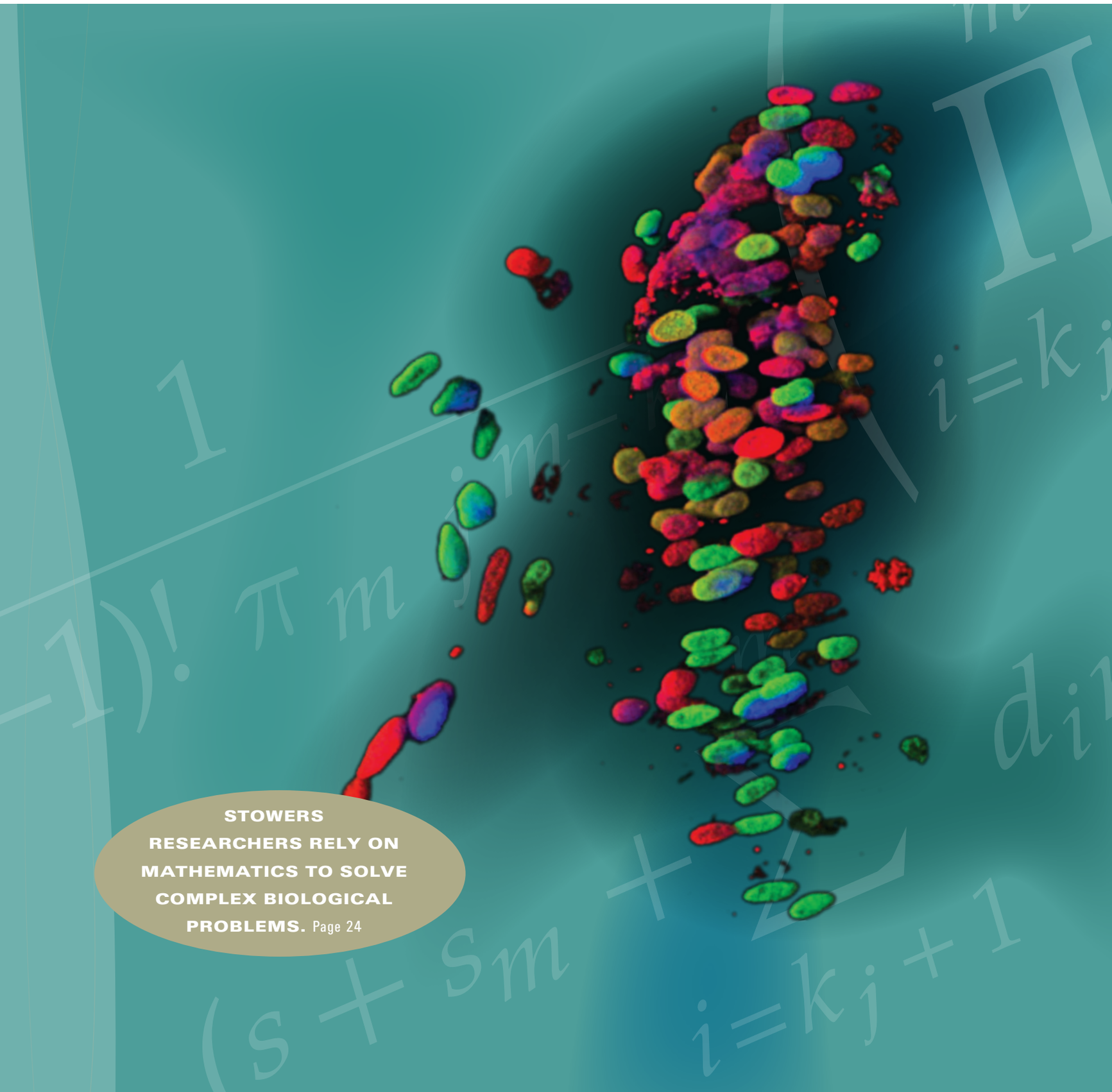
SPRING 2008

# Stowers REPORT

NEWS AND INSIGHT FROM
THE STOWERS INSTITUTE
FOR MEDICAL RESEARCH

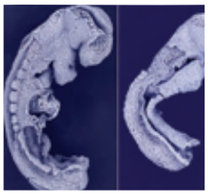


**STOWERS RESEARCHERS RELY ON MATHEMATICS TO SOLVE COMPLEX BIOLOGICAL PROBLEMS.** Page 24

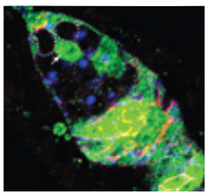
SPRING 2008

# Stowers REPORT

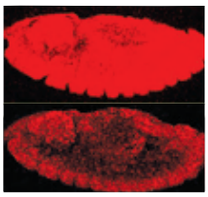
PUBLISHED BY THE STOWERS INSTITUTE FOR MEDICAL RESEARCH



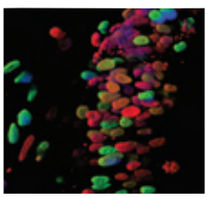














## ALSO IN THIS ISSUE








STOWERS REPORT

*SPRING 2008*
*PUBLISHED BY THE STOWERS INSTITUTE FOR MEDICAL RESEARCH*



*1000 E. 50TH STREET*
*KANSAS CITY, MISSOURI 64110*
*TEL: (816) 926-4000*
*FAX: (816) 926-2000*
*WWW.STOWERS-INSTITUTE.ORG*



CONTRIBUTORS:

*PHOTOS:*
*DON IPOCK**

*WRITING:*
*MARIE FARRELL JENNINGS*

*DESIGN AND LAYOUT:*
*KUHN & WITTENBORN ADVERTISING*

**unless otherwise credited*

# Relating Basic Research to Human Health

BY WILLIAM B. NEAVES, PH.D., PRESIDENT AND CEO

*The Institute is moving ever closer to Jim and Virginia Stowers' goal of fostering laboratory research that will improve human health.*

Jim and Virginia Stowers articulated a clear vision for the Institute a decade ago: it would improve human health by conducting basic biomedical research of high quality and fundamental importance – research that would point the way to more effective means of preventing and treating disease. Almost a decade later, evidence shows how well this vision has guided the Institute's early growth. This issue of the *Stowers Report* describes some of the discoveries emerging from the Institute's labs and how they may lead to cures for diseases that cause much human suffering.

Among several outstanding research accomplishments occurring at the Stowers Institute and featured in this *Stowers Report*, one that richly deserves our readers' attention is the Trainor Lab's carefully designed and meticulously documented demonstration of how a severe birth defect can be prevented (see page 2). The Trainor Lab's successful restoration of normal development in a congenital craniofacial anomaly provides an impressive example of how other birth defects of similar origins might be prevented. Due to the Trainor Lab's findings, as well as the Pourquié Lab's discoveries that lay the foundation for rational tactics aimed at preventing spinal malformations such as scoliosis (see page 4), the Institute has emerged as a major center of clinically relevant basic research on birth defects.

Another notable area of Institute research with profound implications for preventing and curing disease deals with the biology of stem cells. This issue of the *Stowers Report* features discoveries from the labs of Linheng Li and Ting Xie. The team from the Linheng Li Lab recently documented the existence of two subpopulations of cells in a pool of "primitive" bone marrow stem cells that support long-term production of blood cells; one is "primed" to support active blood cell regeneration without delay while the other is "reserved" for long-term maintenance of blood (see page 8). Since leukemias appear to involve two kinds of cancer stem cells – one more latent and the other more active – with each involved in cancer growth in different ways, the discovery from the Linheng Li Lab opens new approaches to developing more effective treatments for leukemias. Meanwhile, the Xie Lab showed that stem cells lacking the ability to develop into functional cell types can take over the microenvironment (i.e., the niche) and displace normal stem cells (see page 6). These abnormal stem cells resemble cancer cells by proliferating instead of differentiating into useful cells. The fact that they can outcompete normal stem cells for occupancy of the niche holds important implications for the behavior of cancerous stem cells in humans.

Also featured in this *Stowers Report* is work from Institute labs that pursue discoveries in chromosome biology relevant to disease. Using a single-cell research model, the Baumann Lab discovered the long-sought gene encoding the enzyme that rebuilds chromosome ends, a finding that should shed new light on the surprising correlations between shortening of chromosome ends and a variety of diseases including cancer and coronary heart disease (see page 11). The same article highlights research in the Shilatifard Lab that reveals how proteins surrounding DNA interact to enable gene transcription to occur, discoveries that are directly relevant to understanding the development of childhood leukemia (see page 12).

I hope you will enjoy reading this issue of the *Stowers Report* as the publication continues its focus on science and strives to let readers know what's happening in laboratories at the Stowers Institute. As you can see by the articles included here, the Institute is moving ever closer to Jim and Virginia Stowers' goal of fostering laboratory research that will improve human health.

Do you have a question about our research? Is there a topic you would like to see covered in a future issue of the *Stowers Report*? We welcome your feedback via E-mail to stowersreport@stowers-institute.org.

## Understanding and Preventing Birth Defects

# SOLVING PRENATAL

IN THE COMPLICATED PROCESS OF PRENATAL DEVELOPMENT, EACH CELL TYPE MUST PERFORM ITS DESIGNATED FUNCTIONS PROPERLY TO AVOID POTENTIALLY CATASTROPHIC ABNORMALITIES.

According to the March of Dimes, one in 33 babies born in the United States each year experiences abnormalities of structure, function, or metabolism that result in physical or mental disabilities or death. Both genetic and environmental factors – and in some instances a combination of the two – can lead to birth defects.

At the Stowers Institute, the Pourquié and Trainor Labs are investigating exactly how genetic factors play into the development of birth defects – and they are having great success.

### Signaling Pathways and the Formation of the Spine

The Pourquié Lab is among the world's leaders in furthering the understanding of how vertebrae develop to form the spine. Notably, the team has made significant contributions to the currently accepted "clock and wavefront" explanation of somitogenesis – the process by which the segments of the early embryo, which eventually become vertebrae, are formed.

The process occurs rhythmically based on the cyclic expression of the genes of three signaling pathways – WNT, Notch, and fibroblast growth factor (FGF). Signaling pathways are created by a series of biochemical reactions inside the cell, and they serve to regulate biological processes.

In somitogenesis, the rhythm is controlled by an internal segmentation "clock" in the layer of cells called the presomitic mesoderm (PSM). The PSM interacts with a molecular "wavefront" of differentiation to convert cues from the clock into positional information, telling somites where to form.

Errors in the process of somitogenesis can lead to significant birth defects like congenital scoliosis, a potentially severe curvature of the spine that affects one in 10,000 people worldwide. With conditions like these in mind, the Pourquié Lab is tackling questions about the precise role of signaling pathways in somitogenesis.

### The Role of FGF

In earlier work, the Pourquié Lab established the role of FGF-signaling in defining the boundaries of the PSM and, therefore, regulating the size of the somite. In the November 2007 issue of *Development*, the team further clarified the role of FGF in somitogenesis.

Previously, the role of FGF-signaling was speculative and relied on insights from gain-of-function experiments in chicken and fish. Evaluating the specific role of FGF in the segmentation process in mice has been difficult because turning FGF-related

# PROBLEMS

genes off completely has a devastating effect on the formation of the early spine, making it impossible to study normal somite formation. In the work published in November, the team overcame that challenge by implementing in mice a conditional deletion of a single FGF receptor, *Fgfr1*.

"Thanks to the use of the *Fgfr1* mutant mice, we were able to confirm the proposed role of FGF-signaling in setting the wavefront. In the process, we also demonstrated that FGF-signaling controls the clock," explained Olivier Pourquié, Ph.D., Investigator. "With this improved model, we will be able to generate genetic crosses with null mutants for other signaling pathways involved in somitogenesis in order to characterize genetically the interplay between the signaling pathways."

## The Role of ß-catenin

The Pourquié Lab has also recently advanced the understanding of the role of ß-catenin, a protein that functions as the principal mediator of the Wnt-signaling pathway, in somitogenesis.

Like FGF, Wnt-signaling has been implicated in both the clock and the wavefront mechanisms, but how the Wnt pathway can perform these two functions simultaneously had remained unclear.

The team used a novel yellow fluorescent protein and real-time imaging in mouse embryos to demonstrate that the rhythmic oscillations of the clock are independent of ß-catenin protein levels. In contrast, the Wnt-signaling gradient is established through a nuclear ß-catenin protein gradient in the posterior PSM. This gradient of nuclear ß-catenin defines the size of the oscillatory field and controls crucial aspects of PSM maturation and segment formation, emphasizing the central role of Wnt-signaling in the process.

"These novel insights demonstrate that the mechanism of maturation and oscillation in the PSM are controlled, in part, by ß-catenin. They also are

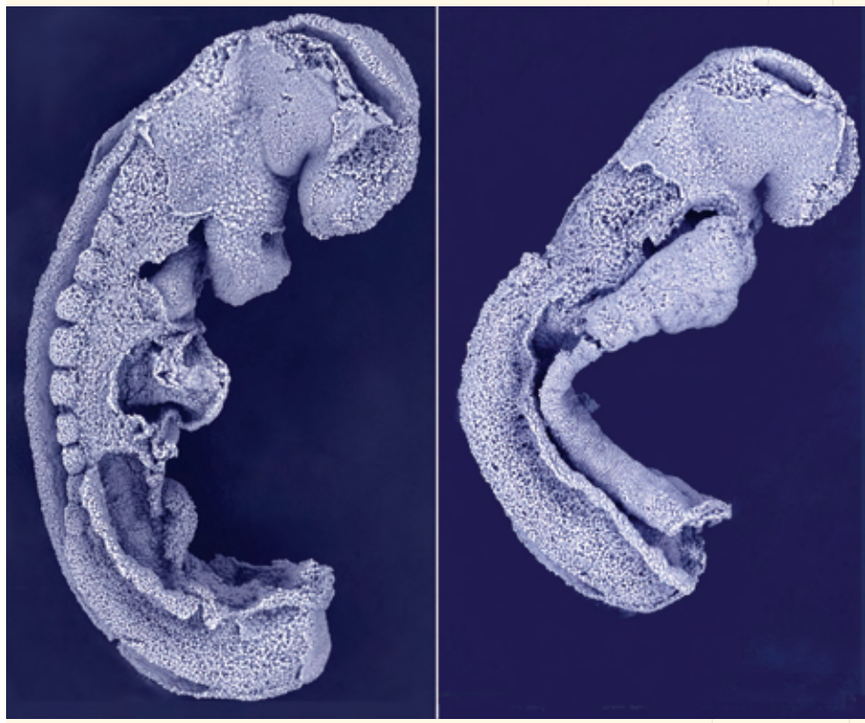
**PAPER:** FGF Signaling Acts Upstream of the NOTCH and WNT Signaling Pathways to Control Segmentation Clock Oscillations in Mouse Somitogenesis

**JOURNAL:** *Development*

**ISSUE:** November 15, 2007

**AUTHORS*:** **Matthias Wahl, Ph.D.**, Postdoctoral Research Associate; **Chuxia Deng, Ph.D.**, Genetics of Development and Diseases Branch, National Institutes of Diabetes and Digestive and Kidney Diseases, National Institutes of Health; **Mark Lewandoski, Ph.D.**, Laboratory of Cancer and Developmental Biology, National Cancer Institute-Frederick, National Institutes of Health; **Olivier Pourquié, Ph.D.**, Investigator

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



*Scans of a healthy mouse embryo (left) and a mutant ß-*catenin *mouse embryo (right) demonstrate the role of ß-*catenin *in the formation of the early spine. The healthy embryo has formed nine somites, while the mutant ß-*catenin *embryo has failed to form any.*

*Aulehla et al.,* Nature Cell Biology, *Feb. 2008, Vol. 10, No. 2*

**PAPER:** A ß–catenin Gradient Links the Clock and Wavefront Systems in Mouse Embryo Segmentation

**JOURNAL:** *Nature Cell Biology*

**ISSUE:** February 2008

**AUTHORS*:** **Alexander Aulehla, M.D.**, Senior Research Associate; **Winfried Wiegraebe, Ph.D.**, Director - Advanced Instrumentation and Physics; **Valerie Baubet, Ph.D.**, The Wistar Institute; **Matthias Wahl, Ph.D.**, Postdoctoral Research Associate; **Chuxia Deng, Ph.D.**, National Institutes of Diabetes and Digestive and Kidney Diseases, National Institutes of Health; **Makoto Taketo, M.D., Ph.D.**, Kyoto University; **Mark Lewandoski, Ph.D.**, Laboratory of Cancer and Developmental Biology, National Cancer Institute-Frederick, National Institutes of Health; **Olivier Pourquié, Ph.D.**, Investigator

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

interconnected," said Dr. Pourquié. "This is a pivotal finding in its own right, but the fact that it was achieved using real-time, fluorescent-protein-based imaging adds significantly to the global ramifications of this work.

"I believe that our improved understanding of the role of FGF-signaling and the role of ß-catenin in Wnt-signaling will bring us closer to a complete understanding of the role of signaling pathways in the intricate workings of the clock and wavefront and, ultimately, how the spine is formed."

## The Role of *Cux2* in Neurogenesis

Neurogenesis is the process by which neurons – cells in the brain and spinal cord that process and transmit information – are created. In the spinal cord, neurogenesis requires the complex integration of four functions: division and multiplication of primitive neural cells, called neuroblasts; cessation of cell division, known as cell-cycle exit; cellular migration; and cellular specialization, or differentiation.

"The process of neurogenesis is incredibly intricate," said Paul Trainor, Ph.D., Associate Investigator. "Not only does each of the four functions need to be carried out properly to form the right number and balance of different types of sensory and motor neurons, but they must all work in concert to form a fully integrated and functioning central and peripheral nervous system."

The central and peripheral nervous systems must work together to relay essential information. For example, when a hand touches something that is extremely hot or cold, the sensory neurons detect the temperature as being dangerous and relay the information to the motor neurons, which contract the appropriate muscles – removing the hand from any imminent danger.

When the process of neurogenesis goes awry, it can affect the ability to process sensory and motor information properly and, in cases where the body's essential organs are affected, it can affect the viability of the fetus.

The Trainor Lab published a paper in the February 15 issue of *Development* identifying the *Cux2* gene as playing a significant role in mediating the complex process of neurogenesis.

To study *Cux2*, the Trainor Lab generated mice with either reduced or enhanced *Cux2* gene activity. The team learned that *Cux2* is critically important for balancing the proliferation of primitive neural cells with their subsequent formation of sensory and motor neurons. Too little *Cux2* leads to an excess of motor neurons relative to sensory interneurons, while too much *Cux2* results in excess interneurons at the expense of motor neurons.

"*Cux2* directly stimulates neuroblast formation by activating proneural genes, which were so-named on the basis of their ability to transform naïve cells into different types of neurons," explains Dr. Trainor. "At the same time, *Cux2* promotes and maintains a primitive neuron pool in the spinal cord by promoting the progression of the cell cycle. The cell division cycle is 'terminal,' and it generates nascent post-mitotic interneurons and motor neurons which migrate to their final destinations at the lateral edges of the spinal cord."

In this manner, *Cux2* helps to ensure formation of a fully integrated nervous system of the correct size and shape by regulating the appropriate ratio of interneuron and motor neuron formation. This ultimately allows for proper interpretation and relay of sensory and motor information between the peripheral and central nervous systems.

**PAPER:** *Cux2 (Cutl2)* Integrates Neural Progenitor Development with Cell-cycle Progression during Spinal Cord Neurogenesis

**JOURNAL:** *Development*

**ISSUE:** February 15, 2008

**AUTHORS*:** **Angelo Iulianella, Ph.D.**, Senior Research Associate; **Madhulik Sharma, Ph.D.**, University of Kansas Medical Center; **Michael Durnin**, Research Specialist II; **Greg Vanden Heuvel, Ph.D.**, University of Kansas Medical Center; **Paul Trainor, Ph.D.**, Associate Investigator

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

*Skeletal stains of a healthy mouse embryo (left), an embryo exhibiting Treacher Collins Syndrome (TCS) traits (center), and an embryo fated to develop TCS traits (right), which was rescued by the inhibition of p53. Bone is stained red. Cartilage is stained blue.*

*Adapted from Jones et al.,* Nature Medicine*, Feb. 2008, Vol. 14, No. 2*

## Homing in on a Prevention Target for a Devastating Birth Defect

# Pursuing Prevention

Each day, more than 470 people come to work at the Stowers Institute – each doing his or her part to unravel the mysteries of disease; each striving for the discoveries that will ultimately bring patients the treatments and cures they anxiously await. One of the Institute's greatest hopes lies in furthering the prevention of devastating diseases and abnormalities – to spare families the fear inherent in words like, "Your baby has not developed normally."

In February, the Trainor Lab made an exciting advance toward the prevention of a devastating craniofacial birth defect called Treacher Collins Syndrome (TCS).

The team has studied TCS for several years. In 2006, they published a description of how mutations in the *Tcof1* gene affect early embryogenesis and cause the death of neural crest cells that are essential for making the head and face. The loss of these cells results in abnormal development of the ear, nose, and upper and lower jaw, and contributes to cleft palate and hearing loss.

More recently, in the February issue of *Nature Medicine*, the Trainor Lab evaluated how preventing the death of neural cells could restore normal head and facial development. Working with pregnant mice whose gestating pups were fated to develop TCS, the team discovered that by chemically inhibiting a single protein (the product of the p53 gene) they could prevent the craniofacial abnormalities caused by the *Tcof1* mutation. They also showed that "turning off" the p53 gene itself enabled neural crest cells to survive and form normal craniofacial structures in embryos carrying the *Tcof1* mutation.

In both instances, the mutations in the *Tcof1* gene and, therefore, the risk of passing TCS to offspring remain, but the Trainor Lab demonstrated that with intervention it is possible to prevent the craniofacial effects of the disease.

Like many genes, p53 performs a variety of functions, and the body requires a certain level of p53 for healthy development. Too much p53, such as in TCS, causes normal cells to die. Too little p53 is commonly associated with failure of abnormal cells to self-destruct, leading to the development of cancerous tumors.

Although blocking the function or activity of p53 during the first trimester of human pregnancy would conceivably prevent manifestation of TCS, it would also put the mother and child at a significant risk of developing cancer.

"Because of the very real possibility of tumor formation as a side effect, simply decreasing p53 levels will not be the ultimate method of preventing TCS," said Paul Trainor, Ph.D., Associate Investigator. "We are now working on alternative approaches to minimize the cell death that is associated with the development of TCS without creating new risks for the mother or the baby. We are moving toward an ability to screen more routinely for the *TCOF1* mutations and, as with folic acid and its broad impact on preventing a variety of birth defects, to administer a similarly preventative measure early in pregnancy to ensure a healthy birth. It is a tremendously motivating possibility for me and the members of my lab. It is always true that basic biomedical research takes time and requires patience, but I believe that a decade from now we will see real options for families carrying the TCS gene."

The Trainor Lab will continue their efforts to understand the factors involved in TCS by evaluating the potential of other genes to mediate the effects of p53 without the risk of cancer. They will also evaluate pharmaceutical interventions that could be used early in pregnancy to suppress the negative but not the positive effects of p53 and prevent the onset of TCS.

"It is gratifying for all of us at the Stowers Institute to see the Trainor Lab's years of work in TCS add up to this important step toward prevention," said William B. Neaves, Ph.D., President and CEO. "Jim and Virginia Stowers dedicated their fortune to establishing the Stowers Institute with faith that discoveries like this one would follow."

**PAPER:** Prevention of the Neurocristopathy Treacher Collins Syndrome through Inhibition of p53 Function

**JOURNAL:** *Nature Medicine*

**ISSUE:** February 2008

**AUTHORS*:** **Natalie Jones, Ph.D.**, formerly a Postdoctoral Research Associate; **Megan Lynn**, Research Technician III; **Karin Zueckert-Gaudenz**, Research Specialist II; **Daisuke Sakai, Ph.D.**, Senior Research Associate; **Kazushi Aoto, Ph.D.**, Postdoctoral Research Associate; **Jean-Phillipe Rey**, formerly a Histology Specialist II; **Earl Glynn**, Scientific Programmer; **Lacy Ellington**, Research Technician II; **Chunying Du, Ph.D.**, Assistant Investigator; **Jill Dixon, Ph.D.**,University of Manchester School of Dentistry; **Michael Dixon, Ph.D.**, University of Manchester School of Dentistry; **Paul Trainor, Ph.D.**, Associate Investigator

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

**Olivier Pourquié, Ph.D.**, Investigator, also is an investigator with the Howard Hughes Medical Institute and a Professor in the Department of Anatomy & Cell Biology at The University of Kansas School of Medicine. Learn more about his work at www.stowers-institute.org/labs/PourquieLab.asp.

**Paul Trainor, Ph.D.**, Associate Investigator, also is an Assistant Professor in the Department of Anatomy & Cell Biology at The University of Kansas School of Medicine. Learn more about his work at www.stowers-institute.org/labs/TrainorLab.asp.

# STICKING TOGETHER

## Adhesion Molecules and the Stem Cell Niche

STEM CELLS RESIDE IN MICROENVIRONMENTS CALLED NICHES. THESE TINY NOOKS, FORMED BY SUPPORTING CELLS, INTERACT WITH STEM CELLS TO REGULATE THEIR FATE.

Within the niche, stem cells generally exist in a state of rest, but damage to surrounding tissue can cause the niche to direct the stem cell to divide. When the stem cell divides, one daughter cell begins to differentiate and leaves the niche to replace an injured cell while the other daughter cell remains in the niche to repeat the process when necessary.

An essential component of the stem cell-niche interaction is the function of adhesion molecules. Previously, the Xie Laboratory used two types of *Drosophila* ovarian stem cells – germline stem cells (GSCs) and somatic stem cells (SSCs) – to characterize adhesion molecules located on the cell surface that bind the stem cell to the niche. Without proper adhesion to the niche, stem cells are unable to be maintained in the niche for continuous self-renewal.

Subsequently, the Linheng Li Laboratory reported that the adhesion molecule N-cadherin works together with the protein ß-catenin to form an adherent complex at the interface between the blood-forming (hematopoetic) stem cell and its niche in mouse bone marrow.

In recent months, the Xie Lab has revealed new functions of the adhesion molecule E-cadherin in stem cell aging and stem cell competition, and the Linheng Li Lab has uncovered additional important roles for the adhesion molecule N-cadherin in hematopoetic stem cells.

### Losing that Youthful Glow

Many of the signs of human aging – from wrinkling skin to decreased organ function – may be due to a decrease in the number and activity of stem cells over time. The factors contributing to stem cell aging have been obscure, but the Xie Lab recently advanced the understanding of the control of stem cell aging.

Working with fruit fly GSCs, the Xie team examined three factors in the control of stem cell aging.

First, they examined the role of bone morphogenic proteins (BMPs), which are important to the development of many tissues, and found that BMP-signaling activity is directly related to stem cell aging. As BMP-signaling in the niche decreases with age, the stem cell's ability to divide is compromised, and the stem cell population declines. Conversely, the team showed that an increase in BMP-signaling can promote division of stem cells and extend their lifespan.

Second, the team established that, over time, E-cadherin levels in the junction between a stem cell and its niche decline, contributing to stem cell aging, while an increase in E-cadherin in aged stem cells can slow the age-dependent decline in stem cell numbers.

Finally, the team discovered that over-expression of an enzyme that eliminates unstable oxygen molecules, either in the stem cells themselves or in their niche, increases division of stem cells and prolongs their lifespan.

**PAPER:** Stem Cell Aging is Controlled Both Intrinsically and Extrinsically in the *Drosophila* Ovary

**JOURNAL:** *Cell Stem Cell*

**ISSUE:** October 2007

**AUTHORS*:** **Lei Pan**, Predoctoral Researcher; **Shuyi Chen, Ph.D.**, Postdoctoral Research Associate; **Changjiang Weng, Ph.D.**, Postdoctoral Research Associate; **Gerald Call, Ph.D.**, Postdoctoral Research Associate; **Dongxiao Zhu, Ph.D.**, formerly a Biostatistician; **Hong Tang, Ph.D.**, Chinese Academy of Sciences; **Nian Zhang, Ph.D.**, Research Scientist; **Ting Xie, Ph.D.**, Associate Investigator

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

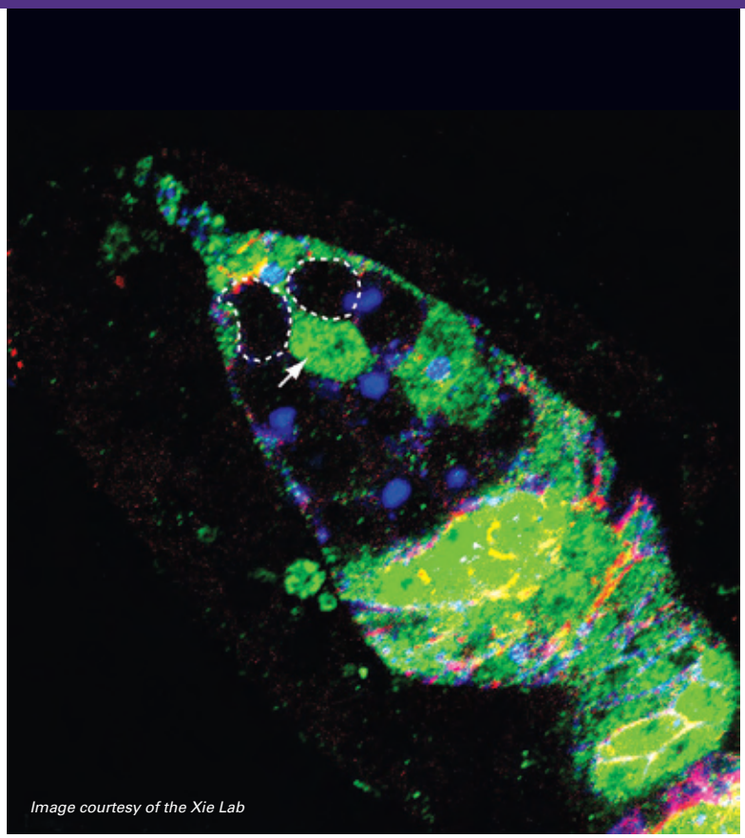


Image courtesy of the Xie Lab

*A normal germline stem cell (indicated by an arrow) in the process of being pushed out of the niche by two mutant stem cells (circled) in the same niche.*

"Establishing a better understanding of stem cell aging provides insights that may prove relevant to diseases associated with human aging," said Ting Xie, Ph.D., Associate Investigator and senior author on the publication. "If we can find a way to slow down stem cell aging in humans as we have done in fruit flies, we may be able to postpone the human aging process and the onset of age-related degenerative diseases."

## Sibling Rivalries

Rapid progress has been made in understanding how the niche controls stem cell function, but little has been established regarding how stem cells in the same niche, called siblings, interact with one another, or how differentiated stem cells leave the niche.

In the January issue of *Cell Stem Cell*, the Xie Lab addressed these issues in work conducted with mutated GSCs from the fruit fly ovary. Like cancer stem cells in mammalian systems, these cells are incapable of differentiating appropriately as their healthy counterparts would under the proper circumstances.

The team observed the behavior of the differentiation-defective GSCs and witnessed them invading the space of neighboring GSCs to gradually push them out of the niche by increasing the level of E-cadherin.

**PAPER:** Differentiation-defective Stem Cells Outcompete Normal Stem Cells for Niche Occupancy in *Drosophila* Ovary

**JOURNAL:** *Cell Stem Cell*

**ISSUE:** January 2008

**AUTHORS*:** **Zhigang Jin, Ph.D.**, Postdoctoral Research Associate; **Daniel Kirilly**, formerly a Predoctoral Fellow; **Changjiang Weng, Ph.D.**, Postdoctoral Research Associate; **Eihachiro Kawase, Ph.D.**, formerly a Postdoctoral Research Associate; **Xiaoqing Song**, Laboratory Manager I; **Sarah Smith**, formerly a Research Technician; **Joel Schwartz, Ph.D.**, Managing Director of Imaging; **Ting Xie, Ph.D.**, Associate Investigator

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

This E-cadherin-dependent control of the niche has two important ramifications. First, it demonstrates that differentiation-defective mutant GSCs can drive healthy stem cells away from their niche. This may explain how cancer stem cells are able to force their healthy neighbors out of the niche as they expand their own populations and spread cancer.

Second, the study offers important insights into how the niche controls stem cell quality by regulating E-cadherin levels to displace differentiated stem cells, ensuring that the niche is always occupied by self-renewing, undifferentiated stem cells.

"This new information about the competitive nature of stem cells may help us understand how cancer stem cells expand themselves and move to new sites during metastasis," said Dr. Xie, senior author on the paper. "This may facilitate new treatments for cancer and devise new strategies to deliver stem cells into the diseased tissues in future stem cell therapy, and it certainly explains how the healthy competition among siblings for niche occupancy provides a reliable quality-control mechanism."

## Multitasking Adhesion Molecules

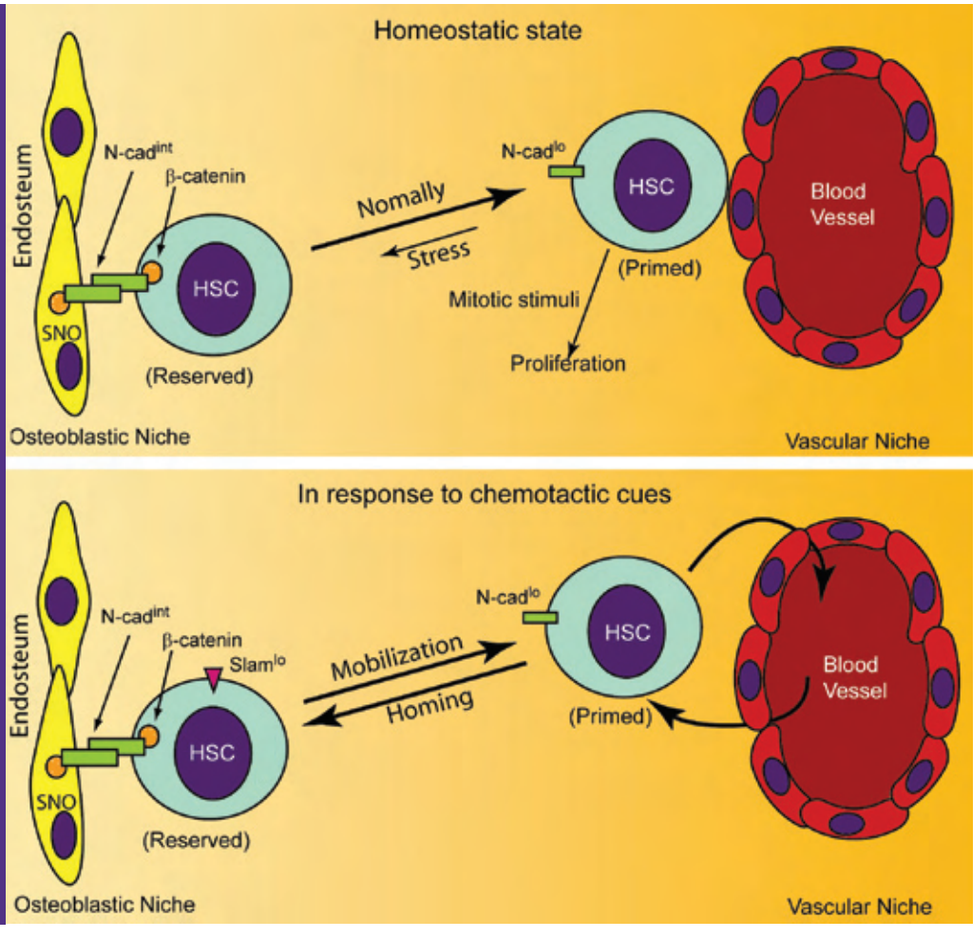
In normal, balanced states, blood-forming hematopoietic stem cells (HSCs) are relatively inactive, but in times of stress, such as chemotherapy or bone marrow transplantation, they are able to respond by rapidly multiplying to replenish their depleted supply.

Doing so requires a precise balance because excessive proliferation can lead to cellular exhaustion and the accumulation of mutations.

In addition to its significant role in anchoring stem cells to their niches, the Linheng Li Lab recently determined that N-cadherin plays a critical role in controlling the balance between the regeneration and long term maintenance of HSCs.

The team was able to demonstrate that low levels of N-cadherin correspond with HSCs in a "primed" state – they are ready to support active blood regeneration and to mobilize in the blood. Cells with intermediate levels of N-cadherin form a

*Haug et al., N-Cadherin Expression Level Distinguishes Reserved versus Primed States of Hematopoietic Stem Cells,* Cell Stem Cell *(2008), doi:10.1016/j.stem.2008.01.017*




*In times of stress, hematopoietic stem cells (HSCs) diverge from their normal cell cycle (top) to produce new HSCs to replace cells damaged by events such as chemotherapy or bone marrow transplants (bottom). This is possible because N-cadherin levels maintain pools of "primed" and "reserved" cells that work together to maintain a delicate cellular balance.*

larger pool of "reserved" HSCs. Cells in the reserved pool have a lower cell cycle entry rate and lower metabolic activity and, therefore, serve a maintenance role in bone marrow.

The findings, published in the April 10 issue of *Cell Stem Cell*, are potentially clinically important in a number of different ways. Primed HSCs regenerate blood cells very effectively. This knowledge may hold potential for improved bone marrow transplantation. Additionally, recognition that a larger pool of HSCs are in a reserved state may ultimately help clinicians use them in therapy or protect them from depletion. Finally, it is possible that cancers may involve two kinds of cancer stem cells, one more latent and the other more active – but both involved in cancer growth in different ways.

This knowledge may be helpful in predicting drug resistance in cancer treatment. More latent cancer stem cells demonstrate greater resistant to chemo- and radio-therapies. With that understanding, it may be possible to develop new strategies for coping with drug-resistant cancer stem cells.

"N-cadherin plays a critical role in stem cell-niche adhesion," said Linheng Li, Ph.D., Associate Investigator and senior author on the *Cell Stem Cell* paper. "It was exciting to establish that it also is involved in maintaining the delicate balance between the regeneration and maintenance of HSCs – an impressive function that contributes to the body's ability to replenish a healthy supply of blood cells via mutual conversion between reserved and primed stem cells under normal conditions and in times of physical stress. Additionally, now that we know more about the role of N-cadherin, we can consider the role of other cadherins in stem cell function."

## The Bigger Picture

Consideration of the recent discoveries of the Linheng Li and Xie Labs together offers interesting additional insight into the function of adult stem cells in the body. The question arises: why do fruit flies of the Xie Lab studies have only one population of germline stem cells, whereas the mice of the Linheng Li Lab studies have two populations of blood-forming stem cells?

According to Dr. Linheng Li, the answer may have to do with lifespan. "Fruit flies generally live for just a few weeks, while the lifespan of mice is closer to two years," he explained. "The longer lifespan of the adult mouse may depend on stem cells that live longer to meet the increased demand for tissue regeneration over time." The Linheng Li Lab's demonstration of the complementary relations between reserved and primed pools of stem cells may explain how adult stem cells increase their lifespan in longer-living organisms, including humans.

The discovery of reserved and primed stem cell pools also helps to explain how adult stem cells reduce the risk of accumulating mutations during DNA replications. In their dormant state, the reserved pools of stem cells are at a significantly reduced risk of accumulating DNA replication errors. The dormant state also protects stem cells from environmental harm, including oxidative stress. These protective functions may explain why the pool of reserved stem cells is significantly larger than the pool of primed stem cells.

**PAPER:** N-cadherin Expression Level Distinguishes Reserved versus Primed States of Hematopoietic Stem Cells

**JOURNAL:** *Cell Stem Cell*

**ISSUE:** April 2008

**AUTHORS*:** **Jeffrey Haug**†, Managing Director - Cytometry Facility; **Xi He, M.D.**†, Senior Research Specialist; **Justin Grindley, Ph.D.**, Senior Research Associate; **Joshua Wunderlich**, Research Technician III; **Karin Gaudenz, Ph.D.**, Research Specialist II; **Jason Ross**, Predoctoral Researcher; **Ariel Paulson**, Programmer Analyst I; **Kathryn Wagner**, Research Technician II; **Yucai Xie**, Predoctoral Research Associate; **Ruihong Zhu**, Research Technician II; **Tong Yin, Ph.D.**, Postdoctoral Research Associate; **John Perry, Ph.D.**, Postdoctoral Research Associate; **Mark Hembree**, Laboratory Manager I; **Erin Redenbaugh**, Research Technician II; **Glenn Radice, Ph.D.**, University of Pennsylvania School of Medicine; **Christopher Seidel, Ph.D.**, Managing Director – Microarray; **Linheng Li, Ph.D.**, Associate Investigator

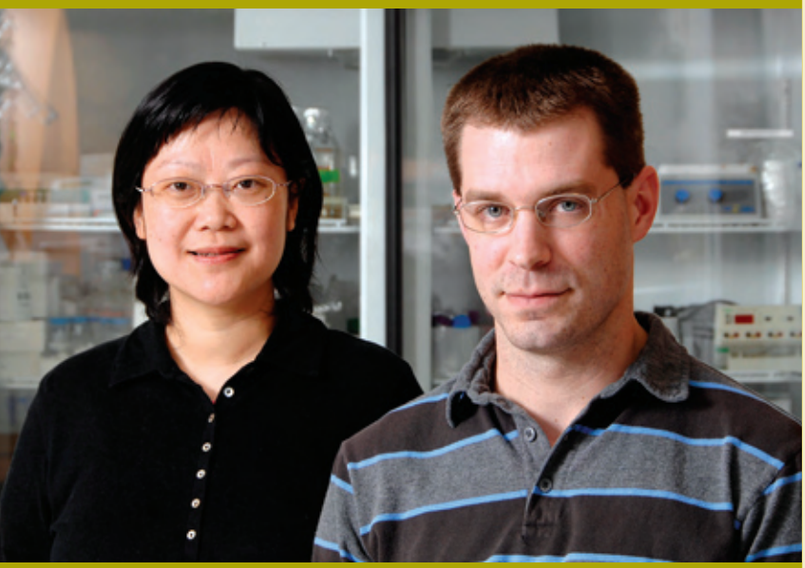
**Authors' primary appointments are with the Stowers Institute for Medical Research unless otherwise noted.*

† *Co-equal contributors to this publication.*

**Linheng Li, Ph.D.**, Associate Investigator, also is an Associate Professor in the Department of Pathology & Laboratory Medicine at The University of Kansas School of Medicine. Learn more about his work at www.stowers-institute.org/labs/LiLab.asp.

**Ting Xie, Ph.D.**, Associate Investigator, also is an Associate Professor in the Department of Anatomy & Cell Biology at The University of Kansas School of Medicine. Learn more about his work at www.stowers-institute.org/labs/XieLab.asp.

# GETTING TO THE BOTTOM OF BLOOD-RELATED DISEASES



*Tong Yin (left) and John Perry (right) were selected for fellowships with the Leukemia & Lymphoma Society.*

The mission of the Leukemia & Lymphoma Society is to cure leukemia, lymphoma, Hodgkin's disease, and myeloma while improving the quality of life of patients and their families. Among their initiatives is funding scientific research that holds promise for the fulfillment of this mission.

In February, two Stowers Institute Postdoctoral Research Associates in the Linheng Li Lab were notified of selection for Leukemia & Lymphoma Society research funding.

Tong Yin, Ph.D., was named a Leukemia & Lymphoma Society Special Fellow. The three-year appointment will begin on July 1, 2008, and will provide a total of $195,000. It will support Dr. Yin's study of bone morphogenetic proteins (BMPs), which are involved in blood and bone development and in tumor formation. Recent reports have shown that BMPs can inhibit acute myeloid leukemia and malignant lymphoma and inhibit cell growth in myeloma.

"With this support from the Leukemia & Lymphoma Society, I will study the roles of Alk2 and Alk3, both components of the BMP receptor complexes that transmit BMP signals," explains Dr. Yin. "The goal is to more fully understand the role of BMP-signaling in blood cells, leukemia, and lymphoma by determining the functions of Alk2 and Alk3 and their relationship to PTEN - a negative regulator of a pathway known to impact the development and treatment of acute and chronic leukemia."

John Perry, Ph.D., was named a Leukemia & Lymphoma Society Fellow. The three-year appointment will begin on June 1, 2008, and will provide a total of $165,000. It will support Dr. Perry's research into the self-renewal of stem cells and how excessive self-renewal can lead to cancer. The Leukemia & Lymphoma Fellowship will allow Dr. Perry to study excessive self-renewal of stem cells in an attempt to expand normal stem cells in culture, which may eventually allow limited sources of stem cells – such as umbilical cord blood – to be used to treat diseases like leukemia.

"Preliminary evidence suggests that two genetic pathways – the Wnt and PTEN pathways – interact to drive self-renewal," said Dr. Perry. "Abnormalities in these pathways result in leukemia development. While permanent genetic damage to these pathways may result in leukemia by forming cancer stem cells, medicines which only briefly activate these pathways in culture may be used to expand normal stem cells, proving promising treatments for blood-related diseases."

# HANDLE WITH CARE

## Expanding Insight into DNA Packaging Structures

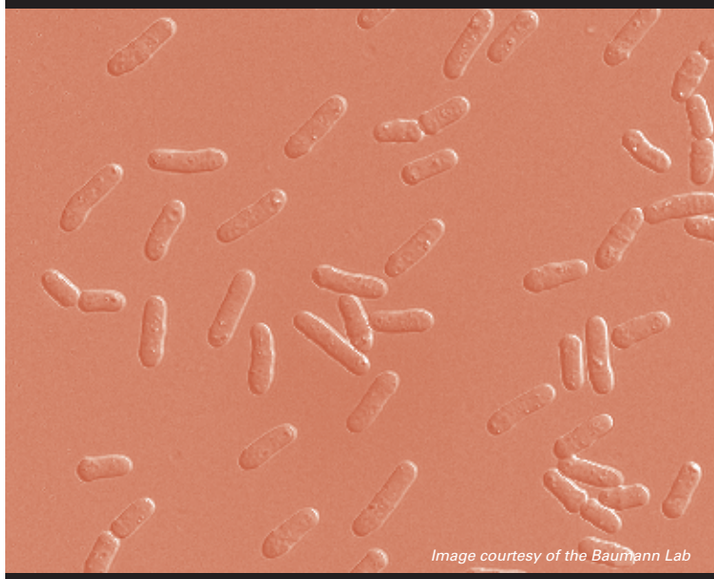


Image courtesy of the Baumann Lab

*Magnification of* Schizosaccharomyces pombe*, or fission yeast - a research model utilized by the Baumann Lab in their study of chromosomes.*

DNA MAY BE THE BLUEPRINT FOR ALL LIFE, BUT CHROMOSOMES HOLD THE KEY TO UNLOCKING THE CODED INFORMATION CONTAINED INSIDE.

Found in the nucleus of cells, chromosomes are complex structures composed of DNA and proteins. Each chromosome contains a single continuous thread of double-stranded DNA that forms a helical coil. If stretched out, the threads of DNA from a single cell could reach to more than six feet.

Because chromosomes play such an important role in the packaging of genetic information, events that damage chromosomes, such as mutations, can have devastating consequences ranging from birth defects to cancer.

In recent months, three Stowers Institute teams have published discoveries that advance chromosome research in significant ways.

### Identifying a Long-Sought Model

Each time a cell divides, its chromosomes shorten. In stem cells and cancer cells, this shortening is mitigated by the function of an enzyme — called telomerase — that adds repeating sequences to the ends of chromosomes to replenish the DNA lost in cell division.

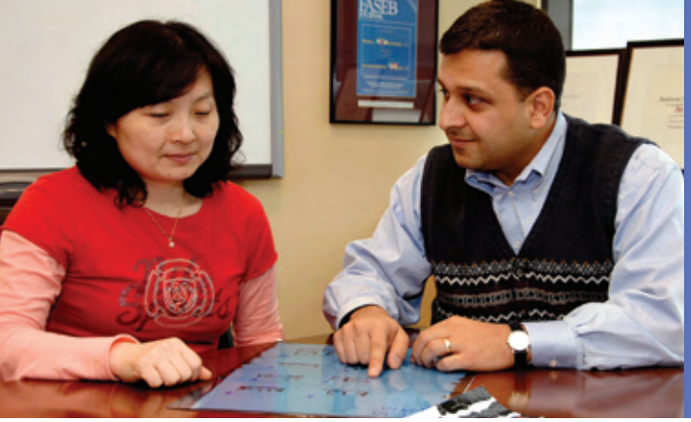
Cancer cells require the enzyme telomerase to support their continued growth, making it a promising target for new anti-cancer drugs. Additionally, a correlation between telomere length and a variety of diseases has further intensified interest in understanding telomerase and its regulation.

The RNA subunit of telomerase is one of its core components. It serves as the template for the short repeats that are added to the ends of chromosomes.

Effective studies of telomerase have been difficult because the architecture of telomeres in many simple model organisms, like budding yeast and cilliates, differs substantially from the telomerase RNA in humans. Without a simple animal model to offer insights that are relevant to human health, basic research is limited, if not impossible.

The Baumann Lab has experienced this frustration first-hand in their work to understand how telomerase is assembled, how it is recruited to chromosome ends, and how its activity is regulated. They are working to shed light on the sometimes surprising correlations between telomere shortening and stress, smoking, obesity, and a variety of diseases including cancer and coronary heart disease.

After much investigation, the team published an exciting breakthrough in the January 2008 issue of *Nature Structural & Molecular Biology*. Using a biochemical approach, they were able to identify the RNA subunit of telomerase in *Schizosaccharomyces pombe*, a fission yeast.



*Jung-Shin Lee (left) and Ali Shilatifard (right) shed light on the molecular machinery required for translation of histone crosstalk in a recent publication in* Cell.

**PAPER:** TER1, the RNA Subunit of Fission Yeast Telomerase

**JOURNAL:** *Nature Structural & Molecular Biology*

**ISSUE:** January 2008

**AUTHORS*:** **Jessica Leonardi**, formerly a Research Technician I; **Jessica Box**, Research Technician I; **Jeremy Bunch**, Research Technician III; **Peter Baumann**, **Ph.D.**, Assistant Investigator

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

Fission yeast is a single-cell eukaryote and serves as a useful research model. Studying the function of RNA telomerase in this simple cell can yield useful insight into its role in human chromosomes and clears the way for rapid progress in the study of telomerase by the Baumann Lab.

"A significant barrier to advancing our work has been lifted," explained Peter Baumann, Ph.D., Assistant Investigator and senior author on the paper. "With fission yeast as a model, we are in a much better position to uncover how and where telomerase is assembled from its components in the cell and what processing it must undergo to become active."

## Breaking the Histone Crosstalk Code

Histones are the primary protein components of chromatin, the complex of DNA and protein that makes up chromosomes. They serve as a spool for strands of DNA, allowing for compact packaging of genetic information within chromosomes.

Histones also play an important role in the regulation of gene expression by influencing the stability of nucleosomal arrays and creating docking sites for the binding of regulatory proteins.

The Shilatifard Lab has made a number of notable findings related to the function of histones. Several years ago, the team identified the first histone H3 lysine 4 (H3K4) methyltransferase, known as COMPASS, in yeast. Soon thereafter, it was established that the Mixed Lineage Leukemia protein in humans also existed in a COMPASS-like complex capable of methylating H3K4.

For histones to function properly, they must communicate with one another using a process called crosstalk. In 2002, the Shilatifard Lab reported the existence of the first histone crosstalk in the context of the COMPASS complex. In the December 14 issue of *Cell*, the Shilatifard Lab shed light on the molecular machinery required for the translations of histone crosstalk.

"We know that histone H3K4 methylase, the Mixed Lineage Leukemia complex, is critical in the origination and development of leukemia," said Ali Shilatifard, Ph.D., Investigator and senior author on the paper. "Defining the molecular machinery involved in this process of histone crosstalk could be highly useful."

**PAPER:** Histone Crosstalk between H2B Monoubiquitination and H3 Methylation Mediated by COMPASS

**JOURNAL:** *Cell*

**ISSUE:** December 14, 2007

**AUTHORS*:** **Jung-Shin Lee, Ph.D.**, Postdoctoral Research Associate; **Shukla Abhijit**, Southern Illinois University School of Medicine; **Jessica Schneider Jackson**, Research Technician; **Selene Swanson**, Research Specialist II; **Michael Washburn**, **Ph.D.**, Director of Proteomics; **Laurence Florens, Ph.D.**, Managing Director of Proteomics; **Sukesh Bhaumik, Ph.D.**, Southern Illinois University School of Medicine; **Ali Shilatifard, Ph.D.**, Investigator

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

*Heterozygous* Drosophila *embryos, which contain the intact Atac2 gene, are visualized in green (upper left) and display high levels of histone H4 lysine 16 acetylation, shown in red (upper right). Homozygous mutant embryos lacking the Atac2 gene (lower left) show reduced levels of histone H4 lysine 16 acetylation (lower right).*

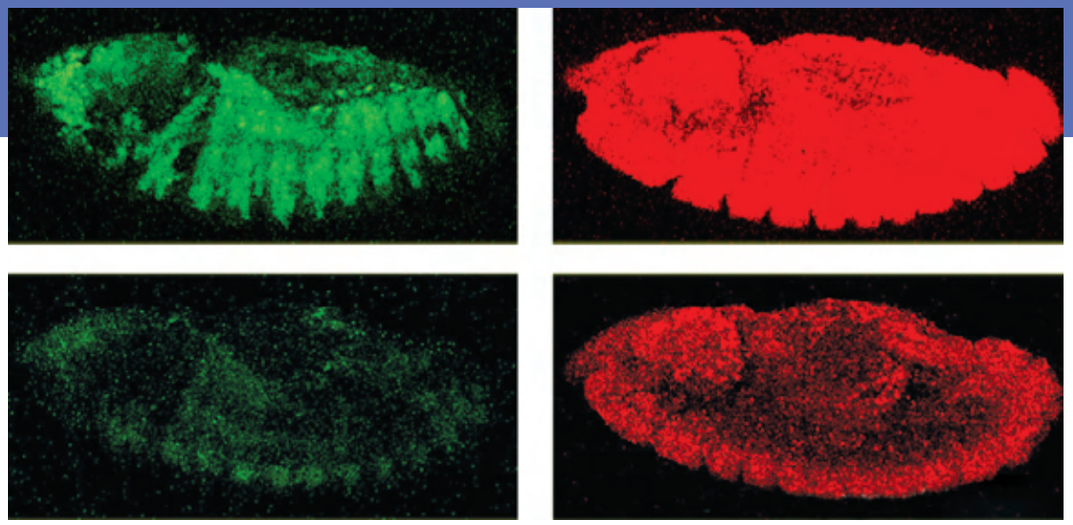


*Image courtesy of the Workman Lab*

## Filling in the Blanks

Chromosome functions are controlled by histone acetyltransferases (HAT) enzymes that add an acetyl group to histones and allow transcription factors to bind to DNA. Without the action of the HAT enzyme, histones protect DNA and prevent transcription of the encoded message.

Most HAT protein complexes contain a single HAT enzyme, but in the April issue of *Nature Structural & Molecular Biology*, the Workman Lab characterized ATAC – a HAT with two distinct acetyltransferase enzymes that is known to play a role in embryonic development.

Working with fruit flies, the team demonstrated that of the two HAT enzymes present in ATAC, one generally activates processes like gene transcription and DNA repair and the other makes a specific modification thought to alter chromosome structure. They also established that ATAC can assist in the movement of protein subunits, called nucleosomes, along the DNA.

"We knew that the ATAC complex existed and that it was only present in multicellular organisms, but we didn't know exactly which proteins it contained or what their functions were," said Jerry Workman, Ph.D., Investigator and senior author on the paper. "We found that the ATAC complex is essential for the development of the fruit fly embryo into an adult, and we expect that it will also be required for development of mammals, including humans. The improved understanding of the functions of ATAC will allow us to better pinpoint its role in developmental defects and cancers."

With the ATAC proteins fully characterized, the Workman Lab will now be able to investigate which chromosomal functions ATAC regulates and how these actions contribute to development.

**PAPER:** ATAC is a Double Histone Acetyltransferase Complex that Stimulates Nucleosome Sliding

**JOURNAL:** *Nature Structural & Molecular Biology*

**ISSUE:** April 2008

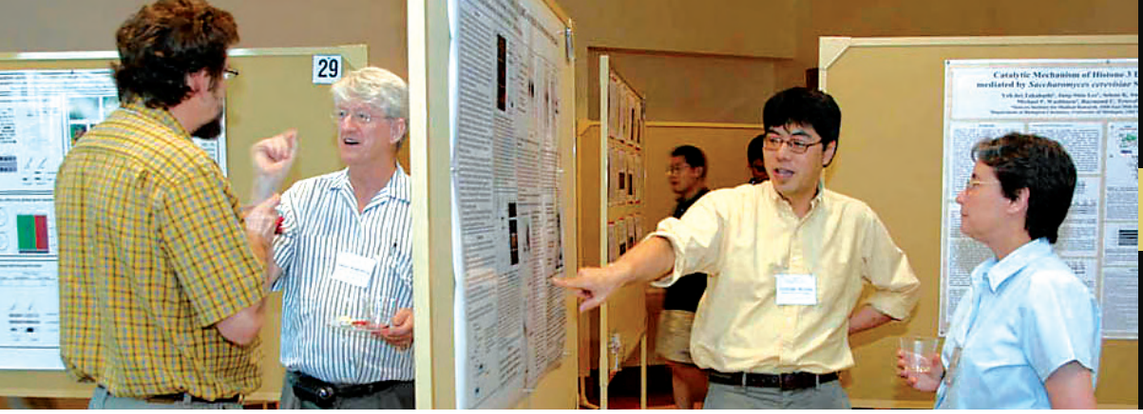
**AUTHORS*:** **Tamaki Suganuma, Ph.D.**, Postdoctoral Research Associate; **Jose Gutierrez, Ph.D.**, formerly a Postdoctoral Research Fellow; **Bing Li, Ph.D.**, Senior Research Associate; **Laurence Florens, Ph.D.**, Managing Director of Proteomics; **Selene Swanson**, Research Specialist II; **Michael Washburn, Ph.D.**, Director of Proteomics; **Susan Abmayr, Ph.D.**, Associate Investigator; **Jerry Workman, Ph.D.**, Investigator

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

**Peter Baumann, Ph.D.**, Assistant Investigator, also is an Assistant Professor in the Department of Biochemistry & Molecular Biology at The University of Kansas School of Medicine and a Pew Scholar in Biomedical Sciences. Learn more about his work at www.stowers-institute.org/labs/BaumannLab.asp.

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

**Jerry Workman, Ph.D.**, Investigator, joined the Stowers Institute in 2003 from The Pennsylvania State University where he was an Associate Investigator of the Howard Hughes Medical Institute. Learn more about his work at www.stowers-institute.org/labs/WorkmanLab.asp.




*Attendees at the Transcription, Chromatin, and Cancer Meeting discuss related work during poster presentations at the Stowers Institute.*

# MEETING OF THE MINDS

## Stowers Researchers Convene Symposium on Transcription, Chromatin, and Cancer

In October 2007, more than 130 scientists came together on the Stowers Institute campus to exchange information and ideas at the Transcription, Chromatin, and Cancer Meeting. The two-day event organized by Investigators Joan Conaway, Ph.D., Ron Conaway, Ph.D., Ali Shilatifard, Ph.D., and Jerry Workman, Ph.D., featured eighteen scientific presentations and a poster session.

Symposia such as this bring leading researchers from around the world together to exchange knowledge on timely scientific issues. The interactions inspire new ideas, approaches, and even collaborations.

The Stowers Institute is home to an impressive concentration of experts working in the area of transcription and chromatin research, so symposium attendees arrived at the Institute with high expectations for a scientifically rigorous agenda. What they may not have expected was the Institute's world-class research environment and the impressive surrounding community.

"Not only did this event bring Stowers Institute transcription and chromatin researchers and our local colleagues together with scientists from around the world, it introduced our visitors to the wonderful research environment of the Institute and the amenities of Kansas City," said Dr. Joan Conaway.

As with many Stowers Institute symposia, each speaker was invited to bring a student to the event. This unique arrangement promotes the exchange of ideas at all levels — bringing together the expertise of senior scientists with the enthusiasm of researchers who are relatively new to the field. The dynamic exchanges that result can not only change the course of a young scientist's career — they can change a field.

"Focused workshops and symposia like the Transcription, Chromatin, and Cancer Meeting offer a first-hand opportunity to hear what people think, to ask questions, and to engage in a dialogue," said Robb Krumlauf, Ph.D., Scientific Director. "It is amazing what can evolve over a coffee break — a casual conversation can grow into a fruitful collaboration or launch a new research direction. Coming together with colleagues at events like this is one of the most important things we can do to advance our fields, and the Stowers Institute is a wonderful environment in which to do that."

## Transcription, Chromatin, and Cancer Meeting Presentations

**Michael Carey** University of California-Los Angeles Los Angeles, California
*Biochemical Mechanism of Gene Inactivation by HP1 and Polycomb*

**Guillermo Calero** Stanford University Stanford, California
*Structural Studies of a Pol-II Transcribing Complex*

**Julia Zeitlinger** Stowers Institute for Medical Research Kansas City, Missouri
*RNA Polymerase Stalling at Developmental Control Genes in the* Drosophila *Embryo*

**Geeta Narlikar** University of California-San Francisco San Francisco, California
*Mechanisms of Chromatin Remodeling Enzymes*

**Kevin Struhl** Harvard University Cambridge, Massachusetts
*Epigenetic Inheritance and the Chicken-and-Egg Relationship between Transcription and Chromatin*

**Ramin Shiekhattar** Center for Genomic Regulation Barcelona, Spain
*Regulation of Transcription through Histone Demethylation*

**Michael Washburn** Stowers Institute for Medical Research Kansas City, Missouri
*Visualizing Protein Complexes and Protein Interaction Networks with Normalized Spectral Abundance Factors*

**Peter Baumann** Stowers Institute for Medical Research Kansas City, Missouri
*Capping the Ends of Chromosomes*

**Susan Gasser** Friedrich Miescher Institute Basel, Switzerland
*The Structure and Dynamics of Silent Chromatin in Yeast*

**Sue Jaspersen** Stowers Institute for Medical Research Kansas City, Missouri
*Budding Yeast Mps3: The Role of SUN Proteins as Telomere Anchors at the Nuclear Periphery*

**Genevieve Almouzni** Curie Institute Paris, France
*Chromatin Assembly Factors, Histone H3 Variants, and Cell Cycle*

**Ken Peterson** University of Kansas Medical Center Kansas City, Kansas
*GATA-1-Mediated Silencing of Fetal Hemoglobin Expression*

**Beverly Emerson** Salk Institute San Diego, California
*Transcriptional Regulation of the Stress Response by the Tumor Suppressor Protein p53*

**Kathy Jones** Salk Institute San Diego, California
*Connecting Transcription Elongation to Histone Methylation*

**Jennifer Gerton** Stowers Institute for Medical Research Kansas City, Missouri
*Building Centromeric Chromatin*

**Shelley Berger** Wistar Institute Philadelphia, Pennsylvania
*The Complex Language of Histone and Factor Post-translational Modifications in Transcription and Beyond*

**Robb Krumlauf** Stowers Institute for Medical Research Kansas City, Missouri
*Hox Regulatory Networks in the Hindbrain*

**Yang Shi** Harvard University Cambridge, Massachusetts
*Histone Demethylases and Dynamic Regulation of Histone Methylation*

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

**Ronald Conaway, Ph.D.**, Investigator, also is a Professor in the Department of Biochemistry & Molecular Biology at The University of Kansas School of Medicine. Learn more about his work at www.stowers-institute.org/labs/ConawayLab.asp.

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

**Jerry Workman, Ph.D.**, Investigator, joined the Stowers Institute in 2003 from The Pennsylvania State University where he was an Associate Investigator of the Howard Hughes Medical Institute. Learn more about his work at www.stowers-institute.org/labs/WorkmanLab.asp.

# AN ENZYME BY ANY OTHER NAME

| | Family of Enzymes | *Drosophila* | *Saccharomyces cerevisiae* | *Saccharomyces pombe* |
|---|---|---|---|---|
| Original Name | Lysine Demethylases | Lid | Jhd2 | Jmj2 |
| New Name | K-Demethylases (KDMs) | dKDM5 | ScKDM5 | SpKDM5 |

Chromatin is the complex of DNA and proteins that makes up our chromosomes. The proteins in chromatin help regulate gene expression, and interest in that specific function has grown rapidly over the past decade. Expanded research in this field has led to the discovery of a significant number of new enzymes that modify the structure of chromatin and thereby regulate gene expression.

The accelerating pace of research in this field has resulted in hastily assigned names to newly discovered enzymes, a circumstance that has fostered a nomenclature that is neither coherent nor consistent among species. The names of these enzymes can be difficult to learn, remember, and translate from one species to another.

Ali Shilatifard, Ph.D., and Jerry Workman, Ph.D., Investigators, joined eleven other colleagues in authoring an article in the journal *Cell* that advocates a new, structured method for naming families of chromatin-modifying enzymes.

"The old nomenclature – a combination of names from different disciplines like genetics and biochemistry and from organisms such as yeast, fruit flies, and humans – was too confusing for new people entering the field to learn and remember," explains Dr. Workman. "We hope that the new nomenclature will be simpler to learn and will unify the names of these enzymes across species."

The team of authors refined the new nomenclature over a number of years.

"We started this initiative with our colleagues several years ago with the hope of developing a logical and user-friendly nomenclature for chromatin-modifying machineries," explains Dr. Shilatifard. "This new nomenclature should allow individuals working with the same enzyme in different organisms to follow one another's work. Furthermore, by employing this nomenclature, students and new scientists entering the chromatin field should have an easier time understanding the chromatin literature."

**PAPER:** New Nomenclature for Chromatin-Modifying Enzymes

**JOURNAL:** *Cell*

**ISSUE:** November 16, 2007

**AUTHORS*:** **C. David Allis, Ph.D.**, The Rockefeller University; **Shelley Berger, Ph.D.**, The Wistar Institute; **Jacques Cote, Ph.D.**, Laval University Cancer Research Center; **Sharon Dent, Ph.D.**, MD Anderson Cancer Center; **Thomas Jenuwein, Ph.D.**, Research Institute of Molecular Pathology; **Tony Kouzarides, Ph.D.**, University of Cambridge; **Lorraine Pillus, Ph.D.**, University of California, San Diego; **Danny Reinberg, Ph.D.**, New York University School of Medicine; **Yang Shi, Ph.D.**, Harvard Medical School; **Ramin Shiekhattar, Ph.D.**, Centre for Genomic Regulation; **Ali Shilatifard, Ph.D.**, Investigator; **Jerry Workman, Ph.D.**, Investigator; **Yi Zhang, Ph.D.**, University of North Carolina, Chapel Hill

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

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

**Jerry Workman, Ph.D.,** Investigator, joined the Stowers Institute in 2003 from The Pennsylvania State University where he was an Associate Investigator of the Howard Hughes Medical Institute. Learn more about his latest work at www.stowers-institute.org/labs/WorkmanLab.asp.

## In Vivo *Analysis of Protein-Protein Interactions*

# Proteins in Their Natural Habitat

When it comes to analyzing the interaction of proteins, the best vantage is often *in vivo* – examining the process directly in the living cell of the model animal. Doing so presents a number of significant challenges, but as technology advances, exciting new opportunities become available.

The Stowers Institute's Imaging Center has invested in creative approaches to examine a number of difficult problems *in vivo*. Most recently, the Rong Li Lab collaborated with the Imaging Center to establish methods for quantitative *in vivo* measurement of the dynamic protein-protein interactions in the mitogen-activated protein (MAP) kinase signaling pathway – a pathway that is critical to growth and differentiation decisions in eukaryotic cells.

The team worked together to perfect the application of these techniques in yeast, calling on the Imaging Center's expertise and cutting-edge instrumentation for microscopy-based technology. Using three fluorescence-based analyses, they assessed the movement, concentration, and state of protein hetero- and homo-oligomerization, the process of protein molecules binding to each other to form larger functional units.

The team published the results in the December 18, 2007 issue of *Proceedings of the National Academy of Sciences*.

"The new approach to *in vivo* measurement of protein interactions represents an exciting emerging direction for molecular analysis in the future," said Rong Li, Ph.D., Investigator and senior author on the paper. "We can now understand biological systems with precise information about when, where, and to what extent molecules interact with each other during important regulatory processes."

**PAPER:** Mapping Dynamic Protein Interactions in MAP Kinase Signaling Using Live-Cell Fluorescence Fluctuation Spectroscopy and Imaging

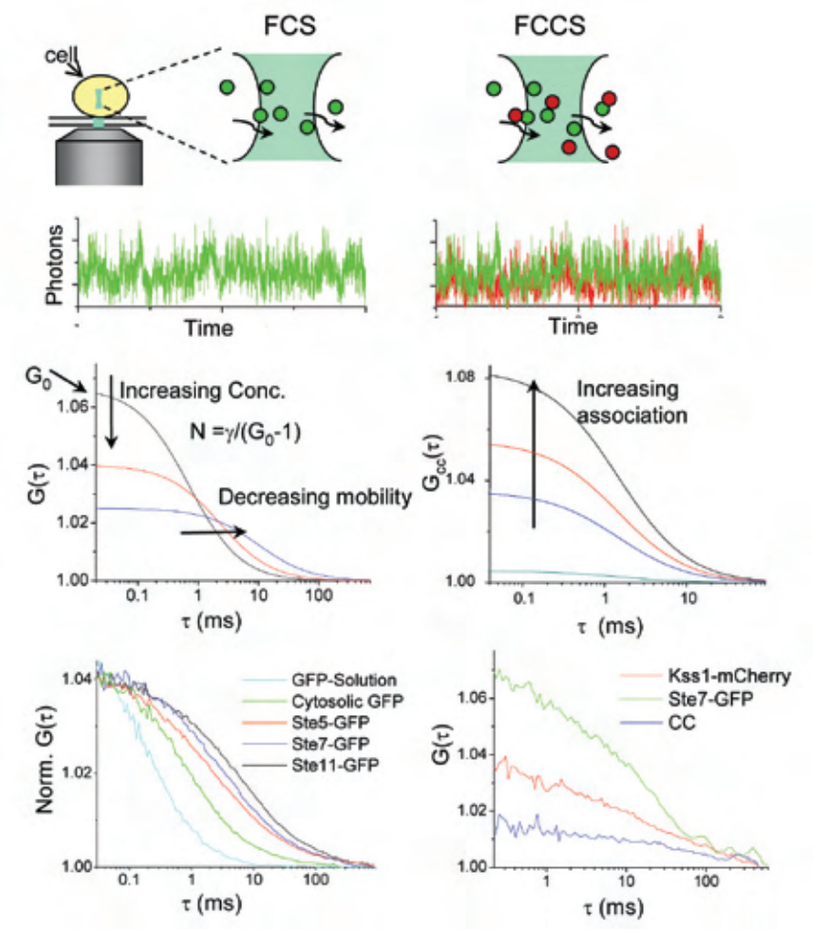
**JOURNAL:** *Proceedings of the National Academy of Sciences*

**ISSUE:** December 18, 2007

**AUTHORS*:** **Brian Slaughter, Ph.D.**, Postdoctoral Research Fellow; **Joel Schwartz, Ph.D.**, Managing Director of the Imaging Center; **Rong Li, Ph.D.**, Investigator

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

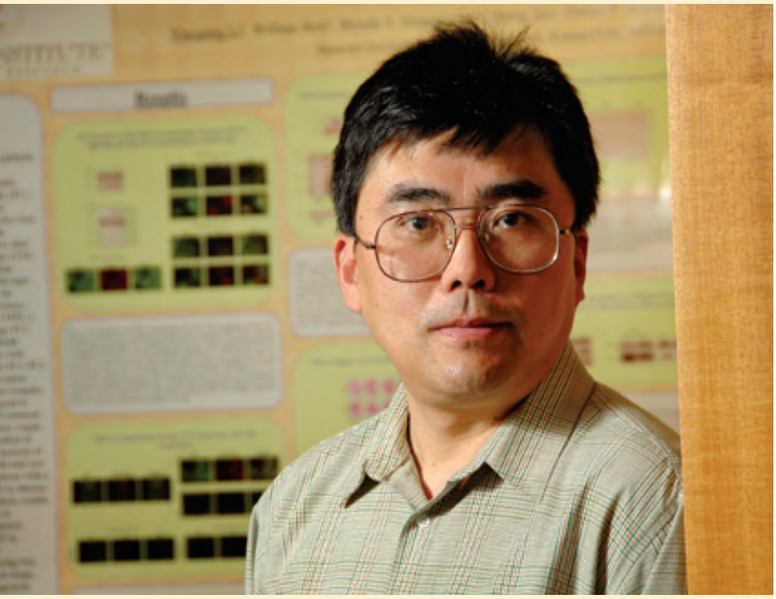
**Rong Li, Ph.D.**, Investigator, also is a Professor in the Department of Molecular & Integrative Physiology at The University of Kansas School of Medicine. Learn more about her work at www.stowers-institute.org/labs/RongLiLab.asp.






*Fluorescence correlation spectroscopy (FCS) and cross-correlation spectroscopy (FCCS) detect emission photons as fluorescent molecules diffuse through a microscope focal volume. The photon trace can be statistically analyzed to yield information about diffusing species in live cells. These techniques were used to examine cytosolic concentration, mobility, and interactions of proteins in the mitogen-activated protein kinase signaling pathway in live yeast.*

# Investigating One of the World's Most Common Life-Threatening Genetic Diseases



*Xiaogang Li*

Polycystic Kidney Disease (PKD) is one of the most common life-threatening genetic diseases, affecting 600,000 Americans and 12.5 million people worldwide. It affects more people than Down's syndrome, cystic fibrosis, muscular dystrophy, and sickle cell anemia combined.

PKD causes cysts to grow throughout the kidneys. Over time, the cysts lead to kidney failure, which necessitates dialysis and – when a donor can be identified – kidney transplantation. Currently, there is no treatment or cure available to slow or stop the growth of the cysts.

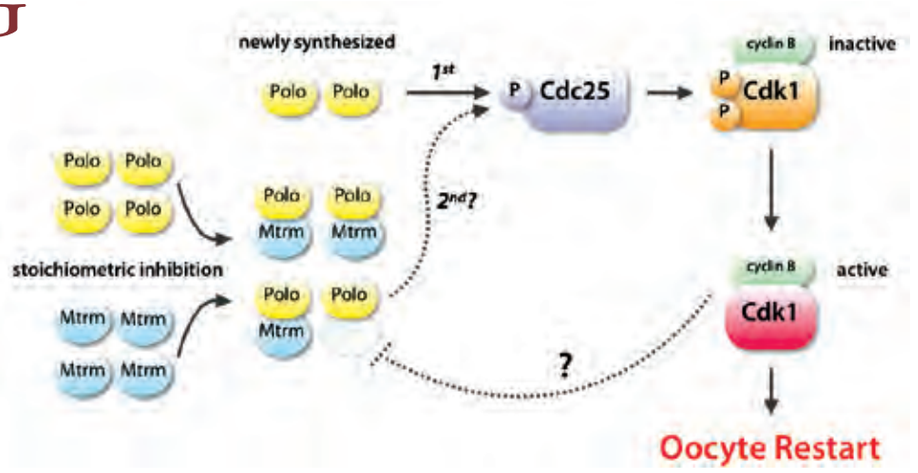
The Stowers Institute's Rong Li Lab is conducting innovative research to establish a better understanding of PKD.

Xiaogang Li, Ph.D., a Senior Research Associate in the lab, has been awarded a grant of $150,000 over two years by the Kansas City-based PKD Foundation. He will study the role of a number of enzymes called histone deacetylases (HDACs). HDACs play a role in cell cycle regulation and in the formation and breakdown of cilia – hair-like projections that extend outwards from cells in the renal tubules inside the kidneys. Mutations affecting the function of cilia cause PKD. New information about the function of HDACs in cells may allow for the identification of new treatment targets in PKD.

"This award will allow me to give special attention to investigating the molecular mechanism of HDACs in cyst formation in PKD," explained Xiaogang Li. "Additionally, I expect that the preliminary data generated by this work will position us for further support by the National Institutes of Health, which will allow us to do even more to uncover the causes of and possible treatments and cures for PKD. I am very grateful for the support of the PKD Foundation."

Reawakening the Meiotic Cycle

# IN SEARCH OF PRINCE CHARMING




*Adapted from Smith et al.,* Cell Cycle, *March 15, 2008, Vol. 7, Issue 6*

Cells that will eventually become oocytes form during fetal development and begin the process of specialized cell division known as meiosis even before birth. But prior to completing meiosis, they enter a lengthy period of dormancy. The "sleeping" oocyte reawakens only upon the sexual maturation of the female, when the process of meiosis resumes.

The extended period of meiotic arrest and its well-timed ending have mystified biologists for over a century. This changed with the December issue of *PLoS Biology* when the Hawley Lab published the results of collaboration with the Institute's Proteomics Center that identified two proteins working together to restart oocyte meiosis.

Using fruit flies – a species that reaches sexual maturity within a few days of hatching and undergoes the same meiotic arrest as humans – the team showed that the restart of meiosis in *Drosophila* depends on two mechanisms: the controlled expression of an 'activator' enzyme known as Polo kinase and the presence of a regulatory protein called Matrimony, the first known protein inhibitor of Polo kinase. Matrimony binds to and physically inactivates Polo kinase, and by doing so, it blocks the resumption of meiosis in oocytes.

*The inhibition of Polo kinase by Matrimony (Mtrm) controls the timing of oocyte reawakening after a period of dormancy. Matrimony physically binds to Polo. A small amount of excess Polo subsequently initiates the chain of events that may ultimately release the remaining Matrimony-bound Polo, allowing for a rapid transition into the next stage of meiosis.*

As the oocyte begins to reawaken, it takes several days to build up enough Polo kinase to properly restart meiosis. The newly made Polo kinase must remain inactive until the proper level has been reached. Matrimony ensures this by inhibiting Polo kinase until just the right moment, when Matrimony is destroyed and a sudden surge of the enzyme is released. It is this precisely timed release of active Polo kinase that restarts meiosis.

"The restart of the meiotic cycle is much like the kiss that awakened Sleeping Beauty," said R. Scott Hawley, Ph.D., Investigator, and senior author on the paper. "The lengthy period of rest can only be ended by Prince Charming – in this case, the dual functions of Polo kinase and Matrimony.

"The long-term implications of this work for human health and biology lie in a better understanding of how eggs are matured and released, knowledge that will have profound implications for treating infertility. Additionally, Polo kinase is strongly expressed in many types of tumor cells, so identifying a Matrimony-like specific inhibitor for this enzyme may aid in the development of improved drugs for treating cancer."

**PAPER:** The Inhibition of Polo Kinase by Matrimony Maintains G2 Arrest in the Meiotic Cell Cycle

**JOURNAL:** *PLoS Biology*

**ISSUE:** December 2007

**AUTHORS*:** **Youbin Xiang, Ph.D.**, Research Specialist II; **Satomi Takeo, Ph.D.**, Postdoctoral Research Associate; **Laurence Florens, Ph.D.**, Managing Director of Proteomics; **Stacie Hughes, Ph.D.**, Postdoctoral Research Associate; **Li-Jun Huo, Ph.D.**, Postdoctoral Research Associate; **William Gilliland, Ph.D.**, Senior Research Associate; **Selene Swanson**, Research Specialist II; **Kathy Teeter**, Research Technician II; **Joel Schwartz, Ph.D.**, Managing Director of Imaging; **Michael Washburn, Ph.D.**, Director of Proteomics; **Sue Jaspersen, Ph.D.**, Assistant Investigator; **R. Scott Hawley, Ph.D.**, Investigator

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

**R. Scott Hawley, Ph.D.**, Investigator, also is an American Cancer Society Research Professor, a Professor of Molecular and Integrative Physiology at The University of Kansas Medical Center, an Adjunct Professor of Biological Sciences at the University of Missouri, Kansas City, and an Adjunct Professor of the Undergraduate Program in Biology at The University of Kansas. Learn more about his work at www.stowers-institute.org/labs/HawleyLab.asp.

# TEACHING TOMORROW'S RESEARCHERS

**The Genetics Society of America (GSA) honored R. Scott Hawley, Ph.D., Investigator, with the Excellence in Education award at a January 7 reception.**

Dr. Hawley is a gifted teacher, and in addition to his research duties at the Stowers Institute, he serves as a Professor of Molecular and Integrative Physiology at the University of Kansas Medical Center; an Adjunct Professor of Biological Sciences at the University of Missouri-Kansas City; and an Adjunct Professor of Biology at The University of Kansas.

*"My desire to teach emanates from a need to share the excitement of the research process with the next generation of scientists."*

He enjoys mentoring students in the laboratory and counts three undergraduate students and four graduate students among the 21 members of his research team at the Stowers Institute.

"My thesis advisor, Larry Sandler, once told me 'there are three functions of a scholar: to learn, to write, and to teach,'" explains Dr. Hawley. "I simply can't separate the three. Just as my desire to write comes directly from a need to share the findings of my research with my colleagues, my desire to teach emanates from a need to share the excitement of the research process with the next generation of scientists."

Dr. Hawley describes the relationship with students as reciprocal, saying, "Just as the comments of my colleagues sharpen the focus of my research program, the process of presenting research to students makes me constantly re-examine the basic principles of my science. Some of the best insights and ideas for experiments came to me while I was giving a lecture or holding office hours – because in the process of going back to the basic theory of my science, I was able to think about a current research problem in a new and different way."

In 2007, the GSA established the award for Excellence in Education in recognition of geneticists who have or have had a significant and sustained impact on genetics education from grades K-12 through graduate school and beyond. Recipients of the GSA award for Excellence in Education have promoted greater exposure to and deeper understanding of genetics through distinguished teaching or mentoring, development of innovative pedagogical approaches or tools, design of new courses or curricula, national leadership, and/or public engagement and outreach.

Founded in 1931, the GSA includes nearly 5,000 scientists and educators interested in the field of genetics. The Society promotes the communication of advances in genetics through publication of the journal *GENETICS*, and by sponsoring scientific meetings focused on organisms widely used in genetic research.

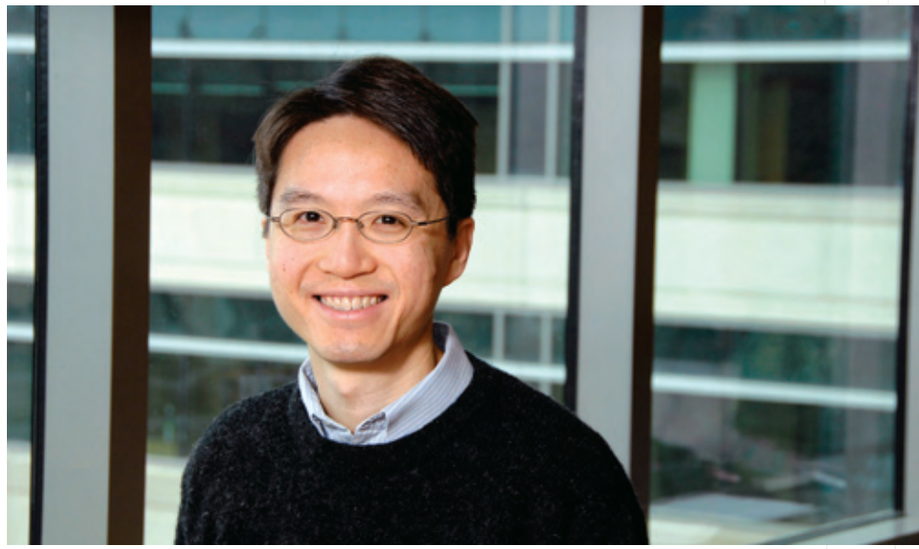
**R. Scott Hawley, Ph.D.**, Investigator, also is an American Cancer Society Research Professor, a Professor of Molecular and Integrative Physiology at The University of Kansas Medical Center, an Adjunct Professor of Biological Sciences at the University of Missouri, Kansas City, and an Adjunct Professor of the Undergraduate Program in Biology at The University of Kansas. Learn more about his work at www.stowers-institute.org/labs/HawleyLab.asp.

*Scott Hawley addresses a Biology 206 class at the University of Missouri-Kansas City.*

# ESTABLISHING THE ROLE OF OBESITY IN BIRTH DEFECTS

**Over the past five years, the March of Dimes has consistently included Stowers Institute researchers among its annual Basil O'Connor Starter Scholar Research Award recipients — six in all. This year's award, bestowed on Ho Yi Mak, Ph.D., Assistant Investigator, brings that total to seven.**

Selected among a group of junior investigators whose work promises insight into the causes of human birth defects, Dr. Mak will receive $150,000 over two years in support of his efforts.



*Ho Yi Mak*

Dr. Mak is working to identify the genes and mechanisms that govern lipid homeostasis. His lab investigates how the nervous system communicates with other tissues to control fat storage and how fat is packaged inside individual cells by using as a model system the nematode *C. elegans*, whose genome encodes many of the metabolic and signaling pathways that are found in humans.

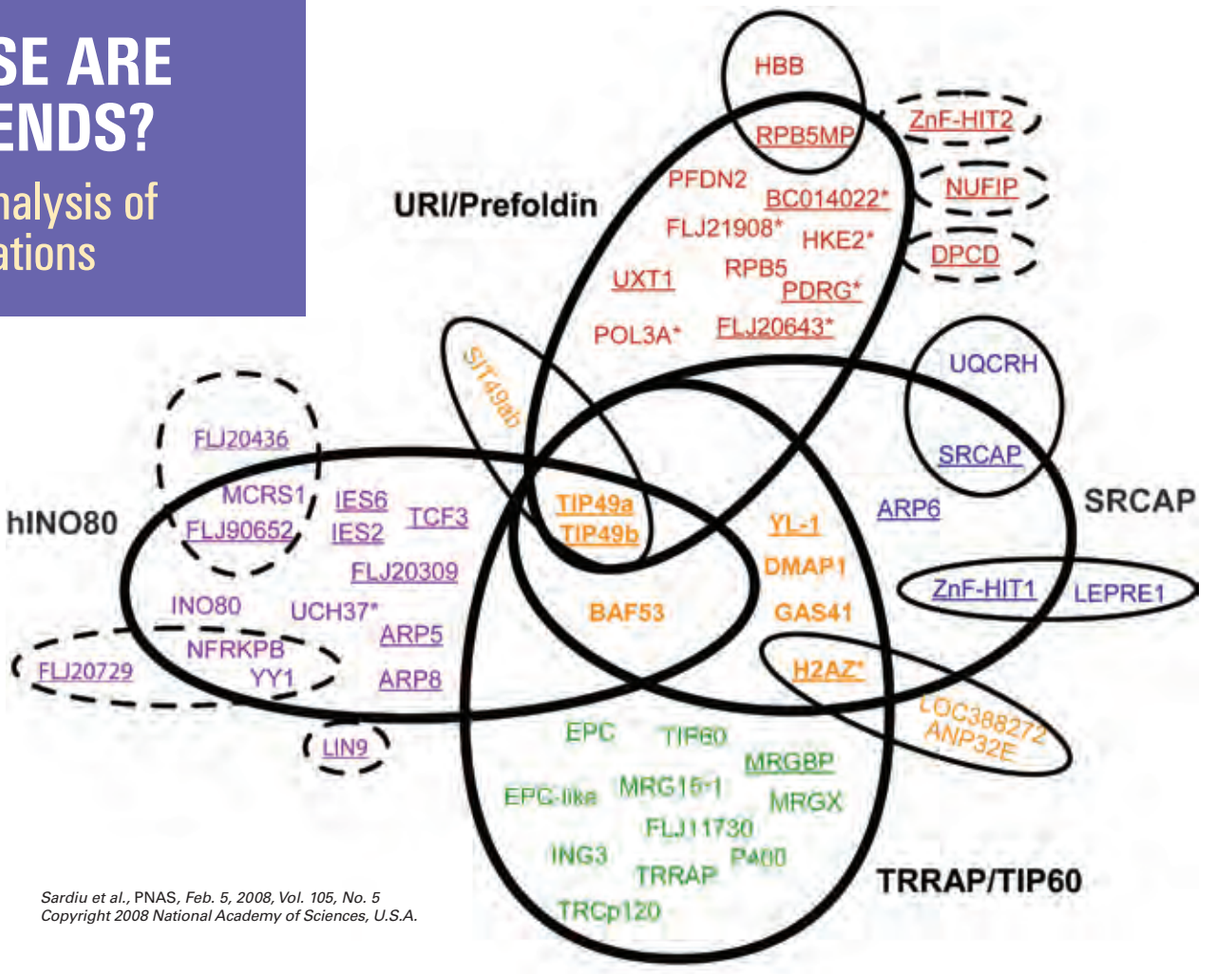
"We are grateful for the funding the March of Dimes award provides," said Dr. Mak. "It will allow us to venture into a new project to study how the size of lipid storage droplets within a cell is controlled, and how that affects systemic fat metabolism."

Obesity is a leading cause of insulin resistance and type-2 diabetes. Diabetes in pregnant women can affect the development of the fetus brain and heart, and can cause miscarriages. Babies born to women with diabetes may also have a higher risk of developing obesity and type-2 diabetes. A better understanding of the genetic factors that contribute to the development of obesity will have a direct impact on the prevention and treatment of diabetes during pregnancy and improve fetal and neonatal care.

**Ho Yi Mak, Ph.D.**, Assistant Investigator, also is 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-institute.org/labs/MakLab.asp.

# HOW CLOSE ARE YOUR FRIENDS?

## Quantitative Analysis of Protein Associations




*Sardiu et al.,* PNAS, *Feb. 5, 2008, Vol. 105, No. 5*


**PAPER:** Probabilistic Assembly of Human Protein Interaction Networks from Label-free Quantitative Proteomics

**JOURNAL:** *Proceedings of the National Academy of Sciences*

**ISSUE:** February 5, 2008

**AUTHORS*:** **Mihaela Sardiu, Ph.D.**, Postdoctoral Research Associate; **Yong Cai, Ph.D.**, Research Specialist I; **Jingji Jin, Ph.D.**, Senior Research Associate; **Selene Swanson**, Research Specialist II; **Ronald Conaway, Ph.D.**, Investigator; **Joan Conaway, Ph.D.**, Investigator; **Laurence Florens, Ph.D.**, Managing Director of Proteomics; **Michael Washburn, Ph.D.**, Director of Proteomics

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

**Michael Washburn, Ph.D.**, Director of Proteomics, joined the Stowers Institute in 2003 from the Torrey Mesa Research Institute in San Diego. Learn more about his work at www.stowers-institute.org/labs/WashburnLab.asp.

Proteomics is the large-scale study of the structure and function of proteins. Traditionally, proteomics has been associated with the analysis of highly complex mixtures of proteins by coupling separation techniques like two-dimensional gel electrophoresis or chromatography with mass spectrometry — an analytical technique that measures the mass-to-charge ratio of charged particles to find the composition of a protein by generating a spectrum representing the masses of sample components.

One helpful function of proteomics is measuring the "closeness of friendship" between two proteins by calculating the probability that they will associate. A stronger association — a 'good friend' — is represented by a higher probability, and a weaker association — an 'acquaintance'— is represented by a lower probability. Previous protein interaction networks built using protein mass spectrometry data were largely based on binary, or 'yes/no' data, demonstrating only if a protein was present in a sample or not.

The Stowers Institute's Proteomics Center recently published in *Proceedings of the National Academy of Sciences* a new method of using normalized spectral counts derived from a series of affinity purifications analyzed by mass spectrometry (APMS) to generate a probabilistic measure of the preference of proteins to associate with one another.

Large-scale APMS studies have played important roles in the assembly and analysis of comprehensive protein interaction networks for lower eukaryotes like yeast. But the development of such networks for human proteins has been slowed by the high cost and significant technical challenges associated with systematic studies of protein interaction.

The Proteomics Center has addressed this challenge by developing a method for building local, focused protein networks. By attaching affinity tags to proteins (allowing proteins to be purified from their crude biological sources using an affinity purification technique), the team was able to calculate the probability for two proteins to associate

*A diagram of the proteins in protein complexes and those associated with proteins in complexes: in the network, analyzed proteins could belong to one or more protein complexes or an individual protein could be associated with only a limited number of other proteins. Four primary protein complexes are represented and defined by large oval black lines. Two proteins at the core of this network, Tip49a and Tip49b were found in all four complexes, INO80, URI/Prefoldin, SRCAP, and TRRAP/TIP60. As a result, they are at the core of this figure. Other proteins, like HBB, were only strongly associated with one protein and are represented by narrow black lines.*

based on just the tagged protein and the pulled protein (the additional proteins isolated from the purification process). This simple method is an improvement over others requiring systematic reciprocal interactions between tagged and pulled proteins or co-purification of both proteins by a third tagged protein.

"A quantitative proteomics approach can provide so much more information than a binary one," said Michael Washburn, Ph.D., Director of Proteomics and senior author on the paper. "We were able to develop a method to generate more information-rich networks, where the preference of two proteins to associate within a defined complex or a larger network assembly can be estimated using probabilities. This is helpful because not all proteins interact in the same way, and this approach adds more information to the analysis of the protein complexes and networks."

The work not only provides a significant advancement in proteomic analysis, it also holds promise for facilitating the development of treatments for disease – insight regarding the most probable contacts within a multi-protein complex may help to devise targeted strategies to disrupt specific interactions, which may lead to the development of new drugs for disrupting protein complexes involved in disease.

# Diversifying the Future of Biomedical Research


*Alejandra Figueroa-Clarevega*

**Each year, the Howard Hughes Medical Institute (HHMI) selects up to five promising young researchers from groups underrepresented in the sciences to receive the Gilliam Fellowship for Advanced Study.**

**This year, Alejandra Figueroa-Clarevega, a Research Technician in the Gibson Lab, was among the distinguished group of fellows.**

The Fellowship, which honors the late James H. Gilliam Jr. – a charter Trustee of HHMI who was committed to fostering a diverse scientific community – provides full support for graduate training in biomedical research.

Ms. Figueroa-Clarevega, a native of Tegucigalpa, Honduras, joined the Stowers Institute for Medical Research in September 2007. She holds an undergraduate degree in Biology and Biomedical Sciences from Washington University in St. Louis.

"I have been fortunate during my time at the Stowers Institute to have gained experience in a wide variety of techniques and experimental procedures under the mentorship of Matt Gibson," said Ms. Figueroa-Clarevega. "The opportunities I've encountered here have helped me develop a clear understanding of exactly what kind of projects I would like to get involved with during my time as a graduate student, and I am confident that I will begin the Gilliam Fellowship with the tools I need to succeed."

Gilliam Fellows may pursue a Ph.D. or Sc.D. in the biological sciences at any institution of higher education in the United States. The total award for each Gilliam Fellow is $44,000 annually. Fellowships are awarded on the basis of the candidate's promise as a scientific investigator, as assessed by a panel of scientists and scientist educators selected by HHMI. More information is available at www.hhmi.org.

## The Role of Mathematics in Stowers Institute Research

# It All Adds Up

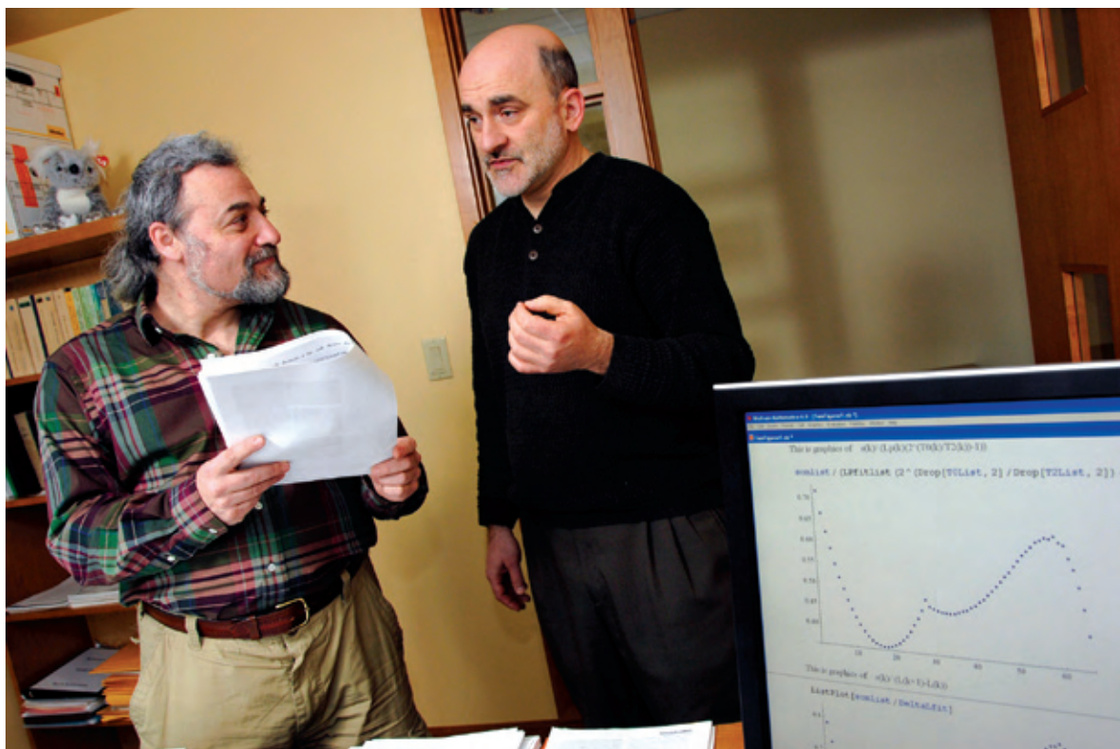
**School children may learn math and science as two distinct disciplines, but those who go on to pursue careers in biomedical research soon learn that mathematics is essential to proper analysis of complex biological data. It is also the basis for the field of computational biology, a discipline that calls on techniques of computer science, applied mathematics, and statistics to address biological problems.**

But how can biological data become numerical data? Although it may seem counterintuitive, all things, including biological processes, are susceptible to quantitative analysis. All things can be described in terms of their measurements: their number, their size, their speed, etc. These measurements can be mathematically analyzed to provide information that would be impossible to gain through simple recording or biological observation.

A mathematical approach to biology allows for sophisticated modeling of biological processes – the conversion of a biological system into a series of equations that describe the process and predict its behavior. Because a range of variables can be plugged into the equations, they can accommodate a spectrum of natural variation that approximates that found in living organisms.

Outside of the constraints of "real-world" biology, these so-called *in silico* models can quickly approximate events that would take months or years to carry out biologically.

Mathematical modeling and quantitative analyses are used broadly across the Institute, but they are especially important in the Institute's technology development programs in bioinformatics, imaging, and proteomics.



*Borris Rubinstein (left) and Arcady Mushegian (right) utilize mathematics as a part of the Bioinformatics Center's computational approach to answering biological questions.*

## Bioinformatics

The Bioinformatics Center uses computational methods to learn about the structure, function, and evolution of genes, proteins, and entire genomes. The staff in the Center work to develop a framework for the analysis of genome-wide numerical data.

"Thanks to modern technology, we can measure a lot of things," said Arcady Mushegian, Ph.D., Director of Bioinformatics. "Each gene in a completely sequenced genome can be associated with a series of numbers, and we can use those numbers to run sophisticated mathematical analyses that provide useful biological data."

For example, scientists can measure the level of transcripts of a gene under various conditions or treatments: with the presence and absence of counterparts of that gene in other complete genomes; with information about proteins that interact with a given gene product; with occupancy of all known cellular compartments and sites by the product of a gene; and with many other variables.

A wealth of data can be translated into meaningful biological information through the use of advanced algorithms, computational and statistical techniques, and mathematical theory.

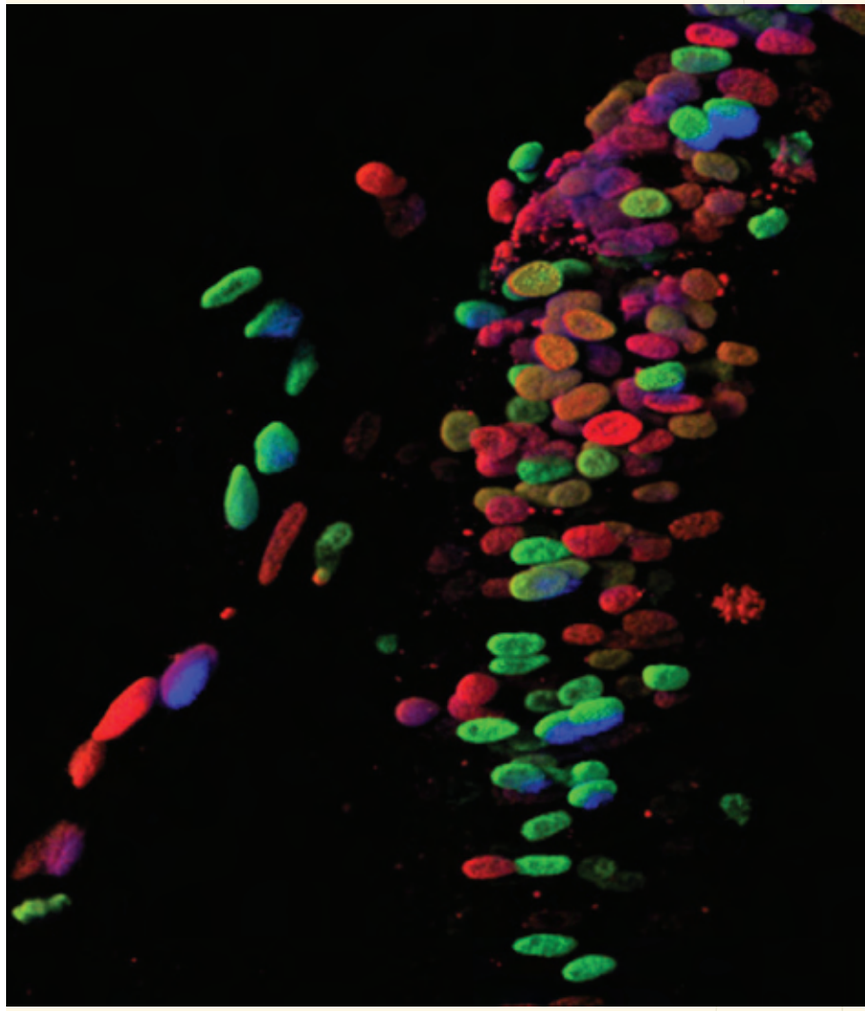
"Biology is much more complex than 'A' causes 'B'," said Dr. Mushegian. "It is about assigning probabilities to interactions and determining the strength of correlations. Fundamentally, these are functions of mathematics, and they are indispensable to modern biology."

## Imaging

The Institute's Imaging Center uses advanced technology to capture visual information about biological processes, but they also rely heavily on mathematical analysis.

A significant portion of the Imaging Center's work uses image processing and sorting and tracking of cells or molecules within living cells, tissues, and organs. Measurements of a cell's speed, direction, number of divisions, and interactions with other cells provide valuable information – as does evidence of correlated behavior between neighboring cells.

*Image courtesy of the Imaging Center*



*In a typical chick embryo, multicolor labeled cells within the developing brain can be more accurately sorted and tracked during embryogenesis using multispectral confocal imaging and mathematical analysis to separate each color.*

"Each of these quantities is based on specific mathematical calculations," said Paul Kulesa, Ph.D., Director of Imaging, "and each provides pieces of the puzzle to gain insight into the underlying biological mechanisms."

Also of interest to the Imaging Center is the ability to track an individual cell within a living chick embryo. Typically, cells can be labeled with a single fluorescent protein to aid in identification and tracking, but when two cells cross paths or exit and re-enter the plane of focus of the microscope, they become indistinguishable from one another, and the cell's trajectory is lost.

In a unique approach, the Imaging Center is developing a multicolor, multispectral method to label and track cells with significantly greater accuracy. Multiple fluorescent color combinations (typically up to three colors) are delivered into cells in the embryo using a cocktail of fluorescent proteins. The microscope uses lasers to excite the fluorescent proteins, and a multispectral detector captures the emission signals and generates images that contain spectral information for each pixel. With the aid of a computer, mathematical analysis uses reference spectra for each fluorescent protein to un-mix the pixel information and separate the colors across the entire image.

In this manner, efficient multicolor cell labeling, multispectral imaging, and mathematical analysis can achieve highly reliable identification of individual cells, allowing for sophisticated and accurate *in vivo* cell tracking.

**Paul Kulesa, Ph.D.**, Director of Imaging Center, also is an Assistant Professor in the Department of Anatomy and Cell Biology at The University of Kansas School of Medicine. Learn more about his work at www. stowers-institute.org/labs/KulesaLab.asp.

**Arcady Mushegian, Ph.D.**, Director of Bioinformatics Center, also is a Professor in the Department of Microbiology, Molecular Genetics & Immunology at The University of Kansas School of Medicine. Learn more about his work at www.stowers-institute.org/labs/MushegianLab.asp.

**Michael Washburn, Ph.D.**, Director of Proteomics, joined the Stowers Institute in 2003 from the Torrey Mesa Research Institute in San Diego. Learn more about his work at www.stowers-institute.org/labs/WashburnLab.asp.

## Proteomics

Mathematics plays an important role in research carried out in the Proteomics Center, where the team works closely with the Bioinformatics Center and the Information Technology department to develop computational proteomics techniques.

On a daily basis, the Proteomics Center produces large sets of raw data which are searched and analyzed by programs on large clusters of computers. The resulting interpreted datasets are organized, evaluated, and converted back into biological information that can shed light on the original problem.

"Together with the mathematicians and computer scientists in both the Proteomics Center and the Bioinformatics Center, we develop new ways to analyze and visualize the quantitative data that a computational approach allows us to generate," said Michael Washburn, Ph.D., Director of Proteomics.

$$W_j(s,\mathbf{d}^m) = \frac{1}{(m-1)!\,\pi_m\, j^{m-k_j}} \left( \prod_{i=k_j+1}^{m} \sum_{r_i=0}^{j-1} \right) B_{m-1}^{(m)}(s+s_m+\sum_{i=k_j+1}^{m} d_i r_i | \mathbf{d}_j^m) \Psi_j(s+\sum_{i=k_j+1}^{m} d_i(r_i+1)).$$

# Solving an Age-Old Problem

**PAPER:** Expression for Restricted Partition Function through Bernoulli Polynomials

**JOURNAL:** *The Ramanujan Journal*

**ISSUE:** February 2008

**AUTHOR:** Boris Rubinstein, Ph.D., Biomathematician

The Bioinformatics Center is made up of a talented group of people, and one of them recently demonstrated his mathematical skill by publishing the solution to a 250-year-old problem. Boris Rubinstein, Ph.D., Biomathematician, solved a problem first posed by the Swiss mathematician Leonhard Euler: assume that there is an infinite number of coins in the values of d1, d2, d3...dk cents – how many ways can one pay any arbitrary sum of N cents using coins of the values above?

Over time, several generations of mathematicians attempted and failed to find an explicit general formula to answer the problem. By the twentieth century, the mathematical community had largely given up – the problem was considered "cold."

Until, that is, Dr. Rubinstein published the solution in *The Ramanujan Journal* in February. Using a rare mathematical tool called the Bernoulli polynomials of higher order, Dr. Rubinstein found that a surprisingly brief, one-line formula solved the problem.

"Members of our team recently developed a new method for building protein interaction networks from quantitative proteomics datasets. Achievements like this help us to cultivate new insights into biology as efficiently and as accurately as possible, which is what our use of mathematics is all about."

## A Maturing Field

Although mathematics has always played a role in science, circumstances have converged over the past few decades to increase the demand for computational biology. Modern computer technology allows for complex calculations and simulations that would have previously been too demanding. Growth in the field of genomics has produced data-rich information sets that are difficult to understand without the help of mathematical analysis, and new mathematical tools have been developed to help understand challenging, non-linear mechanisms in biology.

It is only since the 1990s that computational biology has been recognized as its own field, but since that time the number of degree programs and fellowships has steadily climbed. With the wealth of information that computational biology can provide, and the increasing pace at which technology can provide it, mathematics is sure to remain an integral part in the ever-changing world of research at the Stowers Institute.

"This might be the first known application of these functions to solve a mathematical problem," said Dr. Rubinstein. "And while it is gratifying to solve such an old problem, the implications are much greater. I believe the developed approach can be used for research of more complicated open problems in number theory and combinatorics with application to other fields of science and technology, including coding theory, computer security, and others."

*Architectural renderings of the new Stowers Support Facility show possible exterior improvements.*


*Image courtesy of PGAV Architecture*

# Room to Grow

There was a time when Jim and Virginia Stowers wondered how they would ever fill the 600,000 square-foot research facility they built on Brush Creek to house the Stowers Institute for Medical Research, but less than eight years later, the Institute faces a space crunch.

Although there is still room to accommodate a few additional research teams on the Institute's main campus, more space to house support functions and meet storage needs has become essential.

In response, Jim and Virginia Stowers have purchased a 280,000 square-foot commercial/industrial complex in south Kansas City and donated it to the Institute. The 15 acre site, located approximately seven miles south of the Institute's main campus, currently includes office space, meeting rooms, cafeteria, and a substantial amount of warehouse space. It was previously owned and operated by the pharmaceutical company Sanofi-Aventis.

Over the next year, the complex will undergo an estimated $20 million renovation, including both interior and exterior improvements to the building. When completed, the Stowers Institute and its affiliated translational R&D organization, BioMed Valley Discoveries, will occupy portions of the building complex, leaving ample space for future growth.

"The sheer size of the new building will give us tremendous flexibility to meet the Institute's evolving needs," said Tim Geary, Senior Director of Research Operations. "We were very fortunate to find a facility like this so near to our main campus. The purchase of this building was the culmination of a lengthy search, and I believe it will serve the Institute well for many years into the future."

In 2007, the Institute purchased more than 120 acres of land in Kansas City to accommodate future growth of the Institute's research facilities – estimated to be 600,000 square-feet every decade, in perpetuity. Plans to build additional research space are currently on hold until the environment for embryonic stem cell research in Missouri stabilizes.

"The Institute remains committed to a future in Kansas City, and though we look forward to the time when full-scale Institute expansion can move forward as envisioned, the south Kansas City support facility represents an important interim step," said William B. Neaves, Ph.D., President and CEO.

# Recognizing Recent Hope Shares® Donations

Between October 1, 2007 and February 29, 2008, contributions of at least $1,000, the minimum for establishing a Hope Shares account in the endowments of the Stowers Institute, were received from, in memory of, or in honor of the following:

### $100,000 or More

*American Century Foundation*
*Richard H. Driehaus Charitable Trust*

### In Memory Of

*From Pamela Stowers in Memory of Laura S. Stowers*

### $25,000 or More

*American Century Employees*

### $10,000 or More

*Richard W. and Jeanette Brown*
*Brian Jeter*
*James E. Stowers III*
*Rod and Linda Sturgeon*
*David A. and Wendy B. Welte*

### $5,000 or More

*Enrique Chang and Catherine Farley*
*William B. and Priscilla W. Neaves*

### $1,000 or More

*Don and Christine Alexander*
*Labconco Corporation*
*Drs. Margo Denke and James E. Griffin III*
*Terrence and Peggy Dunn*
*June and Ron Estabrook*
*Banning G. Flynn*
*Allan J. and Margot R. Huber*
*Barbara H. Marshall*
*Amy L. Noelker*
*Dr. and Mrs. Robert E. Peterson*
*Don and George-Ann Pratt*
*Kathleen Stowers*
*David and Jeannine Strandjord*

### In Memory Of

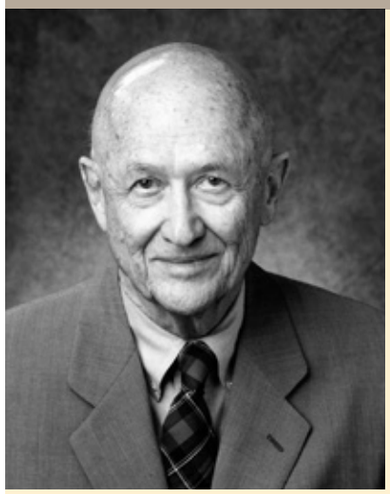
*Frederick N. Coulson Jr.*
*Mark Dover*
*From Drs. Margo Denke and James E. Griffin III in Memory of James E. Griffin Jr.*
*From Bo Kreiling in Memory of Helen Jayne Kreiling*

Hope Shares donations are invested with the Institute's endowments. To track the current value of a Hope Shares account, see page 36 in the 2007 Year in Review section of this Stowers Report. To establish a Hope Shares account, visit www.stowers-institute.org or call (816) 926-4000.

*Every attempt has been made to ensure the accuracy of the above list. In case of error or omission, the Stowers Institute wishes to be advised.*

## Donor Profile

### *James M. Kemper Jr.*



James M. Kemper Jr. has spent a lifetime as a force for progress in Kansas City. After serving in the army and graduating from Yale College, he joined Commerce Trust Company in 1946 and transformed it two decades later into Commerce Bancshares, Missouri's first major bank holding company.

He founded and chaired the Downtown Council of Kansas City and served organizations as diverse as the Kansas City School Board, the Committee for Economic Development, the Federal Reserve Board of Kansas City, and the Smithsonian.

Today, Jim Kemper continues to provide generous support for Kansas City initiatives.

In August 2007, Mr. Kemper established a Hope Shares account at the Stowers Institute with a donation of $250,000.

"Thoughtful people are supporting the Stowers Institute and its research," said Mr. Kemper of his gift. "I felt it was important not only to help fund the Institute's world-class science, but also to demonstrate that citizens of Kansas City are solidly behind this important work."

# 2007
## Year in Review

# Taking Stock

AT THE CLOSE OF 2007, 447 PEOPLE WORKED AT THE STOWERS INSTITUTE EACH DAY. 354 WERE MEMBERS OF THE SCIENTIFIC STAFF, INCLUDING:

- 25 Principal Investigators
- 108 Postdoctoral Research Associates and Fellows
- 23 Predoctoral Research Associates

# Making a Mark


In 2007, Stowers Institute research teams continued to make discoveries that merited publication in leading peer-reviewed scientific journals – 50 published papers in all. Add to those 27 reviews, commentaries, or chapters, and one book: *Foundations of Comparative Genomics* by Arcady Mushegian, Ph.D., Director of Bioinformatics. It all makes for a very successful year. Highlights among 2007's published papers include:

- The **Baumann Lab** identified the long-sought telomerase RNA gene in a single-cell research model in a paper in the December 27 issue of *Nature Structural & Molecular Biology*.
- The **Rong Li Lab** reported protein interactions of the MAP kinase-signaling pathway in the December 18 issue of *Proceedings of the National Academy of Sciences*.
- The **Shilatifard Lab** shed light on the molecular machinery required for translation of histone cross-talk in the December 14 issue of *Cell*.
- The **Hawley Lab** identified factors responsible for the restart of the meiotic cycle in the December 4 issue of *PLoS Biology*.
- **Ali Shilatifard** and **Jerry Workman** joined colleagues in advocating new nomenclature for chromatin-modifying enzymes in the November 16 issue of *Cell*.
- The **Pourquié Lab** demonstrated the role of fibroblast growth factor in vertebrae formation in the November 1 issue of *Development*.
- The **Xie Lab** demonstrated the dual intrinsic and extrinsic control of stem cell aging in the October 11 issue of *Cell Stem Cell*.
- The **Conaway Lab** demonstrated the mechanism by which a transcription factor controls gene expression in the September 1 issue of *Nature Structural & Molecular Biology*.
- The **Gerton Lab** identified a factor responsible for specification of centromeric chromatin in the June 22 issue of *Molecular Cell*.
- The **Workman Lab** demonstrated the mechanism for decoding histone modification marks in the May 18 issue of *Science*.
- The **Baumann Lab** defined proteins that distinguish chromosome ends from DNA double-strand breaks in the May 11 issue of *Molecular Cell*.
- The **Trainor Lab** identified a gene essential for craniofacial development in the May 1 issue of *Genes and Development*.
- The **Rong Li Lab** shed light on the principles of cell polarity in the April 20 issue of *Cell*.
- The **Shilatifard Lab** identified a potential target for the treatment of mixed lineage leukemia in the April 1 issue of *Nature Structural & Molecular Biology*.
- The **Xie Lab** demonstrated the role of the MicroRNA pathway in the self-renewal of germline stem cells in the March 20 issue of *Current Biology*.
- The **Conaway Lab** developed a new model system for understanding a transcription factor involved in leukemia in the February 23 issue of the *Journal of Biological Chemistry*.
- The **Pourquié Lab** clarified the mode of formation of spinal precursors in the February 20 issue of *Proceedings of the National Academy of Sciences*.
- The **Linheng Li Lab** documented the development of cancer stem cells in the February 1 issue of *Nature Genetics*.
- The **Rong Li Lab** demonstrated the process of mammalian egg maturation through asymmetric cell division in the February issue of *Developmental Cell*.

# Accolades

*Front row from left: Macie Walker, Karen Smith, Sue Jaspersen, Brian Slaughter. Back row from left: Tingting Yao, Jennifer Gerton, Ali Shilatifard, Kim Collins, Chunying Du, Kausik Si.*

- **Karen Smith, Ph.D.**, Postdoctoral Research Associate in the Workman Lab, received a National Institutes of Health *Research Fellowship Award*, effective in September.
- **Jennifer Gerton, Ph.D.**, Assistant Investigator, received the 2007 *Hudson Prize* from the M.R. and Evelyn Hudson Foundation, effective in July.
- **Tingting Yao, Ph.D.**, Postdoctoral Research Fellow in the Conaway Lab, was named a *Leukemia & Lymphoma Society Special Fellow*, effective in July.
- **Chunying Du, Ph.D.**, Assistant Investigator, was awarded a *Research Grant* from Susan G. Komen for the Cure, effective in July.
- **Kim Collins, Ph.D.**, Postdoctoral Research Fellow in the Hawley Lab, received a National Institutes of Health *Research Fellowship Award*, effective in July.
- **Brian Slaughter, Ph.D.**, Postdoctoral Research Associate in the Rong Li Lab, received a National Institutes of Health *Research Fellowship Award*, effective in May.
- **Ali Shilatifard, Ph.D.**, Investigator, received the *Innovation Award* at the Outstanding St. Louis Science Awards Ceremony in April.
- **Macie Walker, Ph.D.**, Postdoctoral Research Fellow in the Trainor Lab, received a National Institutes of Health *Research Fellowship Award*, effective in March.
- **Sue Jaspersen, Ph.D.**, and **Kausik Si, Ph.D.**, Assistant Investigators, were awarded *Basil O'Connor Starter Scholar Research Awards*, effective in February.

# Advancing Work, Advancing Careers

The Stowers Institute is pleased to acknowledge the promotion of Paul Trainor, Ph.D., from Assistant Investigator to Associate Investigator, effective January 1, 2008. Dr. Trainor joined the 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 leads a team of scientists who focus on establishing a better understanding of the origins of craniofacial abnormalities. They have made notable strides in furthering the understanding and potential prevention of Treacher Collins Syndrome, which causes severe head and face abnormalities at birth (see page 5 for recent advancements).

Dr. Trainor was the recipient of the Basil O'Connor Starter Scholar Award from the March of Dimes in 2003 and the recipient of the Stowers Institute's 2006 Hudson Prize, awarded by the M.R. and Evelyn Hudson Foundation of Texas. He holds a Ph.D. in Developmental Biology from Children's Medical Research Institute at the University of Sydney, Australia.

# 2007 Board of Directors

**James E. Stowers Jr.**
*Co-Chairman of the Board and Co-Founder*
Stowers Institute for Medical Research
*Founder*
American Century Companies, Inc.

**Virginia G. Stowers**
*Co-Founder*
Stowers Institute for Medical Research

**James E. Stowers III**
*Owner*
Oxford Companies

**Richard W. Brown**
*Co-Chairman of the Board*
Stowers Institute for Medical Research

**Clifford W. Illig**
*Vice Chairman and Co-Founder*
Cerner Corporation

**Robert E. Krumlauf, Ph.D.**
*Scientific Director*
Stowers Institute for Medical Research

**William B. Neaves, Ph.D.**
*President and Chief Executive Officer*
Stowers Institute for Medical Research

**Roderick L. Sturgeon**
*Chief Financial Officer*
Stowers Institute for Medical Research

# 2007 Scientific Advisory Board

**Douglas A. Melton, Ph.D., Chairman**
*Howard Hughes Medical Institute Investigator, Thomas Dudley Cabot Professor in the Natural Sciences in the Department of Molecular & Cellular Biology at Harvard University, Associate Member at Children's Hospital Boston, Biologist at Massachusetts General Hospital, Professor of Molecular & Cellular Biology at Harvard University.*

**Michael S. Levine, Ph.D.**
*Co-Director of the Center for Integrative Genomics and Head of and Professor in the Division of Genetics, Genomics, and Development in the Department of Molecular and Cell Biology at the University of California, Berkeley.*

**Susan Lindquist, Ph.D.**
*Howard Hughes Medical Institute Investigator, Member of the Whitehead Institute for Biomedical Research, and Professor of Biology at the Massachusetts Institute of Technology.*

**Eric N. Olson, Ph.D.**
*Robert A. Welch Distinguished Chair in Science, Annie and Willie Nelson Professorship in Stem Cell Research, Pogue Distinguished Chair in Research on Cardiac Birth Defects, and Professor of Molecular Biology at the University of Texas Southwestern Medical Center at Dallas.*

**Janet Rossant, Ph.D.**
*Chief of Research and Senior Scientist at The Hospital for Sick Children, University Professor at the University of Toronto, Deputy Scientific Director at the Stem Cell Network of Centres of Excellence, and Professor of Obstetrics & Gynecology and Genetics and Microbiology at the University of Toronto.*

**Joshua R. Sanes, Ph.D.**
*Professor in the Department of Molecular and Cellular Biology and Paul J. Finnegan Family Director in the Center for Brain Science at Harvard University.*

**Charles J. Sherr, M.D., Ph.D.**
*Howard Hughes Medical Institute Investigator and Herrick Foundation Chair in the Department of Genetics and Tumor Cell Biology at St. Jude Children's Research Hospital.*

# 2007 Research Leaders

## Laboratories

**Robert E. 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.

**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.

**Peter Baumann, Ph.D., Assistant 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 at Boulder. Dr. Baumann received a Ph.D. in Biochemistry from the Imperial Cancer Research Fund and University College, London.

**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. Dr. Blanchette received a Ph.D. degree in Microbiology from the Université de Sherbrooke, Canada.

**Joan Conaway, Ph.D., Investigator**, joined the Stowers Institute in 2001 from the Oklahoma Medical Research Foundation where she was 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.

**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.

**Chunying Du, Ph.D., Assistant Investigator**, joined the Stowers Institute in 2001 from a postdoctoral fellowship in the laboratory of Dr. Xiaodong Wang at the University of Texas Southwestern Medical Center at Dallas. Dr. Du has a Ph.D. in Molecular, Cellular and Developmental Biology from Iowa State University.

**Jennifer Gerton, Ph.D., Assistant 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.

**Matt Gibson, Ph.D., Assistant Investigator**, joined the Institute in 2006 from a postdoctoral fellowship with Norbert Perrimon at Harvard Medical School. Dr. Gibson received a Ph.D. in Zoology from the University of Washington.

**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 at the Institute for Cancer Research in Philadelphia.

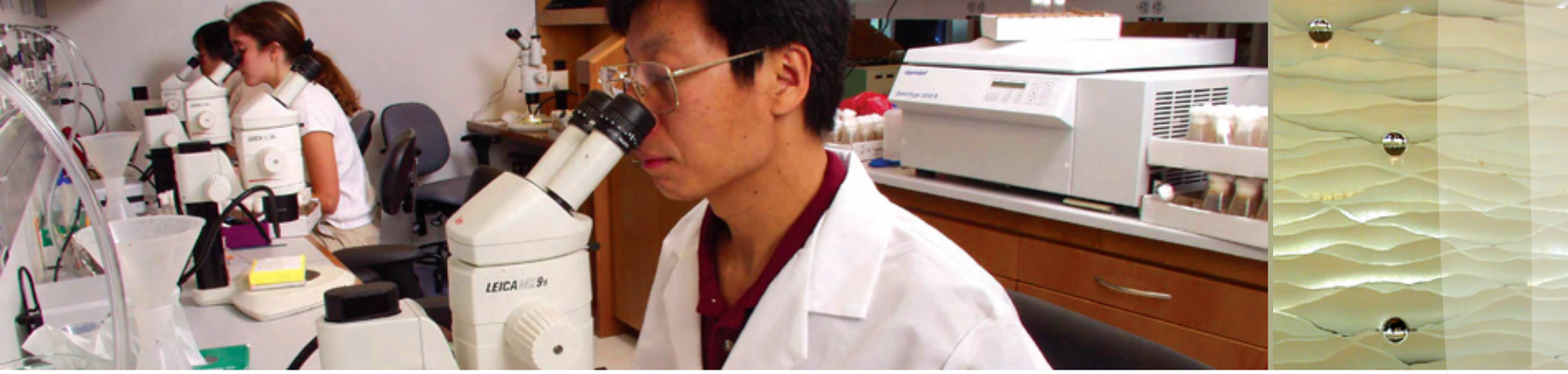
**Sue Jaspersen, Ph.D., Assistant Investigator**, joined the Stowers Institute in 2005 from a postdoctoral fellowship in the laboratory of Dr. Mark Winey at the University of Colorado-Boulder. Dr. Jaspersen received a Ph.D. in Biochemistry from the University of California, San Francisco.

**Linheng Li, Ph.D., Associate 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.

**Rong Li, Ph.D., Investigator**, joined the Stowers Institute in 2005 from the Department of Cell Biology at Harvard Medical School. She was a postdoctoral associate with Dr. David Drubin at the University of California, Berkeley, and earned a Ph.D. in Cell Biology at the University of California, San Francisco with Dr. Andrew Murray.

**Ho Yi Mak, Ph.D., Assistant Investigator**, joined the Stowers Institute in 2006 from a 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.

**Olivier Pourquié, Ph.D., Investigator**, joined the Stowers Institute in 2002 from the position of Director of Research at the Developmental Biology Institute of Marseille, France. Dr. Pourquié received a Ph.D. from the National Institute of Agronomy in Paris.



**Ali Shilatifard, Ph.D., Investigator**, joined the Stowers Institute in 2007 from the Saint Louis University School of Medicine where he was a Professor and Associate Director for Basic Sciences of the Saint Louis University Cancer Center. He earned a B.S. in Organic Chemistry at Kennesaw State University and a Ph.D. from the University of Oklahoma School Of Medicine.

**Kausik Si, Ph.D., Assistant Investigator**, joined the Stowers Institute in 2005 from the Columbia University Center for Neurobiology and Behavior where he conducted postdoctoral research with Dr. Eric Kandel. Dr. Si earned a Ph.D. in Molecular Biology from the Albert Einstein College of Medicine.

**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.

**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 Professor Bob Roeder.

**Ting Xie, Ph.D., Associate Investigator**, joined the Stowers Institute in 2000 after completing a 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.

**Ron Yu, Ph.D., Assistant Investigator**, joined the Stowers Institute in 2005 from the Columbia University Center for Neurobiology and Behavior where he completed post-doctoral studies with Dr. Richard Axel. Dr. Yu earned his Ph.D. in Molecular, Cellular and Biophysical Studies at Columbia University.

**Julia Zeitlinger, Ph.D., Assistant Investigator**, joined the Stowers Institute in 2007 from a postdoctoral fellowship at the Whitehead Institute for Biomedical Research at the Massachusetts Institute of Technology. Dr. Zeitlinger earned a B.Sc. from King's College London, U.K., and a Ph.D. in Molecular Biology from the European Molecular Biology Laboratory in Heidelberg, Germany.

## Technology Centers

**Paul Kulesa, Ph.D., Director of Imaging Center**, joined the Stowers Institute in 2002 after completing a 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.

**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.

**Michael Washburn, Ph.D., Director of Proteomics**, 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.

# 2007 Hope Shares® Values

Many people and institutions have shown their support for the mission of the Stowers Institute by opening Hope Shares accounts. Hope Shares accounts can be established in amounts of $1,000 or more, and donations are invested to increase in value over time. The information listed below represents the December 31, 2007 value of lifetime donations from, in memory of, or in honor of the following:

## $1 Million or More

*American Century Foundation*

### In Memory Of

*Laura S. Stowers*

## $500,000 or More

*Dunn Family Foundation*
*Barnett and Shirley Helzberg*
*Felix and Helen Juda Foundation*
*Margaret Lichtenaur Estate*

## $100,000 or More

*American Century Employees*
*Greater Kansas City Community Foundation Frederick and Louise Hartwig Family Fund*
*Tom and Nancy Juda Foundation*
*James M. Kemper Jr.*
*Polsinelli Shalton Welte Suelthaus*
*Hank Young* (Gameface *book proceeds)*

## $50,000 or More

*Richard W. and Jeanette Brown*
*Country Club Bank*
*Menorah Medical Center (in kind)*
*William B. and Priscilla W. Neaves*
*James E. Stowers III*
*David A. and Wendy B. Welte*

## $25,000 or More

*Mildred E. Coats Trust*
*J.E. Dunn Construction (in kind)*
*Sanders Morris Harris*
*IBM (in kind)*
*Bill and Peggy Lyons*
*Rubin Postaer and Associates*
*John and Shirley Wagner*
*Mr. and Mrs. Michael Zolezzi*

### In Memory Of

*Carlo Jonathan*
*Felix Juda*
*Robert G. Ruisch Jr.*
*Vernon Voorhees II*
*Virginia C. Wimberly*

## $10,000 or More

*Cancer Golf Association*
*Cisco Systems (in kind)*
*Webb R. Gilmore*
*Gilmore and Bell, P.C.*
*Allan J. and Margot R. Huber*
*Jack and Rena Jonathan*
*Irving Kuraner*
*Labconco Corporation*
*Lucent Technologies (in kind)*
*Barbara H. Marshall*
*Mark and Martha Miller*
*Tom W. and Jeanne H. Olofson*
*The J.B. Reynolds Foundation*
*Rick and Betsey Solberg*
*Kathleen Stowers*
*David and Jeannine Strandjord*
*Jonathan and Cyndi Thomas*
*Byron Thompson*

### In Memory Of

*James and Eleanor Drake*
*Helen W. Kirby*
*Helen I. Lebens*
*Richard K. Smith, Wendell E. Smith, and Laura S. Stowers*

## $5,000 or More

*Mary Breed Brink*
*Enrique Chang and Catherine Farley*
*Michael A. and Jenny Cormack*
*David and Nancy Dilley*
*Brian Jeter*
*Otto and Margarete Katke Charitable Foundation*
*David and Susan Keefer*
*Thomas R. Kmak Family*
*Dawn Lind*
*Amy L. Noelker*
*Robert A. Pearson*
*Rod and Linda Sturgeon*
*Howard and Frances Vaughan Charitable Foundation*
*Austin E. and Laura Wilson*

### In Memory Of

*Arthur Brand*
*Frederick N. Coulson Jr.*
*Walter C. Day*
*Paul H. Henson*
*Helen Jayne Kreiling*

## $1,000 or More

*Herbert and Estele Adler*
*Don and Christine Alexander*
*Rob J. Aneweer*
*Elmer M. and Verna M. Armbruster*
*Malcom M. and Kathy B. Aslin Fund*
*Donald A. and Margaret G. Austin*
*Paul D. Jr. and Joan J. Bartlett*
*Bert and Joan Berkley*
*John R. and Sheryl S. Block*
*Gregory Broome*
*Mary Jo Browne*
*Michael A. and Gretchen V. Carter*
*Shirley Christian*
*Gilbert and Lois Cole*
*Michael E. and Joyce P. Cunningham*
*Phillip Davidson*
*Terrence and Peggy Dunn*
*Ron and June Estabrook*
*Jill A. Farrell*
*Banning G. Flynn*
*Jody Anne Frederickson*
*Abby Freeman*
*William and Laura Frick Foundation Fund*
*The William George Family Charitable Trust*
*Mr. and Mrs. Jules Goldman*
*Samuel D. and Melody Goller*
*Mary Louise Greene*
*Laura W. Greenbaum*
*Ed Jr. and Jody Griffin*
*Andrea Lynn Hazle*
*Henson Trust Fund*
*Irv and Ellen Hockaday*
*Robert T. and Lynette E. Jackson*
*Harrison Jedel*
*Jeffrey M. Johnson*
*Mr. and Mrs. Leroy Larsh Johnson*
*Bob and Myrna Krohn*

For information about establishing a Hope Shares account, visit www.stowers-institute.org or call (816) 926-4000.


*Linsley and Jane Lundgaard*
*Mary Kay McPhee*
*Robert and Shirley Meneilly*
*Jeannette Nichols*
*Stephen P. Novak*
*Dr. and Mrs. Robert E. Peterson*
*Michael J. Rainen Family Foundation*
*Isabelle Berry Reed Revocable Living Trust*
*Craig A. and Maryanne L. Roepke*
*Jerry and Tracy Rossi*
*Felix N. Sr. and Carmen C. Sabates*
*Sierra Aviation Inc.*
*Darrell and Marjorie Spaedy*
*Michele Stowers*
*Pamela Stowers*
*Mark A. Susz Revocable Trust*
*Ten Ten Foundation*
*Harold E. and Ruthie Tivol*
*Robert and Roselle Tomsovic*
*Charles and Carol Diane Tritschler*
*David C. Tucker*
*John M. and Ollie K. Urie*
*Dennis and Sally Von Waaden*

## In Memory Of

*Carlene Adkins*
*Kitty Berkowitz and Janice McInrath*
*Carol Ann Brown*
*Evelyn Louise "Lovey" Byrer*
*Alice J. "Penny" Cohn*
*William Cordes*
*Walter C. Day*
*Carol Denicole*
*Mark Dover*
*Dana Eckles*
*William R. Edwards*
*James E. Griffin Jr.*
*Estelline P. Huey*
*Gary Kostuke*
*Jane Lundgaard*
*Hazel Meany*
*John O'Day*
*Albert F. Otten and William F. Ellis*
*Herbert A. Schaadt and Carol E. Barry*
*Barbara R. Searcy*
*Paul J. and Aimee K. Stoffel*
*The Honorable Elwood Thomas*

*Every attempt has been made to ensure the accuracy of the above list. In case of error or omission, the Stowers Institute wishes to be advised.*

# These donors and those they honor will never be forgotten.

*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.*


STOWERS INSTITUTE®
FOR MEDICAL RESEARCH

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


Address Service Requested