor Lab** demonstrated that a protein that regulates cell growth and proliferation also regulates spinal cord formation (July issue of *Development*).
- The **Xie Lab** found that a regulator of protein synthesis keeps stem cells in a high potential state, which makes them capable of differentiating into many cell types (July 14 issue of *Proceedings of National Academy of Sciences*).
- The **Conaway Lab** and **Proteomics Center** collaborated to show that the protein Alc1, a likely contributor to hepatocellular carcinoma, plays a role in packaging DNA into the nucleus (published online by *Proceedings of the National Academy of Sciences* on August 6).
- The **Shilatifard Lab** and **Jaspersen Lab** identified an important step in the modication of DNA packaging which results in gene expression (August 10 issue of *The Journal of Cell Biology*).
- **Rong Li's Lab** found that how sperm DNA is packaged determines how an egg rearranges structurally after a sperm fertilizes it (published online by *PLoS One* on September 29).
- The **Kulesa Lab** and **Imaging Center** pioneered a new way to watch organ development using fluorescently labeled cells and microscopy techniques (October/November/December issue of *Organogenesis*).
- The **Shilatifard Lab** and **Krumlauf Lab** reported that the mixed lineage leukemia gene modifies DNA packaging and may regulate the expression of genes necessary for embryonic development (November issue of *Molecular and Cellular Biology*).
- The **Baumann Lab** identified a human protein which prevents the end-to-end fusion of chromosomes. The protein prevents catastrophic defects in cell proliferation that may underlie the creation of cancer (November 4 issue of *EMBO Journal*).
- The **Gerton Lab** collaborated with the **Microarray Group** to shed light on molecular mechanisms underlying human diseases which cause face and limb abnormalities in infants (published online by *The Journal of Cell Biology* on November 9).
- The **Workman Lab** collaborated with the **Bioinformatics** and **Proteomics Centers** to identify a new complex that regulates gene expression (December 15 issue of *Genes and Development*).

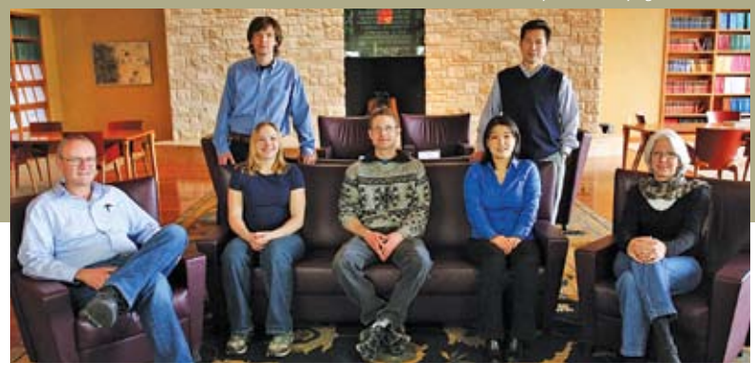
Alumni

At the end of 2009, the Stowers Institute had nearly 750 alumni members, an amount greater than its number of current members. In 2009, the following researchers left the Institute to continue their careers elsewhere:

- **Alexander Aulehla, Ph.D.**, Postdoctoral Research Associate, Pourquié Lab – Group Leader, European Molecular Biology Laboratory
- **Nancy Bae, Ph.D.**, Postdoctoral Research Associate, Baumann Lab – Visiting Assistant Professor, University of Nebraska-Omaha
- **Yong Cai, Ph.D.**, Research Specialist, Conaway Lab – Professor, Jilin University
- **Chunying Du, Ph.D.**, Assistant Investigator – Associate Professor, University of Cincinnati
- **William Gilliland, Ph.D.**, Senior Research Associate, Hawley Lab – Assistant Professor, DePaul University
- **Justin Grindley, Ph.D.**, Postdoctoral Research Associate, Linheng Li Lab – Principal Research Scientist, Pfizer Inc.
- **Angelo Iulianella, Ph.D.**, Postdoctoral Research Associate, Trainor Lab – Assistant Professor, Dalhousie University
- **Jingji Jin, Ph.D.**, Senior Research Associate, Conaway Lab – Professor, Jilin University
- **Ertugrul Ozbudak, Ph.D.**, Senior Research Associate, Pourquié Lab – Assistant Professor, Albert Einstein College of Medicine
- **Olivier Pourquié, Ph.D.**, Investigator – Director of the Institute of Genetics and Molecular and Cellular Biology
- **Mingan Shi, Ph.D.**, Senior Research Associate, Du Lab – Professor, Chinese Academy of Sciences
- **Min Wu, Ph.D.**, Postdoctoral Research Associate, Shilatifard Lab – Professor, Wuhan University

Accolades

All photos this page—J. Casillas



From left: Jerry Workman, Peter Baumann, Karen Smith, Hans-Martin Herz, Shima Nakanishi, Linheng Li, Susan Abmayr

From left: Sue Jaspersen, Ron Yu, Paul Trainor, Kausik Si (not pictured: Paul Kulesa)

- **Karen Smith, Ph.D.**, Postdoctoral Research Fellow in the Workman Lab, received the American Cancer Society Cattle Barron's Ball of Lubbock Postdoctoral Fellowship, effective in January.
- **Ron Yu, Ph.D.**, Assistant Investigator, received two supplements to his National Institutes of Health grant, effective in June and July.
- **Hans-Martin Herz, Ph.D.**, Postdoctoral Research Fellow in the Shilatifard Lab, was appointed a Fellow of The Jane Coffin Childs Memorial Fund for Medical Research, effective in July.
- **Sue Jaspersen, Ph.D.**, Assistant Investigator, received the Hudson Prize from the M.R. and Evelyn Hudson Foundation, effective in July.
- **Shima Nakanishi, Ph.D.**, Postdoctoral Research Fellow in the Shilatifard Lab, received a Leukemia and Lymphoma Society Fellowship, effective in July.
- **Kausik Si, Ph.D.**, Assistant Investigator, received a McKnight Scholar Award from The McKnight Endowment Fund for Neuroscience, effective in July.
- **Paul Kulesa, Ph.D.**, Director of Imaging, was a sub-recipient on a National Science Foundation grant from Montana State University, effective in August.
- **Susan Abmayr, Ph.D.**, Associate Investigator, and **Jerry Workman, Ph.D.**, Investigator, received a supplement to Jerry Workman's National Institutes of Health grant, effective in September

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- **Peter Baumann, Ph.D.**, Associate Investigator, was named a Howard Hughes Medical Institute Early Career Scientist, effective in September.
- **Linheng Li, Ph.D.**, Investigator, received a National Institutes of Health grant, effective in September.
- **Paul Trainor, Ph.D.**, Associate Investigator, was a sub-recipient on a National Institutes of Health grant from Cincinnati Children's Hospital, effective in September.

The following research technicians left the Institute in 2009 to attend professional schools:

- **Alejandra Figueroa-Clarevega**, Gibson Lab – University of California-Berkeley
- **Scarlett Gard**, Gerton Lab – Kansas City University of Medicine and Biosciences
- **Blake Geppert**, LAS – University of Amsterdam
- **Nichole Madison**, Glass Wash – University of Missouri-Kansas City School of Dentistry
- **Michael Morgan**, LAS – William Jewell College School of Nursing
- **Megan Rogge**, Jaspersen Lab – Saint Louis University School of Medicine
- **Danny Stark**, Imaging Center – University of Missouri-Columbia
- **Dana Vietti**, Hawley Lab – University of Kansas School of Medicine

The following graduate students completed their Ph.D. degrees in 2009 and left the Institute to pursue further training:

- **Goncalo Neto, Ph.D.**, Pourquié Lab – Institute of Genetics and Molecular and Cellular Biology
- **Jay Sarthy, Ph.D.**, Baumann Lab – Northwestern University Feinberg School of Medicine

2009 Research Leaders

Laboratories

Robert Krumlauf, Ph.D., Scientific Director and Investigator, joined the Stowers Institute in 2000 from England's National Institute for Medical Research, The Ridgeway, Mill Hill, London, where he was head of the Division of Developmental Neurobiology. Dr. Krumlauf received a Ph.D. in developmental biology from Ohio State University.

Research Focus: Analysis of molecular pathways that regulate how the mammalian head, brain, and nervous system are built, using a variety of vertebrate model systems

Susan Abmayr, Ph.D., Associate Investigator, joined the Stowers Institute in 2003 from the Pennsylvania State University where she served as Associate Professor of Molecular Genetics. She earned a Ph.D. in biochemistry and molecular biology from the Rockefeller University and completed postdoctoral training in the Department of Biochemistry and Molecular Biology at Harvard University under the direction of Professor Tom Maniatis.

Research Focus: Molecular genetics of cell fate specification and differentiation in Drosophila*, using the embryonic development of the musculature as a model system*

Peter Baumann, Ph.D., Associate Investigator and Howard Hughes Medical Institute Early Career Investigator, joined the Stowers Institute in 2002 after completing a Howard Hughes Medical Institute postdoctoral fellowship in the laboratory of Dr. Thomas R. Cech at the University of Colorado-Boulder. Dr. Baumann received a Ph.D. in biochemistry from the Imperial Cancer Research Fund and University College, London.

Research Focus: Functional analysis of telomeres and their roles in cellular immortality and cancer

Marco Blanchette, Ph.D., Assistant Investigator, joined the Stowers Institute in 2006 from a postdoctoral position with Dr. Donald C. Rio at the University of California-Berkeley where he was recipient of a Human Frontier Long-Term Fellowship. Dr. Blanchette received a Ph.D. degree in microbiology from the Université de Sherbrooke, Canada.

Research Focus: Functional genomic analysis of the mechanisms controlling alternative pre-mRNA splicing

Joan Conaway, Ph.D., Investigator, joined the Stowers Institute in 2001 from the Oklahoma Medical Research Foundation where she was an Associate Investigator of the Howard Hughes Medical Institute and interim head of the program in Molecular and Cell Biology. Dr. Conaway received her doctorate in cell biology from Stanford University School of Medicine.

Research Focus: Analysis of the molecular mechanism and regulation of gene transcription

Ronald Conaway, Ph.D., Investigator, joined the Stowers Institute in 2001 from the Oklahoma Medical Research Foundation where he was holder of the Chapman Chair in Medical Research. Dr. Conaway received his Ph.D. in biochemistry from Stanford University School of Medicine.

Research Focus: Analysis of the molecular mechanism and regulation of gene transcription

Jennifer Gerton, Ph.D., Associate Investigator, joined the Stowers Institute in 2002 from a postdoctoral fellowship in the laboratory of Dr. Joseph DeRisi in the Department of Biochemistry and Biophysics at the University of California-San Francisco. Dr. Gerton received a Ph.D. in microbiology and immunology from Stanford University.

Research Focus: Genomic and genetic analysis of chromosome segregation and chromosome dynamics

Matthew Gibson, Ph.D., Assistant Investigator, joined the Stowers Institute in 2006 from a Jane Coffin Childs Memorial Fund postdoctoral fellowship with Dr. Norbert Perrimon at Harvard Medical School. Dr. Gibson received a Ph.D. in zoology from the University of Washington.

Research Focus: Genetic analysis of mechanisms controlling signal transduction, cell proliferation, and epithelial morphogenesis during Drosophila *development*

R. Scott Hawley, Ph.D., Investigator, joined the Stowers Institute in 2001 from the University of California-Davis where he was a professor of genetics in the Molecular and Cellular Biology section. Dr. Hawley earned a Ph.D. in genetics from the University of Washington and completed postdoctoral training as a Helen Hay Whitney Fellow at the Institute for Cancer Research in Philadelphia.

Research Focus: Investigation of mechanisms that influence how chromosomes pair and segregate during meiosis using Drosophila *as an experimental system*

Sue Jaspersen, Ph.D., Assistant Investigator, joined the Stowers Institute in 2005 from the laboratory of Dr. Mark Winey at the University of Colorado-Boulder where she was a Keck Foundation Fellow, a Helen Hay Whitney Fellow, and the recipient of a Leukemia & Lymphoma Society Career Development Award. Dr. Jaspersen holds a Ph.D. in biochemistry from the University of California-San Francisco.

Research Focus: Inner nuclear membrane protein localization and role in chromosome positioning and segregation

Linheng Li, Ph.D., Investigator, joined the Stowers Institute in 2000 from the University of Washington Medical Center where he held a faculty appointment after completing postdoctoral training in the laboratory directed by Dr. Leroy Hood. Dr. Li earned his Ph.D. in molecular and cellular biology from New York University Medical School under the mentoring of Dr. Edward Ziff.

Research Focus: Investigation of molecular and genetic pathways controlling adult stem cell development in the hematopoietic and intestinal systems using transgenic and gene targeting animal model approaches

Rong Li, Ph.D., Investigator, joined the Stowers Institute in 2005 from the Department of Cell Biology at Harvard Medical School where she served as an Associate Professor. She earned a Ph.D. in cell biology at the University of California-San Francisco with Dr. Andrew Murray and held a Damon Runyon-Walter Winchell Cancer Research Fellowship as a postdoctoral associate with Dr. David Drubin at the University of California-Berkeley.

Research Focus: Mechanism of cell polarization and cell motility, biochemical basis of dynamics in the actin cytoskeleton, and how eukaryotic cells divide

Ho Yi Mak, Ph.D., Assistant Investigator, joined the Stowers Institute in 2006 from a Human Frontier Science Program postdoctoral fellowship in the laboratory of

Dr. Gary Ruvkun at Harvard Medical School. Dr. Mak received a Ph.D. in molecular pathology from the Imperial Cancer Research Fund and University College, London.

Research Focus: Genetic and molecular analysis on endocrine control of fat storage

Ali Shilatifard, Ph.D., Investigator, joined the Stowers Institute in 2007 from the Saint Louis University School of Medicine where he was a Professor of Biochemistry and Associate Director for Basic Sciences at the Saint Louis University Cancer Center. Dr. Shilatifard earned a Ph.D. in biochemistry from the University of Georgia and the University of Oklahoma School of Medicine and completed postdoctoral training as a Jane Coffin Childs Fellow at the Oklahoma Medical Research Foundation.

Research Focus: Molecular pathway of leukemogenesis

Kausik Si, Ph.D., Assistant Investigator, joined the Stowers Institute in 2005 from the laboratory of Dr. Eric Kandel at Columbia University Center for Neurobiology and Behavior where he was a Jane Coffin Childs Fellow and a Francis Goelet Fellow in Neuroscience. Dr. Si earned a Ph.D. in molecular biology from the Albert Einstein College of Medicine.

Research Focus: Role of synaptic protein synthesis in information acquisition and memory storage

Paul Trainor, Ph.D., Associate Investigator, joined the Stowers Institute in 2001 from a research position at the National Institute for Medical Research at Mill Hill, London, where he completed postdoctoral training. Dr. Trainor has a Ph.D. in developmental biology from Children's Medical Research Institute at the University of Sydney, Australia.

Research Focus: Investigation of the interactions between distinct tissues in the body and their regulation during normal development to reveal pathways that regulate normal cranial and facial development

Jerry Workman, Ph.D., Investigator, joined the Stowers Institute in 2003 from the Pennsylvania State University where he held the Paul Berg Professorship of Biochemistry and was an Associate Investigator of the Howard Hughes Medical Institute. Dr. Workman earned a Ph.D. in cell and molecular biology from the University of Michigan and completed postdoctoral training at the Rockefeller University with Dr. Bob Roeder.

Research Focus: Study of the protein complexes that modify chromatin

Ting Xie, Ph.D., Investigator, joined the Stowers Institute in 2000 after completing a Howard Hughes Medical Institute postdoctoral fellowship in the laboratory of Dr. Allan C. Spradling at the Carnegie Institution of Washington. Dr. Xie received his Ph.D. from the Joint Graduate Program in Molecular Biology and Biochemistry of Rutgers University and the University of Medicine and Dentistry of New Jersey.

Research Focus: Genetic and molecular analysis of stem cells and germ cell development in Drosophila *and mouse*

C. Ron Yu, Ph.D., Assistant Investigator, joined the Stowers Institute in 2005 from the laboratory of Dr. Richard Axel at Columbia University Center for Neurobiology and Behavior where he held a National Institutes of Health Mentored Research Scientist Award from the National Institute of Mental Health. Dr. Yu earned his Ph.D. in molecular, cellular, and biophysical studies at Columbia University.

Research Focus: How olfactory sensory information is detected, integrated, and processed in the brain to influence specific innate behaviors

Julia Zeitlinger, Ph.D., Assistant Investigator, joined the Stowers Institute in 2007 from the lab of Dr. Richard Young at the Whitehead Institute for Biomedical Research at Massachusetts Institute of Technology where she was the recipient of a long-term postdoctoral fellowship from the Human Frontier Science Program. Dr. Zeitlinger earned a Ph.D. in molecular biology from the European Molecular Biology Laboratory in Heidelberg, Germany.

Research Focus: Analysis of the gene regulatory networks underlying cellular differentiation

Technology Centers

Paul Kulesa, Ph.D., Director of Imaging Center, joined the Stowers Institute in 2002 after completing a Burroughs Wellcome Fund postdoctoral fellowship in the laboratory of Dr. Scott E. Fraser at the California Institute of Technology. Dr. Kulesa received a Ph.D. in applied mathematics under Dr. J.D. Murray at the University of Washington.

Research Focus: Cell migration in development and cancer

Arcady Mushegian, Ph.D., Director of Bioinformatics Center, joined the Stowers Institute in 2001 from Akkadix Corporation in San Diego where he led the bioinformatics program. Dr. Mushegian earned a doctorate in molecular biology at Moscow State University and received training at the University of Kentucky, University of Washington, and with Dr. Eugene Koonin at the National Center for Biotechnology Information at the U.S. National Institutes of Health.

Research Focus: Computational analysis of genes and proteins

Michael Washburn, Ph.D., Director of Proteomics Center, joined the Stowers Institute in 2003 from the Torrey Mesa Research Institute in San Diego where he was a Senior Staff Scientist in Proteomics. He earned a Ph.D. in biochemistry and environmental toxicology from Michigan State University before completing a postdoctoral fellowship with Professor John Yates, III in the Department of Molecular Biotechnology at the University of Washington.

Research Focus: Quantitative proteomics and protein complex dynamics

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Stowers Resource Management (SRM) is a Supporting Organization as that term is defined in the Internal Revenue Code. As such, it is a public charity. Its primary function as a legal entity is to support the Stowers Institute for Medical Research.

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