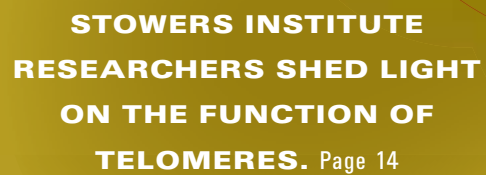


# Stowers

REPORT

NEWS AND INSIGHT FROM  
THE STOWERS INSTITUTE  
FOR MEDICAL RESEARCH

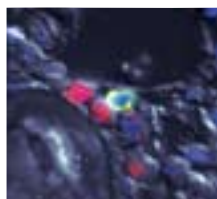
The cover features a central image of a chromosome spread, with individual chromosomes appearing as blue and purple structures. Red dots are scattered across the chromosomes, representing telomeres. This central image is surrounded by several circular inset images, each showing a different view or detail of the telomeres. White arrows point from the text to these inset images. The background is a solid olive green with faint white circular lines.

**STOWERS INSTITUTE  
RESEARCHERS SHED LIGHT  
ON THE FUNCTION OF  
TELOMERES.** Page 14

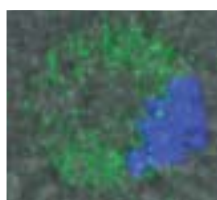
SPRING 2009

# Stowers REPORT

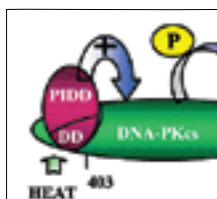
PUBLISHED BY THE STOWERS INSTITUTE FOR MEDICAL RESEARCH



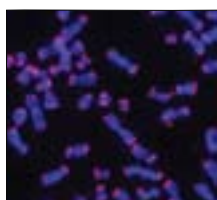
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## STOWERS REPORT

SPRING 2009  
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# LOOKING TO THE FUTURE

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



*William B. Neaves (left) and David Chao*

As I approach my ninth anniversary as President and CEO of the Stowers Institute, I am delighted that the Institute is thriving. An exceptional group of researchers has assembled here, and the results of their work are rapidly building the international reputation of the Institute as a major center of discovery science. Some of the recent successes are highlighted in this issue of the *Stowers Report*. As you read about them, you will appreciate the importance of the Institute's focus on understanding how the behavior of genes and chromosomes enables cells to form tissues and organs and how mistakes lead to disease.

The Institute has an excellent team providing support for its research, and it is fortunate that Robb Krumlauf, Ph.D., continues to serve both as Scientific Director and as a role model of a productive laboratory leader. As I think about the future of the Institute, I am reminded of how important it will be to preserve the elements that have contributed to its early success, and to maintain continuity in leadership.

Although I plan to continue working full time at the Institute for many years, it would be irresponsible not to acknowledge that unforeseen circumstances could intrude. Accordingly, I have proposed and the Institute's Board of Directors has adopted a transition plan for my current role at the Institute. This plan will safeguard the Institute from a sudden and unexpected change in leadership, will stabilize the team that deserves much credit for the Institute's early success, and will preserve the Institute's trajectory of research productivity. The plan accomplishes this by placing a proven leader who has earned our confidence into part of my present role this summer, while beginning an orderly transition toward that person's undertaking my entire present role in the summer of 2010.

The person who will be my successor is David Chao, Ph.D. His career has focused on biomedical research and has included posi-

tions as a basic researcher, a management consultant to life science companies, a founder of biotechnology companies, and an executive in the pharmaceutical industry. He holds a Ph.D. in Biology from Massachusetts Institute of Technology, where he was a predoctoral fellow of the Howard Hughes Medical Institute, as well as an M.A. and B.A. in Biology from Harvard University. Dr. Chao joined us in September 2007 as President and CEO of BioMed Valley Discoveries (BVD), the organization whose mission is to develop basic biomedical discoveries into applications that improve human

health. In the spring of 2008, he began devoting part of his effort to serving as Executive Vice President of the Stowers Institute with responsibility for many of the Institute's research support facilities. He has quickly earned the esteem of all who work with him. Dr. Chao demonstrates the integrity, judgment, and scientific insight to lead the Institute to greater success in the next phase of its growth in Kansas City.

I am delighted to let you know that Dr. Chao will become President of the Stowers

Institute on July 1, 2009. I will continue in the role of CEO through June 30, 2010 when he will become CEO as well as President. At that time, I will become President Emeritus and serve as a resource for him and the Institute while undertaking duties assigned by the Co-Chairman and the Board. Dr. Chao will remain a member of BVD's Board of Directors but will relinquish his role as President and CEO of BVD by July 2009.

I am delighted that Dr. Chao has enthusiastically accepted the responsibility of serving as the President and CEO of the Stowers Institute, and I look forward to working closely with him for many years to come. As I have certainly done, Dr. Chao will find that leading this wonderful organization is the privilege of a lifetime. Please join me in welcoming him to his new roles as he focuses on turning the vision of Jim and Virginia Stowers into reality.

.....  
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.org](mailto:stowersreport@stowers.org).  
.....

# TRACKING PROGRESS



## New Technology Confirms an Influential Finding and Opens Doors for Future Research

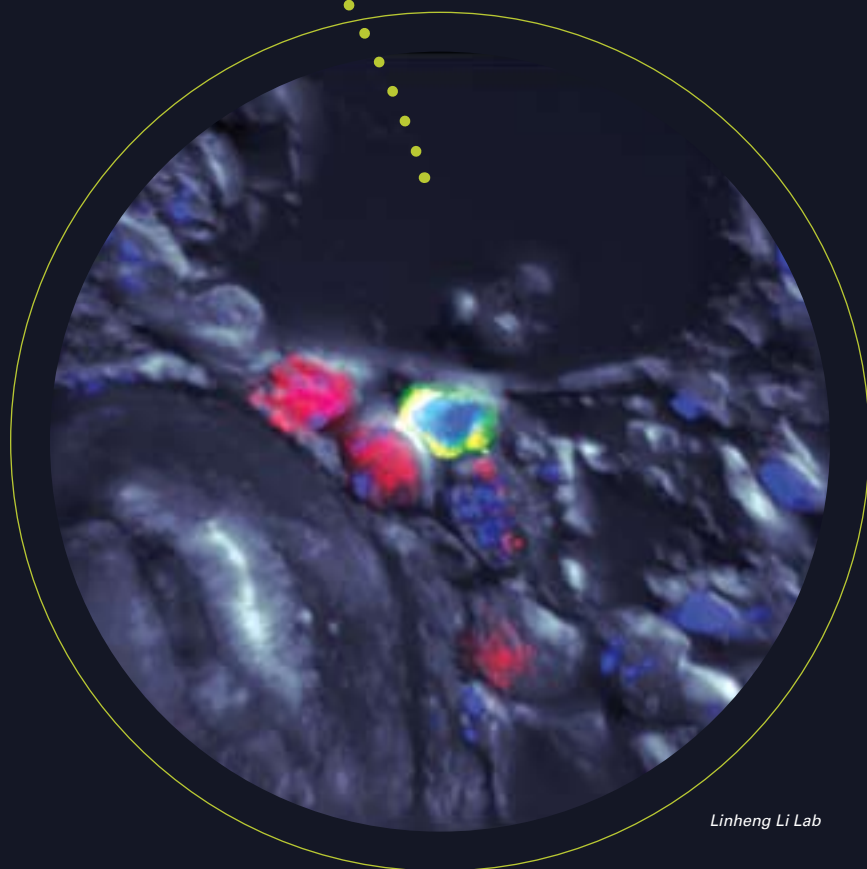
MORE THAN FIVE YEARS AGO, THE STOWERS INSTITUTE'S LINHENG LI LAB ACCOMPLISHED SOMETHING THAT LEADING RESEARCH TEAMS AROUND THE WORLD HAD BEEN ATTEMPTING FOR MORE THAN 25 YEARS: THEY DISCOVERED THE HEMATOPOIETIC STEM CELL (HSC) NICHE. THIS MICROENVIRONMENT IN THE BONE MARROW NURTURES HSCs AND SUSTAINS THEIR ABILITY TO SELF-RENEW, MULTIPLY, AND PRODUCE ALL THE CELL TYPES FOUND IN BLOOD.

Recently, the team collaborated with the Stowers Institute's Imaging Center to devise new methods that allowed them to validate their earlier findings about the location of the HSC niche and to monitor the dynamic behavior of stem cells in a new way. The work was published in the journal *Nature*. The technique, called *Ex Vivo* Imaging Stem Cell (EVISC) Technology, allowed the team to track the movement of HSCs modified to express a fluorescent green protein that makes them easily visible.

The team was able to watch the labeled HSCs converge on the inner bone surface at the periphery of the bone marrow cavity, and in doing so, to resolve a debate in the field over the nature of the true HSC niche – whether it is formed by osteoblasts (bone-forming cells) or by endothelial cells (blood-vessel-forming cells). Surprisingly, the answer is both. The inner bone surface of the marrow cavity where the HSC niche resides is a specialized zone that includes both osteoblastic and vascular components.

“Understanding how HSCs are maintained in the niche and how they behave in the bone marrow is critical to improving the use of HSCs in regenerative medicine,” said Linheng Li, Ph.D., Investigator and senior author on the publication. “Today, the best way to aid a patient whose HSCs are failing due to blood diseases like leukemia is to perform a bone marrow transplant – a procedure that introduces not just HSCs but all of the cells of the bone marrow from the donor to the recipient. We are hopeful that with a greater understanding of the HSC niche, it will be possible to isolate HSCs and induce them to divide and multiply in a lab dish before transplanting them into a patient. This ability would improve the efficiency of bone marrow transplants and would allow far greater control over the number of HSCs transferred by the procedure.”

The development of the EVISC Technology has applications that reach well beyond the tracking of HSCs in the bone marrow. The team believes that the method will allow them to observe the behavior of cancer cells – to locate their niches, define their functional states, and determine their response to drugs and novel treatments.



Linheng Li Lab

*A hematopoietic stem cell (bordered in yellow and green) is nestled between a blood vessel and bone among niche cells (red) that connect to bone-forming osteoblasts covering the bone surface.*

**PAPER:** Detection of Functional Hematopoietic Stem Cell Niche Using Real-time Imaging

**JOURNAL:** *Nature*

**ISSUE:** January 1, 2009

**AUTHORS\*:** Yucai Xie<sup>†</sup>, Predoctoral Researcher; Tong Yin<sup>†</sup>, Ph.D., Postdoctoral Research Fellow; Winfried Wiegraebe, Ph.D., Director of Microscopy; Xi He, M.D., Senior Research Specialist; Diana Miller, Ph.D., University of Maryland School of Medicine; Danny Stark, Research Technician III; Katherine Perko, Research Technician I; Richard Alexander, Senior Research Technician; Joel Schwartz, Ph.D., formerly the Managing Director of Imaging; Justin Grindley, Ph.D., Senior Research Associate; Jungeun Park, Research Technician II; Jeffrey Haug, Managing Director - Cytometry Facility; Joshua Wunderlich, formerly a Research Technician; Hua Li, Ph.D., Biostatistician; Simon Zhang, formerly a Laboratory Assistant; Teri Johnson, Managing Director - Histology Facility; Ricardo Feldman, Ph.D., University of Maryland School of Medicine; and Linheng Li, Ph.D., 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.**, 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.org/labs/LiLab.asp](http://www.stowers.org/labs/LiLab.asp).

# Ensuring the Integrity

WHEN A RESEARCHER SUBMITS ORIGINAL WORK TO A JOURNAL FOR PUBLICATION, THE EDITOR MUST BE ASSURED THAT IT MEETS ESTABLISHED STANDARDS OF ETHICAL CONDUCT AND SCIENTIFIC INTEGRITY. DEVIATIONS FROM THESE STANDARDS ARE RARE, BUT WHEN THEY OCCUR, THE CONSEQUENCES OF SCIENTIFIC MISCONDUCT CAN BE DEVASTATING.

In 2005, South Korean researcher Hwang Woo-Suk drew international ire when he was found to have fabricated the data in two groundbreaking stem cell studies. The resulting media frenzy threatened public support of stem cell research and demonstrated just how much damage a single instance of scientific misconduct can inflict.

The Stowers Institute believes that the best way to avoid scientific misconduct is to help its researchers learn to identify and avoid ethical pitfalls. To that end, the Institute offers an eight-week course titled *Research Integrity* taught by President and CEO William B. Neaves, Ph.D. The course is offered in even-numbered years and is required for postdoctoral associates and fellows, graduate students, members of research support facilities, and newly recruited principal investigators who have not previously enrolled in such a course. In 2008, more than 140 Institute members participated in the course.

“The course uses selected case studies gleaned from actual allegations of scientific misconduct at a research-intensive academic medical center over an interval of two decades,” said Dr. Neaves. “By using real-world examples, the course encourages practicing scientists to think about the principles of research integrity; to appreciate the devastating effect of scientific misconduct on public trust, institutional reputation, and individual careers; and to understand why the Stowers Institute has zero tolerance for material deviation from commonly accepted standards for proposing, conducting, and reporting research.

“This course fulfills the obligation of the Stowers Institute, as a NIH-grant recipient, to provide instruction in research integrity to its trainees and research staff. Most importantly, it prepares our researchers to conduct their careers in accordance with the highest ethical standards.”

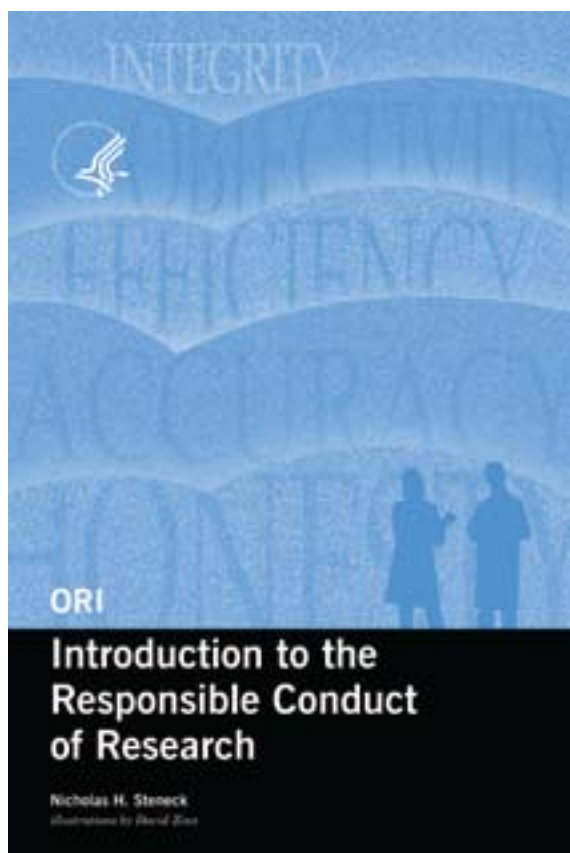
Designed to teach researchers to think critically about issues of scientific behavior, the course forgoes a lecture format and relies instead on spirited dialogue among the participants. Each week, a postdoctoral researcher leads a discussion based on a set of presenting facts from an actual case of alleged scientific misconduct. As the dialogue among the participants progresses, the discussion leader reveals additional details about the incident and, eventually, its resolution. Topics represented in these case studies include plagiarism, inappropriate data editing, data falsification, data fabrication, and promotion of a high-pressure environment that encourages misconduct. During the course, students learn to identify potential hazards and methods for avoiding and resolving them.

“The course provides individuals with information on the serious consequences of involving themselves in scientific misconduct,” said Ali Shilatifard, Ph.D., Investigator, who participated in the most recent course. “These consequences may not have been known previously, unless picked up from random conversations or over ‘lunchtime’ stories. I have attended other courses at different institutions and found the organization of this one to be excellent — using actual cases and encouraging involvement by the audience.”

The course reinforces the significance of specific laboratory practices, such as scrupulously maintaining unalterable laboratory records, ensuring that no one involved in data collection knows which specimens are experimental and which are controls, designing experiments that are repeatable and reproducible, and declining co-authorship on a research publication unless all aspects of the work are understood and the integrity of the data and its interpretation is evident. These habits may take extra time, but they ultimately protect a researcher and the host institution from impropriety and, more importantly, they result in higher quality research.

# of Stowers Research

“Dr. Neaves’ class really stressed the damage that is done when scientific misconduct occurs, not only to the individual scientist, but also to the many other groups working in the same area who may misdirect time and resources trying to reproduce or build upon the faulty result,” said Brian Slaughter, Ph.D., a Postdoctoral Research Fellow in the Rong Li Lab and a participant in the 2006 course and section leader in the 2008 course. “The practice of each author being personally accountable for the accuracy of all aspects of a research manuscript – a mandate that is emphasized in this course – is something I will apply throughout my career.”



*Steneck, Nicholas, Introduction to the Responsible Conduct of Research. Washington, U.S. Department of Health and Human Services, 2007.*

*The U.S. Department of Health and Human Services’ ORI Introduction to the Responsible Conduct of Research serves as a resource for students in the Stowers Institute’s Research Integrity course.*

## SAMPLE CASE STUDY:

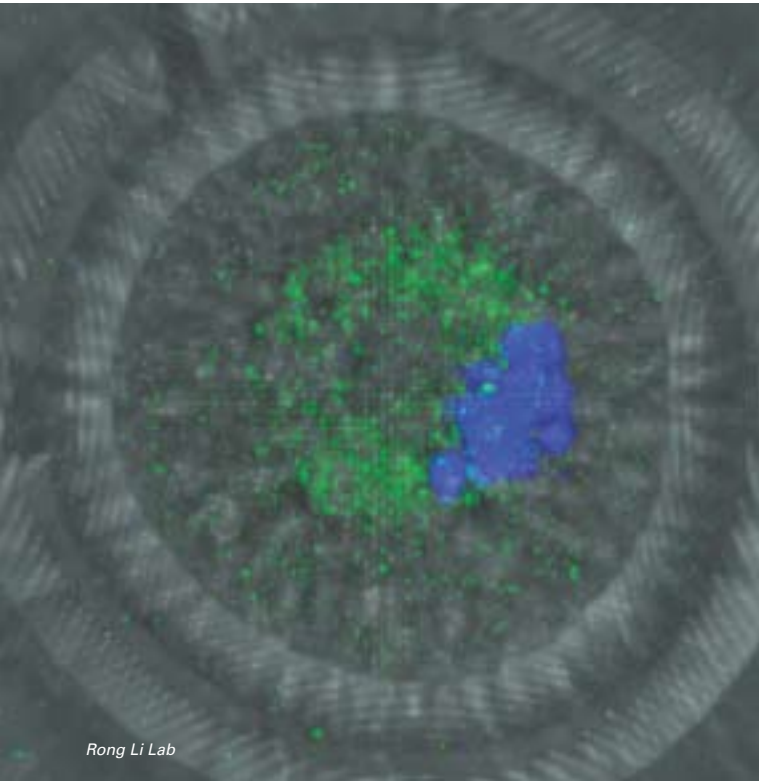
### Postdoc Accuses Mentor of Unethical Data Editing

Postdoctoral Fellow X requested a meeting with the dean to raise a troubling issue. He had recently joined the lab of Professor Y, a neurophysiologist who studied electrical signals from individual neurons. X had recently finished a Ph.D. in the lab of a neurochemist who studied the biochemistry of synaptic transmission. X told the dean he believed Y was engaging in unethical editing of experimental data.

X described Y’s practice of conducting an experiment, recording data, and then discarding some data before interpreting the results of the experiment using only a selected subset of the original data. X stated that he had participated in a research ethics course at his previous institution, and he believed that Y’s editing of data constituted scientific misconduct.

# THE INCREDIBLE

## Documenting the Surprising Capacity for Biological Problem Solving



Rong Li Lab

*Filamentous actin (green) exerts the force that moves meiotic chromosomes (blue) from the center to the cortex of mouse oocytes.*

THE CELLS OF ALL ORGANISMS, INCLUDING HUMANS, LIVE IN AN EVER-CHANGING ENVIRONMENT. OVER TIME, THEY HAVE ADAPTED TO DEAL WITH A BROAD RANGE OF CHANGES AND CHALLENGES THAT AFFECT THEIR ABILITY TO FUNCTION NORMALLY. HOW CELLS EVOLVE TO MEET THEIR CHANGING CONDITIONS CAN TEACH US MUCH ABOUT HUMAN HEALTH AND DISEASE.

That is why the Stowers Institute's Rong Li Lab strives to understand how cells have the ability to establish and maintain the distinct form and organization that support their specialized functions. In recent months, the team has made two notable discoveries regarding a cell's ability to perform both ordinary and extraordinary functions.

### Unequal Inheritance in Oocyte Meiosis

Under most circumstances, cell division is a symmetrical process resulting in two daughter cells with the same fate and behavior. But there are instances where an equitable division does not occur, for example, the meiotic cell division of oocytes. In this case, asymmetrical cell division produces two daughter cells that are strikingly different. One daughter is the oocyte that retains the majority of the parent cell's cytoplasm (which will eventually be required to form the cells of the earliest embryo if or when the oocyte is fertilized) and the other is a tiny cell (a polar body) that receives only minimal cytoplasm and subsequently dies.

Researchers have long understood that the asymmetry of oocyte meiosis occurs because chromosomes move from the center of the oocyte to a location near the cell's cortex before they are segregated into the two daughter cells. Half of the chromosomes are extruded from the oocyte and are accompanied by only a minimal amount of cytoplasm after division. The other half move deeper into the oocyte during division and remain associated with the majority of the cytoplasm. Until now, no one knew exactly how chromosomes make the short yet important journey to the periphery of the oocyte just prior to meiotic division.



# EVOLVING CELL

The Rong Li Lab approached this question in work reported in a recent publication in *Nature Cell Biology*. Together with the Institute’s Microarray, Molecular Biology, and Histology support facilities, the team tracked chromosome movement in live mouse oocytes and observed that the process begins when chromosomes recruit a protein called Formin-2 to their vicinity. Formin-2 triggers a cytoskeletal protein known as actin to generate forces that push the chromosomes toward the cortex – disrupting the natural symmetry of the oocyte. These movements ensure that one set of chromosomes ends up with the majority of the cytoplasm required for earliest embryonic development after meiotic division is completed.

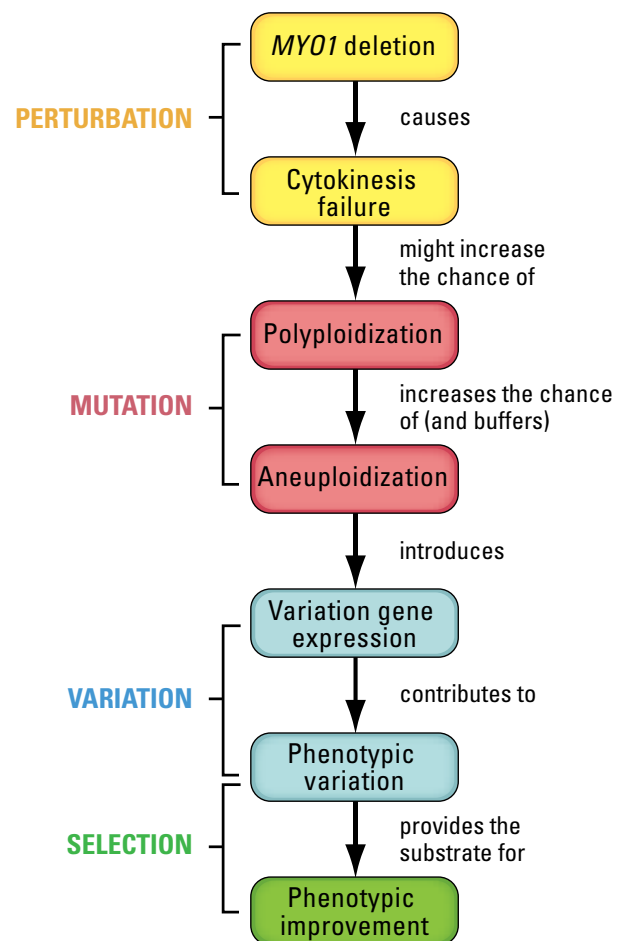
“The ability to drive asymmetrical division in oocyte meiosis is absolutely critical for successful reproduction,” said Rong Li, Ph.D., Investigator and senior author on the publication. “Without the chromosome’s ability to recruit Formin-2 and launch the symmetry-breaking movement of chromosomes to the cortex, an oocyte can’t properly mature, and the female will face both infertility and the possibility of birth defects. Now that this work has revealed a mechanism by which actin drives chromosome movement in oocytes, we can carry out more detailed dissections of the molecular components and interactions to understand why this process sometimes fails and how we might intervene to prevent it.”

## Creative Solutions in Situations of Life or Death

When cells become cancerous, the human body has strategies for fighting them, and medical interventions like chemotherapy can attack the aggressively multiplying culprits. But it isn’t always enough. Cancer cells are resourceful, and they are often capable of developing workarounds – changes to their structure and function that allow them to multiply even in the face of hard-hitting opposition.

The Rong Li Lab has revealed new insight into the ability of cells to adapt to disruptions of the basic machinery of cell division (i.e., cell multiplication) – findings that may help to explain how cancer cells elude the body’s natural defense mechanisms and even chemotherapy treatments.

*Adapted from Rancati et al. Aneuploidy underlies rapid adaptive evolution of yeast cells deprived of a conserved cytokinesis motor. Cell. 2008;135:879-893.*



*A conceptual representation of the pathway of adaptive evolution discovered in this study demonstrates how polyploidization and aneuploidization events may lead to gene expression changes that can be selected to restore cells’ ability to divide and proliferate.*

In work recently published as a Featured Article in the journal *Cell*, the team disabled a motor protein called type II myosin in yeast cells. Type II myosin normally powers cell division, so the team predicted that when it was turned off, the cell's ability to grow and divide would be compromised. Amazingly, within just a few cellular generations, some of the new cells seemed to have overcome the disability. Their ability to divide without myosin II rapidly improved when the scientists imposed repeated selection for best growers until a point when they divide nearly as well as normal cells.

Upon further inspection by the team, cells that regained the ability to divide rapidly had more chromosomes than would have been found in a normal cell – these cells had extra individual chromosomes (aneuploidy) and as well as entire extra sets of chromosomes (polyploidy). These extra chromosomes allowed the cells to change their pattern of gene expression in a way that compensated for the loss of type II myosin. And the cells with extra chromosomes passed that capability on to each of their daughter cells as they continued to divide and multiply.

“Aneuploidy and polyploidy are frequently observed in cancerous cells,” said Dr. Li, senior author on the paper. “These findings suggest that they may represent a direct link to the ability of cancer cells to evolve and multiply, even in the face of the body's natural defense mechanisms and chemotherapeutic drug treatment. These findings are particularly exciting for our team, as we can now evaluate whether different evolutionary mechanisms are involved, whether those mechanisms correlate with different disruptions of cellular behavior, and whether we can predict the likely evolutionary paths and outcomes based on molecular regulatory networks present in the cell.”

**PAPER:** Actin-driven Chromosomal Motility Leads to Symmetry-Breaking in Mammalian Meiotic Oocytes

**JOURNAL:** *Nature Cell Biology*

**ISSUE:** November 2008

**AUTHORS\*:** Hongbin Li, Ph.D., Senior Research Associate; Fengli Guo, Ph.D., Senior Electron Microscopy Specialist; Boris Rubinstein, Ph.D., Biomathematician; and Rong Li, Ph.D., Investigator

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

**PAPER:** Aneuploidy Underlies Rapid Adaptive Evolution of Yeast Cells Deprived of a Conserved Cytokinesis Motor

**JOURNAL:** *Cell*

**ISSUE:** November 28, 2008

**AUTHORS\*:** Giulia Rancati, Ph.D., Postdoctoral Research Associate; Norman Pavelka, Ph.D., Postdoctoral Research Associate; Brian Fleharty, Microarray Research Technician II; Aaron Noll, Molecular Biology Programmer Analyst III; Rhonda Trimble, Electron Microscopy Specialist; Kendra Walton, Molecular Biology Research Technician III; Anoja Perera, Molecular Biology Lab Manager II; Karen Staehling-Hampton, Ph.D., Managing Director of Molecular Biology; Chris Seidel, Ph.D., Managing Director of Microarray; and Rong Li, Ph.D., Investigator

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

**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.org/labs/RongLiLab.asp](http://www.stowers.org/labs/RongLiLab.asp).

# H3 MARKS THE SPOT

*Drosophila polytene chromosomes stained for over-expressed dKDM4A histone demethylase (red) and Histone H3 tri-methylated on lysine 36 (green). The red and green do not overlap, which is consistent with the demethylation of H3 lysine 36 by dKDM4A.*

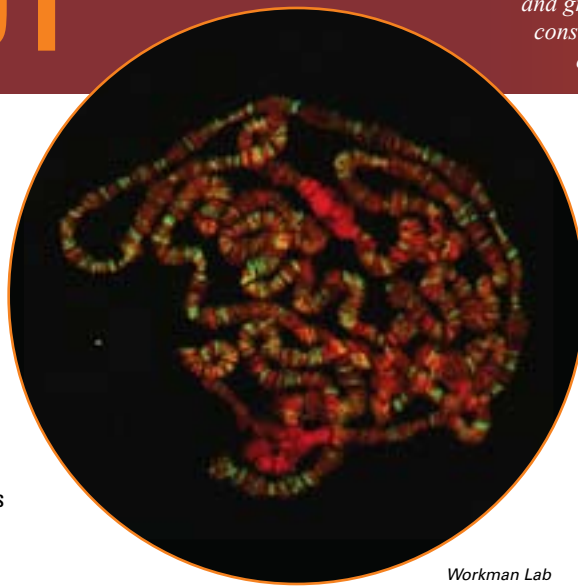
## Shedding Light on Histone Landmarking in Transcription

When genes are transcribed, a messenger RNA molecule is constructed using a DNA molecule as a template. The messenger RNA then serves as the template for assembling the protein molecule encoded by the DNA. The process of transcribing DNA into RNA exposes some of the genetic information found within chromosomes to inappropriate use.

While not being transcribed, the genetic information within chromosomes is normally protected by a packaging component called chromatin. To avoid problems, cells mark regions of chromosomes that should be transcribed with a "landmark" telling the cell how to treat these specific sequences of DNA. Later, at the appropriate time, cells un-mark the region and allow it to return to its protected and inactive state.

Histone H3 is a protein that plays a pivotal role in the marking of chromosomes. It can be altered by adding (methylating) or removing (demethylating) methyl groups — simple chemical additions that each consist of a single carbon molecule and three hydrogen molecules. Surprisingly, these simple chemical additions to the protein protecting a chromosome can communicate essential information about when and where transcription should be carried out.

Working with fruit flies, the Stowers Institute's Workman and Abmayr Labs and Proteomics Center have been collaborating to study the function of the methylated histone H3 lysine 36 (H3K36) that often marks the transcribed regions of chromosomes. Recently, in work published in *Molecular Cell*, the team investigated how cells direct the novel histone demethylase protein known as dKDM4A to specific locations to allow for the removal of a landmark histone modification during the stage of transcription when the messenger RNA molecule is being elongated.



Workman Lab

They observed that dKDM4A can actually remove specific forms of H3K36, reversing methylation and helping to regulate transcription elongation. The team established that it may do so by associating itself with Heterochromatin Protein 1a (HP1a), a protein whose ability to suppress transcription through a process called transcription silencing is well established. Binding with HP1a stimulates the histone demethylation activity of dKDM4A.

"HP1a has long been known to act as a scaffold of sorts during transcription silencing, but recent verification of HP1's involvement in actively transcribed regions had confounded the chromatin community," said Jerry Workman, Ph.D., Investigator and senior author on the publication. "Based on our results, it is possible that HP1a plays a role in the activation of transcription by facilitating the histone demethylase dKDM4A to remove an important histone mark during elongation."

The findings offer promise for a number of potential treatments for disease. The human enzyme that adds methylation marks on histone H3K36 interacts with the huntingtin protein, which causes Huntington's disease. Additionally, the human versions of dKDM4A remove H3K36 and can cause a healthy cell to become cancerous. Work contributing to the understanding of the dynamic regulations of H3K36 may open the door to important treatments and cures in the future.

**PAPER:** Heterochromatin Protein 1a Stimulates Histone H3 Lysine 36 Demethylation by the *Drosophila* dKDM4A Demethylase

**JOURNAL:** *Molecular Cell*

**ISSUE:** December 5, 2008

**AUTHORS\*:** Chia-Hui Lin, Predoctoral Researcher; Bing Li, Ph.D., Senior Research Associate; Selene Swanson, Research Specialist II; Ying Zhang, Ph.D., Proteomics Research Specialist II; Laurence Florens, Ph.D., Managing Director of Proteomics; 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 unless otherwise noted.*

**Susan Abmayr, 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 her work at [www.stowers.org/labs/AbmayrLab.asp](http://www.stowers.org/labs/AbmayrLab.asp).

**Michael Washburn, Ph.D.**, Director of Proteomics Center, joined the Stowers Institute in 2003 from the Torrey Mesa Research Institute in San Diego. Learn more about his work at [www.stowers.org/labs/WashburnLab.asp](http://www.stowers.org/labs/WashburnLab.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.org/labs/WorkmanLab.asp](http://www.stowers.org/labs/WorkmanLab.asp).

# THINKING ON THE BRAIN

## Examining the Development of the Embryonic Hindbrain

THE HUMAN BRAIN IS AN ASTOUNDINGLY COMPLICATED ORGAN THAT DEVELOPS THROUGH AN AMAZINGLY INTRICATE PROCESS. THE STOWERS INSTITUTE'S KRUMLAUF LAB STRIVES TO KNOW HOW THE BRAIN DEVELOPS AND WHERE PARTICULAR KINDS OF STRUCTURES NEED TO FORM. THE TEAM HAS MADE A NUMBER OF IMPORTANT DISCOVERIES RELATED TO THE DEVELOPMENT OF THE BRAIN AND ESPECIALLY THE HINDBRAIN.

Made up of the cerebellum, pons, and medulla oblongata, the hindbrain functions collectively to coordinate motor activity, posture, equilibrium, and sleep patterns, and to regulate essential unconscious functions like breathing and blood circulation.

In work published recently in *Proceedings of the National Academy of Sciences*, the team – led by Robb Krumlauf, Ph.D., Scientific Director of the Stowers Institute, and Leanne Wiedemann, Ph.D., Staff Scientist – investigated the expression of one of the master control genes of hindbrain development, a member of the Hox gene family. These genes specify the anterior-posterior (head-tail) axis and regional properties of tissues during development, ensuring the proper number and placement of embryonic structures.

Working with both mouse and chicken embryos, the team established how the expression of a key regulatory protein encoded by the *Hoxa2* gene is controlled.

In the mammalian genome, DNA sequences that encode proteins and DNA sequences that control the expression of those proteins are usually separate from one another. However, in an unexpected and surprising discovery, the Krumlauf Lab found the DNA sequence containing instructions for controlling *Hoxa2* expression embedded within the sequence that codes for the *Hoxa2* protein. The work establishes for the first time that protein-coding regions can also contain DNA sequences that modulate gene expression – insight that has important implications for understanding the regulatory logic of mammalian genomes.

"This is an exciting discovery on two levels," said Dr. Wiedemann, a co-investigator in the Krumlauf Lab and senior author on the publication. "We answered an important question about how the hindbrain forms and which proteins and genes function in regulating its development. We also established that regulatory information inside protein-coding regions of DNA may play an important role in embryonic development. With this new understanding, we can design stronger experiments and interpret data more effectively because we finally understand that the regulatory information from coding regions may be influencing development."

Made up of the cerebellum, pons, and medulla oblongata, the hindbrain coordinates motor activity, posture, equilibrium, and sleep patterns.

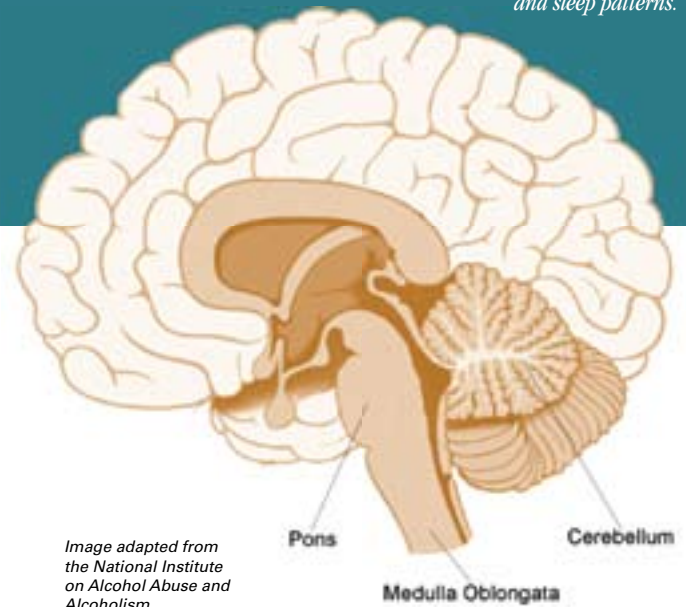


Image adapted from the National Institute on Alcohol Abuse and Alcoholism

**PAPER:** A regulatory module embedded in the coding region of *Hoxa2* controls expression in rhombomere 2

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

**ISSUE:** December 23, 2008

**AUTHORS\*:** Stefan Tümpel, formerly a Predoctoral Research Fellow; Francisco Cambronero, Ph.D., formerly a Post-doctoral Research Associate; Carrie Sims, Ph.D., Research Specialist I; Robb Krumlauf, Ph.D., Scientific Director and Investigator; Leanne Wiedemann, Ph.D., Staff Scientist

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**Robb Krumlauf, Ph.D.**, Scientific Director and Investigator, also is a Professor in the Department of Anatomy & Cell Biology at The University of Kansas School of Medicine, a Professor in The University of Kansas Neurosciences Graduate Program, and a Professor in the Department of Oral Biology at The University of Missouri at Kansas City Dental School. Learn more about his work at [www.stowers.org/labs/KrumlaufLab.asp](http://www.stowers.org/labs/KrumlaufLab.asp).

**Leanne Wiedemann, Ph.D.**, also is an Associate Professor in the Department of Pathology at The University of Kansas School of Medicine. Learn more about her work at <http://research.stowers-institute.org/krumlauflab/LeanneWiedemann.htm>.

# HOME IMPROVEMENTS

## Building on the Function of the Uch37 Enzyme in Chromatin Remodeling

Chromatin is the complex combination of DNA, RNA, and proteins that makes up chromosomes. Throughout the cell division cycle, chromatin must undergo dynamic structural changes that range from local changes necessary for transcription of the DNA code to global changes required for chromosome segregation. Collectively, these modifications are known as chromatin remodeling.

The Stowers Institute's Conaway Lab focuses on understanding how genes are turned on and off during transcription and how the regulation of chromatin structure contributes to this process. The team has made significant progress in understanding the role of the Uch37 enzyme in chromatin remodeling – first by demonstrating that Uch37 is associated with another multiprotein complex, the proteasome (a large protein complex that degrades unneeded or damaged proteins), and more recently, with a second discovery related to Uch37 published in the journal *Molecular Cell*.

In the recent work, the team collaborated with the Institute's Proteomics Center to demonstrate how Uch37 is kept in check when it is part of the human chromatin remodeling complex known as INO80. INO80 is believed to function in both gene regulation and DNA repair by "unpacking" DNA from nucleosomes – around which chromatin is tightly packaged – to allow access to chromosomal DNA.

Uch37 is a "deubiquitinating enzyme" that can remove protein tags (known as ubiquitin) from other proteins. The presence of one kind of ubiquitin tag on a protein can mark it for destruction, and other types can direct the activity of the protein. In this work, the team discovered that when bound to INO80, Uch37 can be activated in the presence of proteasomes. The mechanism involved is not yet fully understood, but the activation seems to occur via a "touch and go" mechanism in which proteasomes interact very briefly with Uch37.

"Essentially, what our lead author Tingting Yao observed was a method of communication between INO80 and the proteasome," said Joan Conaway, Ph.D., Investigator and senior author on the publication. "This communication provides new insight into the functions of both INO80 and proteasomes, and also sheds light on how deubiquitinating enzymes can be regulated, which is important because indiscriminate removal of ubiquitin marks can lead to a failure to properly regulate the activities or levels of essential enzymes and proteins within the cell."

The Conaway Lab's efforts to better understand transcription and the regulation of chromatin structures have potential implications for a broad range of diseases. Proper gene regulation is essential for both development and the maintenance of long-term health. The misregulation of gene expression can contribute to a variety of diseases, and a better understanding of the factors that influence these problems can only improve our ability to change the course of devastating diseases.

**PAPER:** Distinct Modes of Regulation of the Uch37 Deubiquitinating Enzyme in the Proteasome and in the INO80 Chromatin-Remodeling Complex

**JOURNAL:** *Molecular Cell*

**ISSUE:** September 26, 2008

**AUTHORS\*:** Tingting Yao, Ph.D., formerly a Postdoctoral Research Fellow; Ling Song, Ph.D., Carver College of Medicine, University of Iowa and University of California, Berkeley; Jingji Jin, Ph.D., Senior Research Associate; Yong Cai, Research Specialist I; Hidehisa Takahashi, Ph.D., Postdoctoral Research Associate; Selene Swanson, Research Specialist II; Michael Washburn, Ph.D., Director of Proteomics; Laurence Florens, Ph.D., Managing Director of Proteomics; Ronald Conaway, Ph.D., Investigator; Robert Cohen, Ph.D., Johns Hopkins University; and Joan Conaway, Ph.D., Investigator

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

**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.org/labs/ConawayLab.asp](http://www.stowers.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.org/labs/ConawayLab.asp](http://www.stowers.org/labs/ConawayLab.asp).

**Michael Washburn, Ph.D.**, Director of Proteomics Center, joined the Stowers Institute in 2003 from the Torrey Mesa Research Institute in San Diego. Learn more about his work at [www.stowers.org/labs/WashburnLab.asp](http://www.stowers.org/labs/WashburnLab.asp).

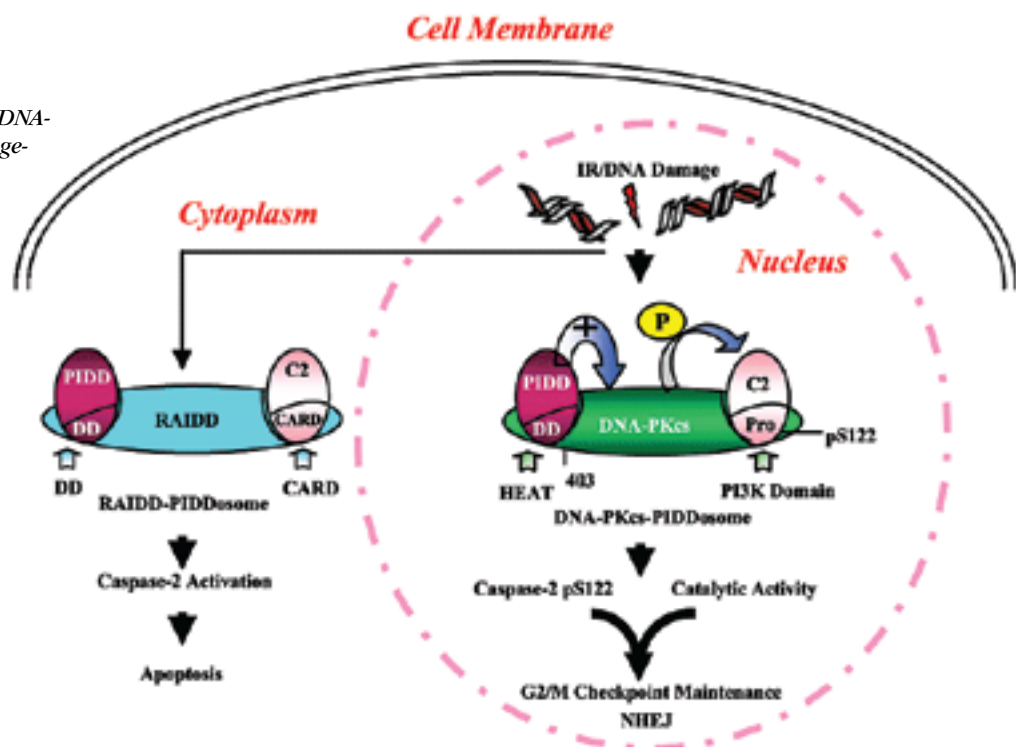
# CELLULAR MARTYRS

CELLS SERVE A SEEMINGLY INFINITE NUMBER OF FUNCTIONS IN THE HUMAN BODY, BUT SOMETIMES THE MOST IMPORTANT THING THEY CAN DO IS DIE. THIS IS ESPECIALLY TRUE WHEN DNA IS DAMAGED AND A PROCESS OF PROGRAMMED CELL DEATH, CALLED APOPTOSIS, IS ACTIVATED.

The Stowers Institute's Du Lab focuses on the mechanisms of apoptosis in mammalian cells. Recently, they worked with a number of the Institute's core facilities and with colleagues at the University of Texas Southwestern Medical Center at Dallas and the Innsbruck Medical University to make significant strides in understanding the role of nuclear caspase-2, an enzyme known to be involved in a variety of apoptotic processes. The work was published in the journal *Cell*.

Apoptosis in mammalian cells is mediated mainly by caspases – a family of enzymes thought of as “executioners” of apoptotic cell death. Caspase-2 is an initiator caspase that splits other protein substrates within the cell to trigger apoptosis. Unlike other caspases, a fraction of caspase-2 is

*A working model for the role of DNA-PKcs-PIDDosomes in DNA damage-induced cellular responses.*



*Shi et al. DNA-PKcs-PIDDosome: A Nuclear Caspase-2-Activating Complex with Role in G2/M Checkpoint Maintenance. Cell. 2008;136:508-520.*

# Characterizing the Enzymes Involved in Programmed Cell Death

continually present in the cell nucleus. Until now, however, it has remained a mystery whether the nuclear caspase-2 contributes to apoptosis or to other processes in response to DNA damage.

Using immunoprecipitation and mass spectrometry, the team discovered a new protein complex in the cell nucleus that activates caspase-2, and they named it DNA-PKcs-PIDDosome. Part of this complex is an enzyme (DNA-PKcs) involved in repair of breaks in DNA, and it is the central molecule that binds to a protein associated with cell death (PIDD) and to caspase-2 to form a complex that remains latent unless or until DNA is damaged. When that happens, DNA-PKcs activates caspase-2 while PIDD promotes the enzymatic activity of DNA-PKcs.

When activated in this way, caspase-2 maintains the DNA-damage checkpoint to block cell division and also affects the repair of DNA breaks. That means the influence of caspase-2 extends beyond its role in apoptosis – in this case by slowing down cell division to allow for DNA repair.

There were a number of suspected sites in caspase-2 where the DNA-PKcs enzyme could act, so to pinpoint which one is targeted in response to DNA damage, the Proteomics Center used a state-of-the-art mass spectrometry technique that identified a single site that is affected when DNA damage occurs. The Institute's Cytometry Facility and Molecular Biology Facility also provided excellent support for the project.

This discovery may have potential therapeutic implications, since mistakes in maintaining the DNA-damage checkpoint and malfunctions in the process of DNA repair can lead to cancer.

"Until now, we knew a lot about the role of caspase-2 in apoptosis, but relatively little about how it functions in the cell nucleus. In discovering the novel nuclear protein complex DNA-PKcs-PIDDosome, we were able to highlight a new connection of caspase-2 to the DNA-damage response pathway," said Chunying Du, Ph.D., Assistant Investigator and senior author on the publication. "This discovery provides insight into the complexity of how regulation of the response to DNA damage is mediated by caspase-2, an enzyme long implicated in the execution of apoptosis."

**PAPER:** DNA-PKcs-PIDDosome: A Nuclear Caspase-2-Activating Complex with Role in G2/M Checkpoint Maintenance

**JOURNAL:** *Cell*

**ISSUE:** February 6, 2009

**AUTHORS\*:** Mingan Shi, Ph.D., Senior Research Associate; Carolyn Vivian, formerly a Lab Manager; Kyung-Jong Lee, Ph.D., University of Texas Southwestern Medical Center, Dallas; Chumin Ge, Ph.D., Postdoctoral Research Associate; Keiko Morotomi-Yano, University of Texas Southwestern Medical Center, Dallas; Claudia Manzl, Innsbruck Medical University; Florian Bock, Innsbruck Medical University; Shigeo Sato, Ph.D., Research Specialist I; Chieri Tomomori-Sato, Ph.D., Senior Research Associate; Ruihong Zhu, Research Technician III; Jeffrey Haug, Managing Director - Cytometry Facility; Selene Swanson, Research Specialist II; Michael Washburn, Ph.D., Director of Proteomics; David Chen, M.D., Ph.D., University of Texas Southwestern Medical Center, Dallas; Benjamin Chen, Ph.D., University of Texas Southwestern Medical Center, Dallas; Andreas Villunger, Ph.D., Innsbruck Medical University; Laurence Florens, Ph.D., Managing Director of Proteomics; and Chunying Du, Ph.D., Assistant Investigator

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

**Chunying Du, Ph.D.**, Assistant Investigator, also is an Assistant Professor in the Department of Biochemistry & Molecular Biology at The University of Kansas School of Medicine. Learn more about her work at [www.stowers.org/labs/DuLab.asp](http://www.stowers.org/labs/DuLab.asp).

**Michael Washburn, Ph.D.**, Director of Proteomics Center, joined the Stowers Institute in 2003 from the Torrey Mesa Research Institute in San Diego. Learn more about his work at [www.stowers.org/labs/WashburnLab.asp](http://www.stowers.org/labs/WashburnLab.asp).

# THE END IS IN

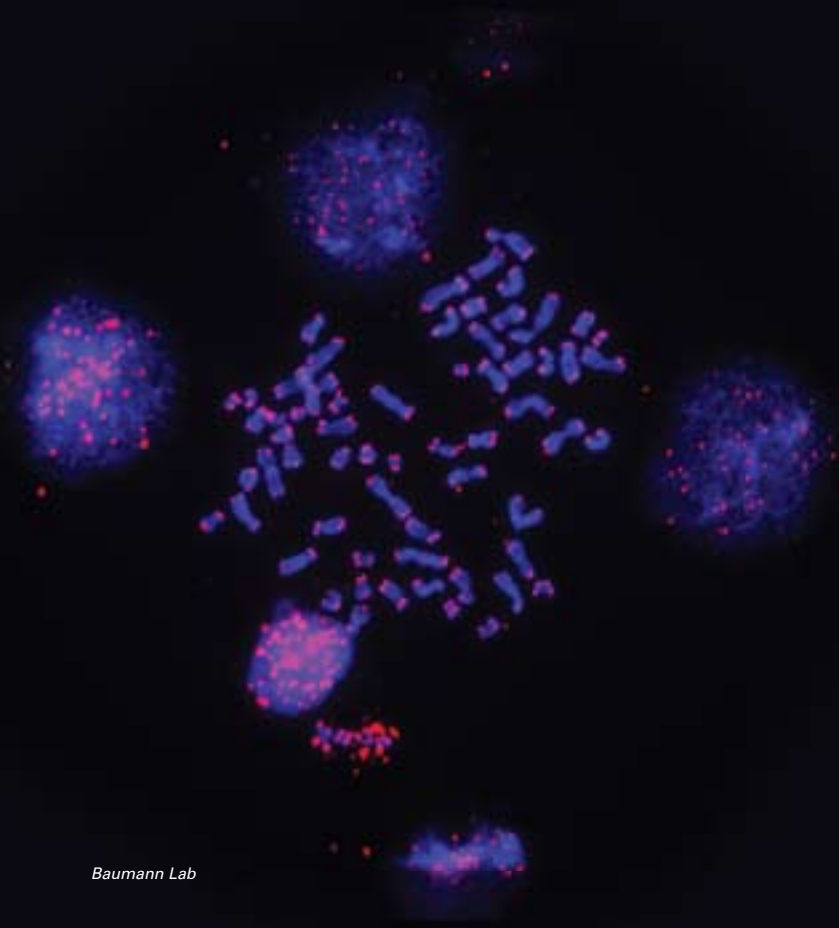
ZOOM IN ON THE END OF A CHROMOSOME, AND YOU WILL FIND A REPETITIVE SEQUENCE OF DNA KNOWN AS A TELOMERE. ACTING A BIT LIKE A SHOELACE TIP, TELOMERES PROTECT CHROMOSOME ENDS FROM DESTRUCTION, THEREBY SAFEGUARDING THE TWO CRITICAL ROLES OF CHROMOSOMES — STORING LARGE AMOUNTS OF GENETIC INFORMATION WITHIN THE TINY NUCLEUS OF THE CELL AND ENSURING THAT DNA IS ACCURATELY COPIED AND DISTRIBUTED DURING CELL DIVISIONS.

But telomeres face their own challenges. Each time a cell divides, a portion of its telomere is consumed. Over time, the telomere gets shorter — an effect that is ultimately believed to be responsible for the aging of cells and which limits the number of times cells can divide.

The shortening of telomeres has been linked to both aging and cancer, making telomeres a topic of significant interest to research teams around the world, including the Stowers Institute's Baumann Lab that works to understand how defects in telomere maintenance contribute to the onset of cancer, aging, and other diseases. Using an interdisciplinary approach, the Baumann Lab employs techniques from biochemistry, molecular genetics, and cell biology to shed light on the function of telomeres. In recent months, the team has made two notable discoveries.

## Mediating Chromosome Fusion

One of the impressive functions of chromosomes is their ability to tell the difference between their natural ends and unnatural breaks that require repair. Without this ability to differentiate, chromosomes would employ their repair machineries on their ends, causing them to fuse with another end of the same chromosome or with another chromosome — leading in both cases to dangerous instability. By



Baumann Lab

*Chromosomes spread during the Metaphase stage of cell division. Telomeres have been labeled with red and DNA has been stained with blue.*



# SIGHT

## Elucidating the Function of Chromosome Ends

fundamentally changing the structure of the chromosome, fusions make the cell vulnerable to a range of problems including the initiation of cancerous growth.

Fortunately, these misguided repairs are rare, but as telomeres naturally shorten over time, improper fusions become more likely, and the associated dangers increase.

Curious about the process of chromosome fusion, the Baumann Lab set out to determine what mechanism or pathway mediates it as the telomere is depleted. Working in fission yeast, the team found a surprising role for a little-studied process called single strand annealing (SSA). SSA is a process for repairing a chromosome break in which a single strand of DNA is created and bonded to the chromosome's damaged double strand of DNA.

Although previous work had nearly ruled out a role for SSA in mediating chromosome fusions, the Baumann Lab took a closer look. Using tools from both genetic and molecular biology, they characterized the fusion junctions and identified the specific repair factors responsible for fusion in work published in *Molecular Cell*. These studies unequivocally demonstrated a critical role for SSA in the process.

"This is the first time that the SSA pathway has been implicated in mediating chromosomal fusions," said Peter Baumann, Ph.D., Associate Investigator and senior author on the publication. "This pathway had not previously been on the radar screen of researchers studying genome instability, so this work has opened an exciting new avenue of inquiry. The discovery of novel functions for SSA factors at telomeres suggested this pathway may play a far more important role than previously anticipated. Further analysis of this DNA repair pathway is expected to shed new light onto how cells defend themselves against DNA damage as well as how misguided repair can contribute to cancer."

In the course of this work, the team also observed that there is no single path to telomere repair. Just as telomeres can be damaged in a number of different ways — such as gradual telomere shortening or the mutation-associated loss of a telomere binding protein — cells also employ a number of different pathways for repair. As with much novel research, the Baumann Lab's answer to one question has opened the door to a series of exciting new questions.

### Maturation of a Critical Enzyme

It isn't all bad news when it comes to telomere length and cell division. With the help of the enzyme telomerase, telomeres are able to replenish themselves. Although they can't completely reverse the shortening effect of cell division, they can mitigate it.

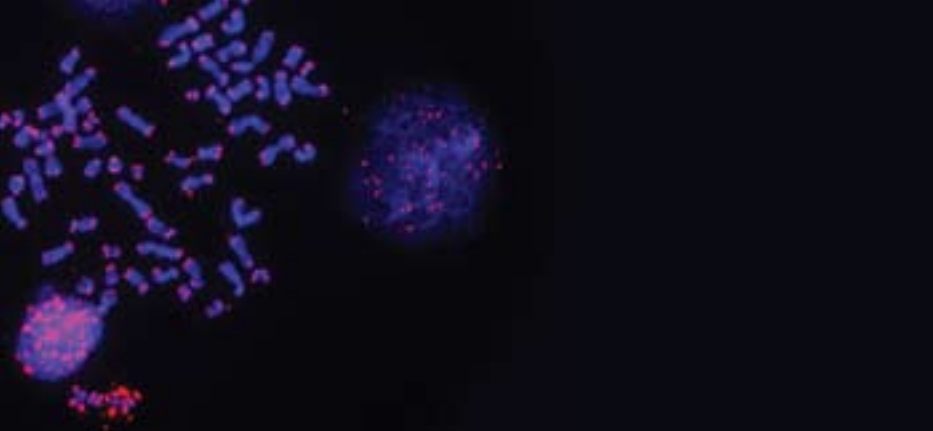
Interestingly, high levels of telomerase activity are associated with most forms of cancer. When telomerase is activated in certain cell types, the cells and their offspring become immortal — continuing to divide and multiply well beyond their natural lifespan. Immortality is a hallmark of cancer cells, and it is this ability to divide indefinitely that can lead to tumors.

The selective inhibition of telomerase is viewed as a promising treatment for cancer. If researchers were able to develop a drug that could turn off telomerase in cancer cells, they could return the natural life-cycle controls to the cancer cells. A more thorough understanding of telomerase and its function would represent an important advance in these efforts.

The Baumann Lab is pursuing innovative research aimed at providing a better understanding of telomerase and identifying small molecules with the potential to block it. In doing so, the team has identified a key step in the maturation pathway of telomerase.

Telomerase helps to lengthen telomeres by using part of an RNA subunit as a template to add telomeric DNA to the ends of chromosomes. The Baumann Lab demonstrated that this RNA subunit must first be established in a longer, inactive form, which is then processed into a shorter mature form that allows telomerase to perform its intended function.

Telomerase RNA is a subunit of a stable ribonucleoprotein particle required for telomere replication. The tail end of telomerase RNA is referred to as the 3' (three prime) end. The 3' ends of many RNAs must be processed to produce a mature and functional form, and this involves the gradual removal of nucleotides one at a time until the mature end has been reached — a process known as exonucleolytic degradation. Some RNAs are cleaved near the end before exonucleolytic degradation proceeds to generate the mature end.



Working in fission yeast, the Baumann Lab has demonstrated that 3' end processing for telomerase RNA uses a fundamentally different and novel pathway. The machinery that removes introns (DNA regions that are not translated into proteins) from messenger RNAs in a process called splicing also functions in generating the mature 3' end of the telomerase RNA subunit.

The work is believed to represent the first example of uncoupling of the first and second steps of splicing to generate a functional product in a single-step reaction.

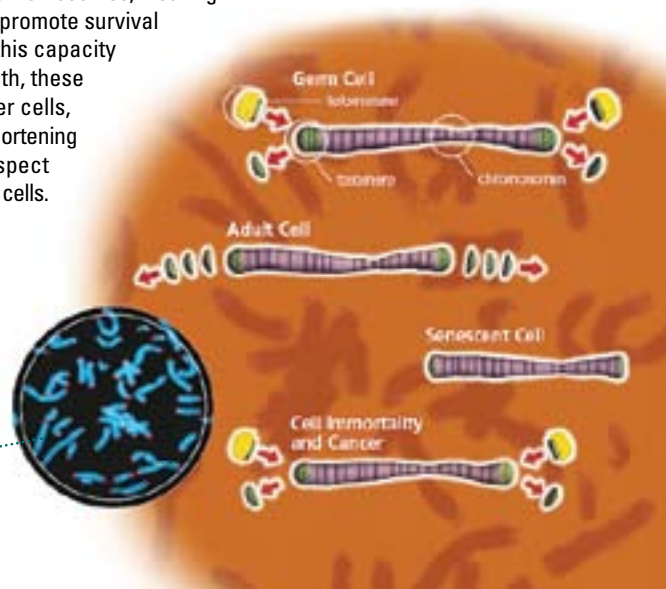
"Our work shows that interfering with telomerase maturation can inactivate telomerase," said Dr. Baumann. "Looking to the future, our research has the potential to open a plethora of new targets that may be more easily inhibited by small molecules than the catalytic activity of telomerase itself. In extrapolating from fission yeast to humans, the implication of our results is that defects in the processing machinery for human telomerase will also compromise telomerase function and may thus contribute to a variety of degenerative diseases. Additionally, the identification of factors involved in telomerase RNA processing could provide promising new targets for telomerase inhibition in cancer cells."

## TELOMERES: The Cancer Connection

Certain cells such as egg and sperm cells, use telomerase, an enzyme, to restore telomeres to the ends of their chromosomes, insuring that they can continue to reproduce and promote survival of the species. But most adult cells lack this capacity and when telomeres reach a critical length, these cells stop proliferating. In immortal cancer cells, telomeres act abnormally — they cease shortening with each cell division. Investigators suspect telomerase is somehow activated in cancer cells.

### TELOMERES

At the end of every chromosome (blue) are telomeres (red), repetitive DNA sequences that appear to help regulate cellular replication. Gerontologists are working to learn more about telomere structure and function.



National Institute of Health, National Institute on Aging

**PAPER:** Chromosome Fusions following Telomere Loss Are Mediated by Single-Strand Annealing

**JOURNAL:** *Molecular Cell*

**ISSUE:** August 22, 2008

**AUTHORS\*:** Xiaorong Wang, Ph.D., formerly a Postdoctoral Research Associate; and Peter Baumann, Ph.D., Associate Investigator

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

**PAPER:** Spliceosomal Cleavage Generates the 3' end of Telomerase RNA

**JOURNAL:** *Nature*

**ISSUE:** December 18, 2008

**AUTHORS\*:** Jessica Box<sup>†</sup>, Research Laboratory Coordinator; Jeremy Bunch<sup>†</sup>, Senior Research Technician; Wen Tang, Predoctoral Researcher; and Peter Baumann, Ph.D., Associate Investigator

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<sup>†</sup> Co-equal contributors to this publication.

**Peter Baumann, Ph.D.**, Associate Investigator, also is an Assistant Professor in the Department of Molecular and Integrative Physiology at The University of Kansas School of Medicine and a Pew Scholar in Biomedical Sciences. Learn more about his work at [www.stowers.org/labs/BaumannLab.asp](http://www.stowers.org/labs/BaumannLab.asp).

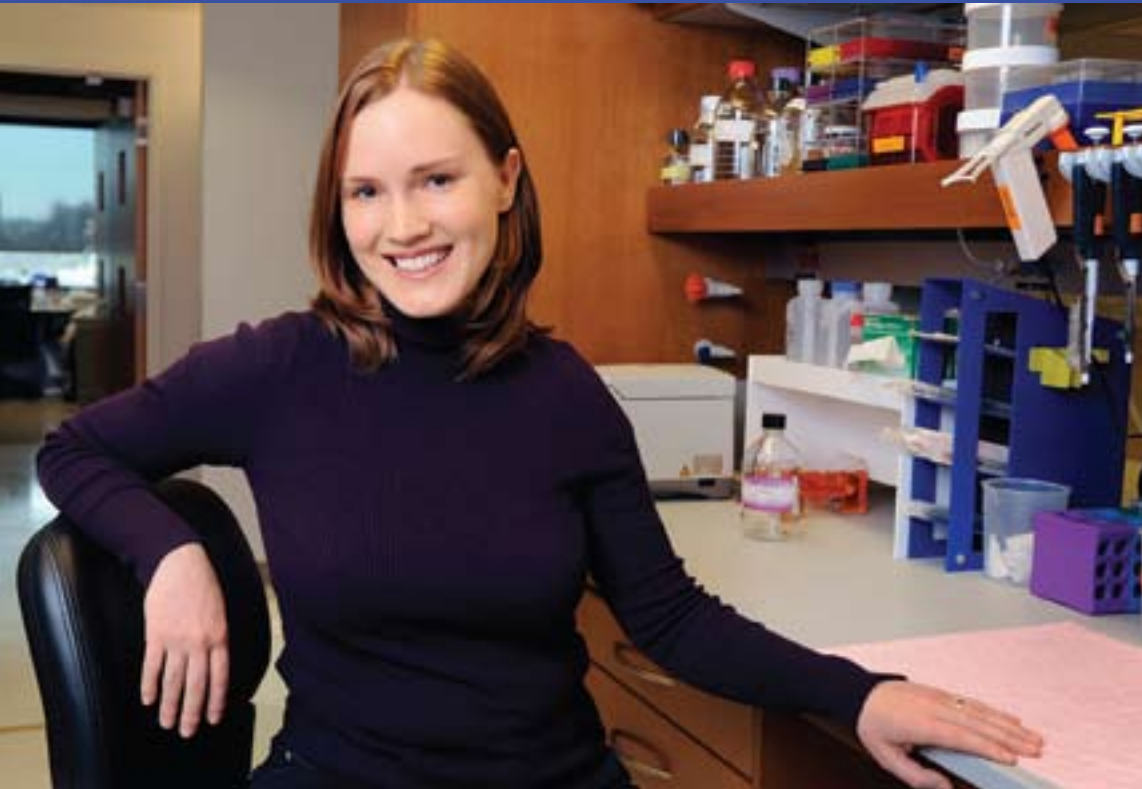


# STOWERS SUPPORT FACILITY OPENS

After nine months of construction and \$22.9 million in improvements, the Stowers Institute's 280,000 square foot support facility – a few miles south of the Brush Creek Campus – is now ready for occupancy. The former Sanofi-Aventis site will be home to a variety of the Institute's support functions, including mechanical shops and storage of supplies. The facility also accommodates BioMed Valley Discoveries – the translational research and development company established by the Institute. Redevelopment of the 15-acre site has liberated space for additional research teams on the Brush Creek Campus while providing BioMed Valley Discoveries with 10,000 square feet of office space and more than 5,000 square feet of laboratories for preclinical research.



## JULIA ZEITLINGER AWARDED NIH DIRECTOR'S NEW INNOVATOR AWARD



While competition for federal research dollars is becoming more intense in these challenging budgetary times, the Director of the National Institutes of Health (NIH) has encouraged innovation among early career investigators with a new category of research grant.

Julia Zeitlinger, Ph.D., Assistant Investigator, was among 31 early career scientists who were each granted \$1.5 million in direct research support over five years as recipients of the NIH Director's New Innovator Award. The NIH Director expects these awards will enable a small number of highly qualified scientists to pursue exceptionally creative approaches that could transform biomedical and behavioral science.

Dr. Zeitlinger will use the NIH Director's New Innovator Award to analyze the function of chromatin in the context of gene regulatory networks during development. She hypothesizes that the way DNA is packaged and poised for transcription can predict the developmental potential of a cell. By identifying and interpreting the significance of markers on proteins surrounding chromosomal DNA, Dr. Zeitlinger expects to improve our understanding of normal development while revealing early indicators that may predict the onset or outcome of disease.

**Julia Zeitlinger, Ph.D.**, Assistant Investigator, also is an Assistant Professor in the Department of Pathology and Laboratory Medicine at The University of Kansas School of Medicine. Learn more about her work at [www.stowers.org/labs/ZeitlingerLab.asp](http://www.stowers.org/labs/ZeitlingerLab.asp).

# SCOTT HAWLEY ELECTED TO LEADERSHIP OF THE GENETICS SOCIETY OF AMERICA



Since joining the Stowers Institute in 2001, Scott Hawley, Ph.D., Investigator, has established his leadership in the field of genetics. Through innovative research, a generous dedication of his time to teaching and mentoring, and a commitment to the work of the Genetics Society of America (GSA), Dr. Hawley has earned the respect of colleagues around the world.

In November, Dr. Hawley's preeminence in the field was formalized by his election as the 2009 vice president and the 2010 president of the GSA.

Dr. Hawley has been an active member of the GSA for many years, making significant contributions to the Society's journal, *GENETICS*, writing for the GSA newsletter, *GENetics*, and attending and organizing the GSA's annual *Drosophila* meetings. He served as a director on the GSA Board from 1996-99 and as the first content editor of the Society Web site from 2001-06. He is well known within the GSA community for his commitment to undergraduate and graduate student genetics education. In recognition of this commitment, Dr. Hawley was named the 2008 recipient of the GSA's Elizabeth W. Jones Award for Excellence in Education.

Among the goals for his terms as vice president and president, Dr. Hawley plans to expand the Society's efforts to address the current crisis in federal research funding, to increase the Society's role in teaching genetics in high schools and colleges, and to accelerate the Society's renewal of its principal publication, the journal *GENETICS*.

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 model organisms widely used in genetics 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.org/labs/HawleyLab.asp](http://www.stowers.org/labs/HawleyLab.asp).

# PETER BAUMANN WINS HUGHES



*Peter Baumann*

AMONG THE MOST COMPETITIVE AND HIGHLY SOUGHT DISTINCTIONS IN BIOMEDICAL RESEARCH, ONE RISES TO THE TOP: SELECTION FOR APPOINTMENT BY THE HOWARD HUGHES MEDICAL INSTITUTE (HHMI).

Created by the aviator-industrialist Howard Hughes in 1953, HHMI holds the largest research endowment of any medical research organization in the world, valued at the close of the 2008 fiscal year at \$17.5 billion. HHMI supports 354 Investigators at 71 institutions across the United States.

At intervals of a few years, HHMI conducts rigorous national competitions to identify researchers with the potential to make major advances in science. Candidates are evaluated by review committees made up of distinguished scientists who are often current or past members of the Hughes Medical Advisory and Scientific Review Boards and by HHMI's scientific staff.

This year, Peter Baumann, Ph.D., Associate Investigator, was selected as an Early Career Scientist from among more than 2,000 candidates in the latest HHMI competition. Dr. Baumann becomes the second Stowers laboratory leader selected by HHMI (Olivier Pourquié, Ph.D., Investigator, was appointed in 2005).

Dr. Baumann and his team will continue to work in laboratories at the Stowers Institute's Kansas City campus. In addition to his generous Stowers funding, Dr. Baumann will receive substantial annual support from HHMI, allowing him to expand his program by adding new members to the research team and conducting more experiments.

## THE EVOLUTION OF HHMI INVESTIGATOR SELECTION

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

Over the history of the Howard Hughes Medical Institute (HHMI), its selection of scientists for appointment as Investigators has changed significantly. From the time HHMI was formed in 1953 until the mid-1980s, primary responsibility for the process resided with a small number of medical schools chosen by the leadership of HHMI to be affiliated institutions.

In 1984, after several years of effort, the University of Texas Southwestern Medical School in Dallas (UTSW) persuaded HHMI to make it the 11th institution to host a Hughes Unit, and it secured a commitment from HHMI to support 12 new Investigators. UTSW selected the Investigators on its own

initiative, subject to approval by George Cahill, M.D., Professor of Medicine at Harvard and HHMI's Director of Research, with the concurrence of George Thorn, M.D., also Professor of Medicine at Harvard and President of HHMI.

In 1987, Purnell Choppin, M.D., became the President of HHMI, and he and his Chief Scientific Officer, Max Cowan, B.M./B.Ch., D. Phil., inherited the previous *modus operandi* for selecting HHMI Investigators. While temporarily allowing host institutions to replace vacant HHMI positions subject to their approval of candidates, Drs. Cowan and Choppin quickly implemented a more visible and competitive

# APPOINTMENT

A native of Ulm, Germany, Dr. Baumann joined the Institute in 2002 after completing an HHMI postdoctoral fellowship in the laboratory of Thomas R. Cech, Ph.D., at the University of Colorado at Boulder. He earned his Ph.D. in Biochemistry at the Imperial Cancer Research Fund, Clare Hall (U.K.); a Master's degree at the Wellcome/CRC Institute, University of Cambridge (U.K.); and his Bachelor's degree in Cellular and Molecular Biology from the University of Cambridge (U.K.).

Dr. Baumann received a highly competitive Pew Scholar Award in the Biomedical Sciences in 2003 and a Basil O'Connor Starter Scholar Award from the March of Dimes Birth Defects Foundation in 2004.

Since joining the Institute, Dr. Baumann and his research team have been interested in how cells maintain the ends of their chromosomes, called telomeres. Telomeres shorten as we get older, and mutations that result in accelerated shortening have been linked to several degenerative diseases. On the other hand, telomerase, a protein central to telomere elongation, is activated in most cancer cells and is considered a promising target for anticancer drugs. By understanding how telomere lengthening is regulated and how telomeres are prevented from becoming overly short, Dr. Baumann's research team hopes to lay the foundation for the development of treatments for cancer as well as several degenerative diseases. Learn more about his research program on page 14.

Dr. Baumann leads an eight-person team at the Stowers Institute composed of postdoctoral researchers, graduate students, and scientific staff. Dr. Baumann's laboratory has published ten papers in peer-reviewed journals, including four papers of remarkable influence in the field of chromosome dynamics in the last two years.

In the May 11, 2007 issue of *Molecular Cell*, his team employed a biochemical assay for double-strand break repair to define the minimal requirements for the protection of telomeric DNA at the ends of chromosomes. They established that neither long single-stranded overhangs nor telomeric loop formation is essential to prevent illegitimate fusion of chromosome ends. Instead, a short tandem array of telomeric repeats bound by a RAP1/TRF2 complex is sufficient to impede non-homologous end joining in a highly directional manner. By establishing an *in vitro* assay for chromosome end protection and by implicating specific proteins, the team opened the door to elucidate the mechanism by which RAP1/TRF2 inhibits double-strand break repair at chromosome ends. The work sheds light on the formation of tumors because genomic instability and gross chromosomal rearrangements are hallmarks of cancer cells.

In the January 2008 issue of *Nature Structural & Molecular Biology*, the Baumann Lab identified the long-sought telomerase RNA gene in fission yeast, a single-cell research model. The RNA subunit of telomerase is of particular

appointment process. By the early 1990s, HHMI Investigators were appointed only through national competitions among nominees submitted by a select group of research-intensive institutions.

Eligible institutions periodically received invitations from Drs. Cowan and Choppin to nominate a faculty member for evaluation by an HHMI selection panel. Larger institutions were sometimes allowed to nominate more than one. Typically, a few dozen nominees would compete for a handful of new positions, and the rivalry within institutions to be one of the nominees was as intense as that among the nominees seeking a HHMI appointment.

After Tom Cech, Ph.D., became HHMI President in 2000, the first invitation to nominate candidates in a national competition came in 2004, and the process followed the model introduced by Drs. Cowan and Choppin in the previous decade. HHMI invited the Stowers Institute to submit a single nomination. Olivier Pourquié, Ph.D., was the Institute's nominee, and he became one of 43 new HHMI Investigators selected from more than 300 candidates.

HHMI announced a new approach in the competition in 2007. For the first time, candidates were able to apply directly to HHMI without being nominated by their institutions. The rationale for change

included the concern that institutional politics in selecting nominees sometimes prevented the most meritorious candidates from entering the national competitions for HHMI Investigatorships.

HHMI continued the new approach in the 2008-2009 competition that resulted in the appointment of Peter Baumann, Ph.D., Associate Investigator. More than 2,000 applicants vied for appointments – almost an order of magnitude more than when candidates were restricted to institutional nominees.



interest, as it represents one of the two core components of telomerase and provides the template for the short repeats that are added to the ends of chromosomes. Telomerase RNA had been studied in a variety of simple model organisms, but telomere maintenance turned out to be quite different in those species than in human cells. The Baumann Lab used a biochemical approach to identify and clone the RNA subunit of telomerase in *Schizosaccharomyces pombe*, or fission yeast, a simple yet versatile research model. The identification of the fission yeast equivalent of the human telomerase RNA gene provided a critical tool to study telomerase in a genetically tractable, single-cell organism with a telomere maintenance machinery that shares many features with human cells.

In the August 22, 2008 issue of *Molecular Cell*, Dr. Baumann reported research showing that a rarely studied pathway plays a critical role in chromosome fusion – a misguided attempt by cells to repair damage to the ends of chromosomes. Cells sometimes mistake the ends of their chromosomes for a break and activate the cellular machineries for DNA double-strand break repair, causing the chromosome ends to fuse. Such fusions can eventually convert a cell from a pre-cancerous state to a cancerous one, so chromosome fusions – especially inter-chromosome fusions – often lead to cancer. How chromosome fusions are formed and which DNA repair pathway is responsible has been a matter of great interest for some time. The Baumann Lab found that a process known as

DNA single-strand annealing mediates the fusion of chromosome ends. The discovery of the role of this DNA repair pathway in chromosome fusion opens new opportunities to understand how misguided repair can result in disease.

In the December 18, 2008 issue of *Nature*, Dr. Baumann and colleagues reported the discovery of an important step in the maturation pathway of telomerase, the enzyme that replenishes the sequences that are lost at chromosome ends with every cell division. When the telomere is gradually eroded away, the cell can no longer divide and will eventually die. Telomerase is a promising target for cancer treatment because its inhibition selectively kills cancer cells. In order to identify small molecules that block telomerase, it is critical to decipher how the enzyme is made and assembled from its components. The Baumann Lab found that the RNA subunit of telomerase, the component of the enzyme that serves as the template for adding DNA to chromosome ends, is first made as a longer inactive form that must be processed into a shorter mature form for telomerase to function. They discovered a novel pathway for processing telomerase RNA that is fundamentally different from the method cells use to process other classes of RNAs. By showing that interfering with telomerase maturation can inactivate telomerase, Dr. Baumann and his colleagues have made a significant step towards identifying a whole set of potential new targets for therapeutic exploitation in cancer. They also



## HHMI INVESTIGATORS AT THE STOWERS INSTITUTE

noted that defects in the processing machinery for human telomerase are likely to contribute to diseases such as dyskeratosis congenita, aplastic anemia, and idiopathic pulmonary fibrosis.

"It is gratifying to see how Dr. Baumann's discoveries have advanced the field of telomere biology," said Robb Krumlauf, Ph.D., Scientific Director of the Stowers Institute, "and he richly deserves a Hughes appointment. All of us here at Stowers congratulate him on his success in the intense competition for support from the HHMI."

"Peter Baumann's HHMI appointment is a significant landmark in his successful career as a laboratory leader, and it is a source of pride for the Stowers Institute," said William B. Neaves, Ph.D., President and CEO. "Selection by the HHMI after rigorous, comprehensive review represents an enormous vote of confidence in a biomedical scientist, and all of us at the Institute are delighted that Dr. Baumann will have the additional resources provided by this appointment to accelerate his innovative research in chromosome dynamics and telomere biology."



*Joan Conaway*



*Jerry Workman*

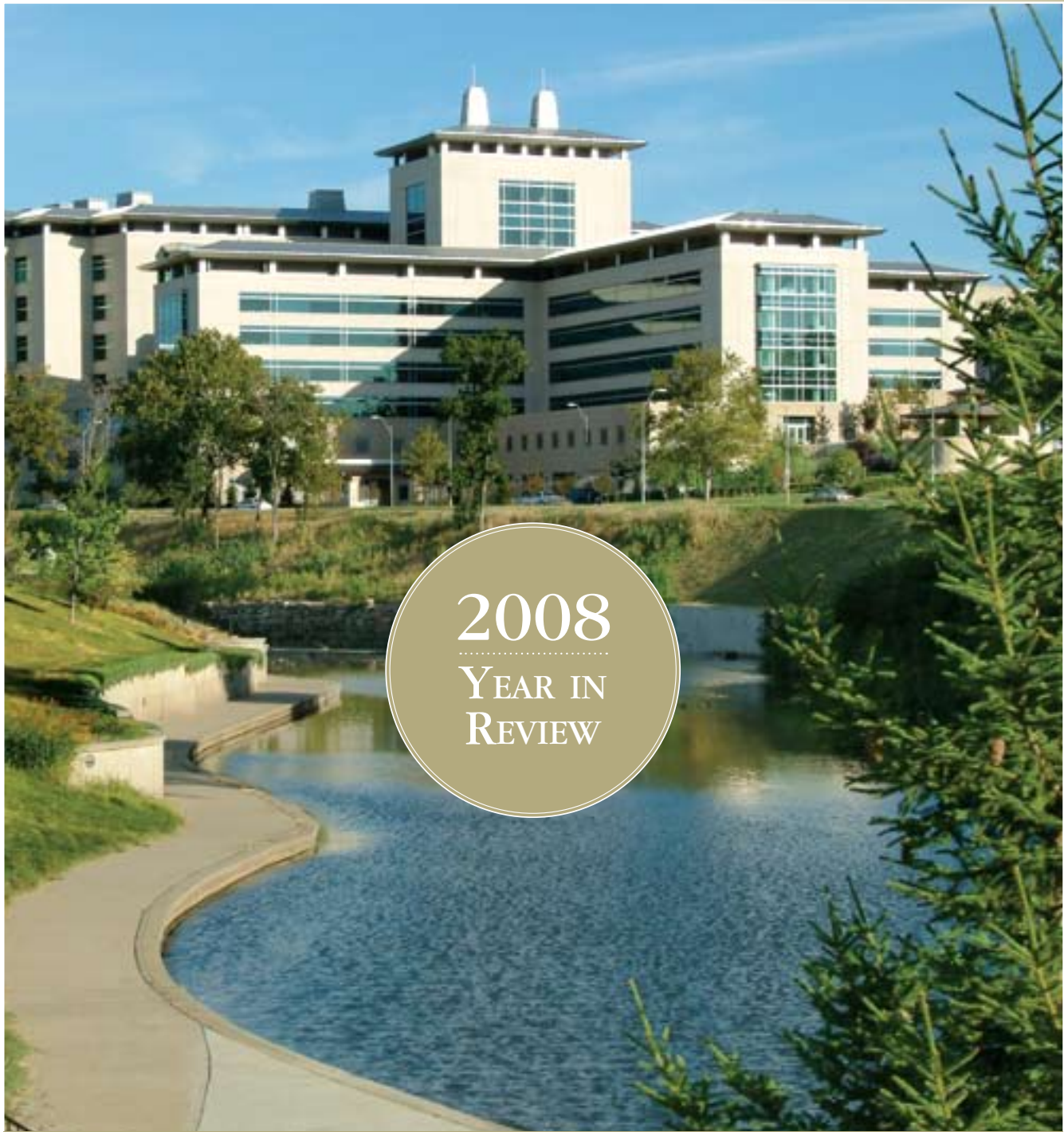


*Olivier Pourquié*

The Stowers Institute is now home to two Howard Hughes Medical Institute (HHMI) Investigators - Olivier Pourquié, Ph.D., Investigator, and Peter Baumann, Ph.D., Associate Investigator. However, four laboratory leaders in the Stowers Institute have been selected for the honor. In 1997, while on the faculty of the Oklahoma Medical Research Foundation, Joan Conaway, Ph.D., Investigator, was named an Associate Investigator with HHMI. A year later, Jerry Workman, Ph.D., Investigator, was selected while he was on the faculty of The Pennsylvania State University.

In 2001, Dr. Conaway resigned her HHMI appointment to accept a position with the Stowers Institute, and Dr. Workman did so in 2003. Neither Dr. Conaway nor Dr. Workman was able to transfer the HHMI appointment because the Stowers Institute was not yet an official affiliate of HHMI, a status that can only be acquired by the success of an institution's candidate in a national competition for new HHMI appointments. However, after Drs. Conaway and Workman joined the Stowers Institute, HHMI agreed to invite the Stowers Institute to nominate a candidate in the next national competition. That occurred in 2004, and the Stowers Institute nominated Olivier Pourquié, Ph.D.

Dr. Pourquié was one of 43 successful candidates in the 2004 competition, and he became an HHMI Investigator in 2005. With his appointment, the Stowers Institute became an HHMI affiliate. Had Drs. Conaway and Workman joined the Institute after 2005, they would have been allowed to transfer their HHMI appointments to the Stowers Institute. Each HHMI Investigator is allowed one institutional transfer in his or her career, and it can occur during a window of opportunity following each successful reappointment review. Now that the Stowers Institute is a formal affiliate of HHMI, any eligible HHMI Investigator joining the Institute in the future will be able to exercise this option.



2008  
YEAR IN  
REVIEW



# TAKING STOCK



AT THE CLOSE OF 2008, 490 PEOPLE WORKED AT THE STOWERS INSTITUTE EACH DAY. 349 WERE MEMBERS OF THE SCIENTIFIC STAFF, INCLUDING:

- 25 Principal Investigators
- 99 Postdoctoral Research Associates and Fellows
- 32 Predoctoral Research Associates

# ACCOLADES



Back row from left: Kausik Si, Ho Yi Mak, Paul Kulesa, Ron Yu, Scott Hawley, John Perry, Kimberly Inman, Paul Trainor.  
Front row from left: Jennifer Gerton, Julia Zeitlinger, Michael Washburn, Tong Yin, Alejandra Figueroa-Clarevega.

- **Alejandra Figueroa-Clarevega**, a Research Technician in the Gibson Lab, was selected in January for the Howard Hughes Medical Institute (HHMI) Gilliam Fellowship for Advanced Study.
- **R. Scott Hawley**, Ph.D., Investigator, was honored with the Excellence in Education Award by the Genetics Society of America (GSA) in January and was subsequently elected president of the GSA for the 2010 term.
- **Ho Yi Mak**, Ph.D., Assistant Investigator, received a March of Dimes Basil O'Connor Starter Scholar Award, effective in February.
- **Xiaogang Li**, Ph.D., formerly a Senior Research Associate in the Rong Li Lab, was awarded a grant from the PKD Foundation, effective in February.
- **Michael Washburn**, Ph.D., Director of Proteomics, was presented the John A. Boezi Alumnus Award by Michigan State University in April.
- **Joel Schwartz**, Ph.D., formerly the Managing Director of Imaging Center, received a Kansas City Area Life Sciences Institute grant, effective in June.
- **Paul Trainor**, Ph.D., Associate Investigator, received a grant from the March of Dimes, effective in June.
- **Kimberly Inman**, Ph.D., Postdoctoral Research Fellow in the Trainor Lab, received a National Institutes of Health Fellowship, effective in June.
- **Ron Yu**, Ph.D., Assistant Investigator, received the Hudson Prize from the M.R. & Evelyn Hudson Foundation, effective in July.
- **Kausik Si**, Ph.D., Assistant Investigator, received the Klingenstein Fellowship in the Neurosciences from the Esther A. & Joseph Klingenstein Fund, effective in July.
- **John Perry**, Ph.D., Postdoctoral Research Fellow in the Linheng Li Lab, received a Leukemia & Lymphoma Society Fellowship, effective in July.
- **Tong Yin**, Ph.D., Postdoctoral Research Fellow in the Linheng Li Lab, received a Leukemia & Lymphoma Society Special Fellowship, effective in July.
- **Julia Zeitlinger**, Ph.D., Assistant Investigator, was named a Pew Scholar by the Pew Charitable Trust, effective in July, and received a National Institutes of Health Director's New Innovator Award, effective in September.
- **Jennifer Gerton**, Ph.D., Associate Investigator, received a National Institutes of Health grant, effective in September.
- **Paul Kulesa**, Ph.D., Director of Imaging, received a National Institutes of Health grant, effective in September.

## ADVANCING WORK, ADVANCING CAREERS

The Stowers Institute is pleased to acknowledge the promotions of four principal investigators – Linheng Li, Ph.D., and Ting Xie, Ph.D., from Associate Investigators to Investigators, effective May 1, 2008; and Peter Baumann, Ph.D., and Jennifer Gerton, Ph.D., from Assistant Investigators to Associate Investigators, effective January 1, 2009.



**Dr. Li** joined the 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. His research focuses on understanding the molecular mechanisms and genetic pathways that regulate adult stem cell development.

# MAKING A MARK

In 2008, Stowers Institute research teams continued to make discoveries that merited publication in leading peer-reviewed scientific journals – 53 published papers in all. Add to those 39 reviews, commentaries, chapters, and one book. It all makes for a very successful year. Highlights among 2008's published papers include:

- The **Krumlauf Lab** demonstrated the modulation of gene expression by protein coding regions involved in the development of the brain (published online by *Proceedings of the National Academy of Sciences* on December 22).
- The **Baumann Lab** identified a crucial step in the maturation pathway of telomerase (December 18 issue of *Nature*).
- The **Workman Lab**, **Abmayr Lab**, and **Proteomics Center** collaborated on the discovery of a novel histone demethylase protein complex (December 5 issue of *Molecular Cell*).
- The **Linheng Li Lab** expanded the understanding of the bone marrow stem cell niche (published online by *Nature* on December 3).
- The **Rong Li Lab** offered insight into the adaptive ability of cells (November 28 issue of *Cell*).
- The **Rong Li Lab** probed the mechanism of asymmetry in meiotic cell division (published online by *Nature Cell Biology* on October 5).
- The **Conaway Lab** identified a novel mechanism for the regulation of gene expression (September 25 issue of *Molecular Cell*).
- The **Baumann Lab** identified a critical chromosome fusion pathway (August 21 issue of *Molecular Cell*).
- The **Pourquié Lab** and the **Bioinformatics Center** collaborated on a novel mathematical approach to identify patterns of gene expression (August 8 issue of *PLoS ONE*).
- The **Rong Li Lab** discovered a possible treatment for Polycystic Kidney Disease (August issue of *Nature Medicine*).
- The **Shilatifard Lab** and the **Molecular Biology Facility** collaborated to develop a mutant library to study histone crosstalk involved in childhood leukemia (August issue of *Nature Structural & Molecular Biology*).
- The **Pourquié Lab** uncovered a mechanism contributing to appropriate formation of the spine (July 17 issue of *Nature*).
- The **Shilatifard Lab** identified a new role for a factor involved in gene transcription (June 24 issue of *Proceedings of the National Academy of Science*).
- The **Pourquié Lab** and the **Molecular Biology Facility** collaborated to identify a gene linked to vertebral defects in children (June 2008 issue of *The American Journal of Human Genetics*).
- The **Yu Lab** revealed new insights into how the nervous system processes sensory information (April 25 issue of *Science*).
- The **Linheng Li Lab** shed light on the maintenance of blood-forming stem cells (April 10 issue of *Cell Stem Cell*).
- The **Workman Lab** revealed the functional details of a novel regulator of chromosome function (April issue of *Nature Structural & Molecular Biology*).
- The **Trainor Lab** characterized a gene essential for the development of the nervous system (February 15 issue of *Development*).
- The **Proteomics Center** devised a method for assigning probabilities to human protein interactions (February 5 issue of *Proceedings of the National Academy of Sciences*).
- The **Pourquié Lab** linked a  $\beta$ -catenin gradient to the process of somite formation (February issue of *Nature Cell Biology*).
- The **Trainor Lab** prevented a rare birth defect by inactivating the p53 gene (February issue of *Nature Medicine*).
- The **Xie Lab** showed how differentiation-defective stem cells out-compete normal stem cells for occupancy of the stem cell niche (January issue of *Cell Stem Cell*).
- The **Baumann Lab** identified the elusive telomere RNA subunit in a single-cell model organism (January issue of *Nature Structural & Molecular Biology*).



**Dr. Xie** joined the Institute in 2000 after completing a postdoctoral fellowship in the laboratory of Dr. Allan 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. His research focuses on the genetic and molecular analysis of stem cells and germ cell development.



**Dr. Baumann** joined the Stowers Institute in 2002 after completing a Howard Hughes Medical Institute postdoctoral fellowship in the laboratory of

Dr. Thomas 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. His work focuses on telomeres, the end pieces of chromosomes that act as a molecular clock to determine how many times a cell can divide before dying.



**Dr. Gerton** joined the Stowers Institute in 2002 from an American Cancer Society 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. Her research is focused on understanding the mechanisms that ensure fidelity of chromosome distribution to dividing cells.

# 2008 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., Associate 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., Associate Investigator**, joined the Stowers Institute in 2002 from a postdoctoral fellowship in the laboratory of Dr. Joseph DeRisi in the Department of Biochemistry and Biophysics at the University of California, San Francisco. Dr. Gerton received a Ph.D. in Microbiology and Immunology from Stanford University.

**Matt Gibson, Ph.D., Assistant Investigator**, joined the Stowers Institute in 2006 from a postdoctoral fellowship with Dr. 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., 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.



## MEETINGS AND SYMPOSIA

**Ting Xie, Ph.D., 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 postdoctoral 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.

As recognized leaders in their fields, Stowers Institute investigators are often invited to organize meetings and symposia that bring researchers from around the world together to share their work and their ideas. These events encourage collaboration and foster important advancements in research. In 2008, Stowers investigators played leading roles in organizing a number of important events including:

Topic	Dates	Location	Attendees	Organizers
Molecular Embryology of the Mouse	June 4 – 24	Cold Spring Harbor Laboratory Cold Spring Harbor, NY	14	David Threadgill, Ph.D., University of North Carolina, Chapel Hill Paul Trainor, Ph.D., Stowers Institute for Medical Research
Society for Developmental Biology 67th Annual Meeting	July 25 – 30	University of Pennsylvania Philadelphia, PA	1,000	Phil Benfey, Ph.D., Duke University Robb Krumlauf, Ph.D., Stowers Institute for Medical Research Arthur Lander, M.D., Ph.D., University of California, Irvine Susan Mango, Ph.D., University of Utah Scott Poethig, Ph.D., University of Pennsylvania Eric Wieschaus, Ph.D., Princeton University
MLL Translocations and Human Leukemia	September 6 – 7	Stowers Institute for Medical Research Kansas City, MO	60	Ali Shilatifard, Ph.D., Stowers Institute for Medical Research Leanne Wiedemann, Ph.D., Stowers Institute for Medical Research
Advanced Microscopy Workshop	September 9 – 12	Stowers Institute for Medical Research Kansas City, MO	45	Stowers Institute Imaging Center
Transcriptional Regulation by Chromatin and RNA Polymerase II	October 16 – 19	Granlibakken Conference Center and Lodge Lake Tahoe, CA	125	Ali Shilatifard, Ph.D., Stowers Institute for Medical Research
Epigenetics: Mechanisms & Regulation	December 7 – 10	Cold Spring Harbor Laboratory Cold Spring Harbor, NY	35	Shelley Berger, Ph.D., Wistar Institute Ramin Shiekhattar, Ph.D., Center for Genomic Research Ali Shilatifard, Ph.D., Stowers Institute for Medical Research

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The Stowers Institute's scientific effort is made possible by the proceeds we receive from our Hope Share Endowment. The Institute welcomes contributions to the Endowment in any amount. Individual or cumulative contributions of \$1,000 or more establish a Hope Shares account, which can be opened in your name or in memory or honor of someone you love.

## 2008 Contributions

In 2008, contributions of at least \$1,000 were received from, in memory of, or in honor of the following:

### \$100,000 or More

*American Century Foundation  
Cerner Corporation (in kind)  
Richard H. Driebause Charitable Trust  
From Pamela Stowers in Memory of  
Laura Stowers*

### \$10,000 or More

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### \$100,000 or More

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Cerner Corporation (in kind)  
Country Club Bank  
Felix and Helen Juda Foundation  
Tom and Nancy Juda Foundation  
Greater Kansas City Community  
Foundation; Frederick and Louise  
Hartwig Family Fund  
James Kemper Jr.  
The Richard H. Driebaus Charitable  
Lead Trust  
Hank Young (Gameface book proceeds)*

### \$50,000 or More

*Richard and Jeanette Brown  
Polsinelli Shugbart PC  
James Stowers III  
David and Wendy Welte*

### \$25,000 or More

*Mildred E. Coats Trust  
JE Dunn Construction Company  
(in kind)  
Menorah Medical Center, Inc. (in kind)  
William and Priscilla Neaves  
Rubin Postaer and Associates  
In Memory of Robert Rutsch Jr.  
John and Shirley Wagner  
From Bruce and Laurie Wimberly  
in Memory of Virginia Wimberly*

### \$10,000 or More

*Cisco Systems, Inc. (in kind)  
Webb Gilmore  
Gilmore and Bell  
Allan and Margot Huber  
IBM  
The J.B. Reynolds Foundation  
Brian Jeter  
In Memory of Carlo Jonathan  
Jack and Rena Jonathan  
From Jim and Virginia Stowers  
in Memory of Felix Juda  
In Memory of Helen Kirby  
Irving Kuraner  
Labconco Corporation  
In Memory of Helen Lebens  
Bill and Peggy Lyons  
Barbara Marshall  
Mark and Martha Miller  
Tom and Jeanne Olofson  
Landon Rowland, Kansas City  
Impact Fund  
Sanders Morris Harris  
In Memory of Richard Smith, Wendell  
Smith, and Laura Stowers  
Rick and Betsey Solberg  
Kathleen Stowers-Potter  
David and Jeannine Strandjord  
Roderick and Linda Sturgeon  
Jonathan and Cyndi Thomas  
Byron Thompson  
In Memory of Vernon Voorbees II  
Michael and Louise Zolezzi*

### \$5,000 or More

*Clay Blair Family Foundation  
Mary Breed Brink  
Cancer Golf Association  
Enrique Chang and Catherine Farley*



*Michael and Jenny Cormack  
David and Nancy Dilley  
In Memory of James and Eleanor Drake  
David and Susan Keefer  
Thomas Kmak Family  
From Bo Kreiling in Memory of  
Helen Jayne Kreiling  
Dawn Lind  
Lucent Technologies (in kind)  
Amy Noelker  
From John and Susan McMeel  
in Memory of John O'Day  
In Memory of Albert Otten and  
William Ellis  
Austin and Laura Wilson*

**\$1,000 or More**

*Don and Christine Alexander  
From Rob Aneweer in Memory of  
Dave Aneweer and Jim Aneweer  
Elmer and Verna Armbruster  
Malcolm M. and Kathy B. Aslin Fund  
Donald and Margaret Austin  
From Michael and Dana Schaad in  
Memory of Carol Barry and  
Herbert Schaad  
Paul Jr. and Joan Bartlett  
From Bert and Joan Berkley in Memory of  
Kitty Berkowitz and Janice McInrath  
John and Sheryl Block  
From Jim and Virginia Stowers in Memory  
of Arthur Brand  
Gregory Broome  
In Memory of Carol Ann Brown  
Mary Jo Browne  
In Memory of Evelyn Louise "Lovey" Bryer  
Michael and Gretchen Carter  
Shirley Christian  
In Memory of Alice "Penny" Cohn  
Gilbert and Lois Cole  
From Lauren and Ryan Contillo and  
Kathleen Stowers-Potter in Memory of  
Lawrence Joseph Contillo*

*From Cathryn and Jay Linney in Memory  
of William Cordes  
From Frederick Coulson III in Memory  
of Frederick Coulson Jr.  
Michael and Joyce Cunningham  
Phillip Davidson  
From Jim and Virginia Stowers in Memory  
of Walter Day  
In Memory of Walter Day  
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Denke in Memory of James Griffin Jr.  
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of Paul Henson  
Henson Trust Fund  
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Jeffrey Johnson  
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*In Memory of Gary Kostuke  
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In Memory of Jane Lundgaard  
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of Caryn Lisnek O'Connell  
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From Jim and Alex Potter; Lauren and Ryan  
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Memory of James William Potter  
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Michele Stowers  
Pamela Stowers  
Mark A. Susz Revocable Trust  
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David Tucker  
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Howard and Frances Vaughan Charitable  
Foundation  
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