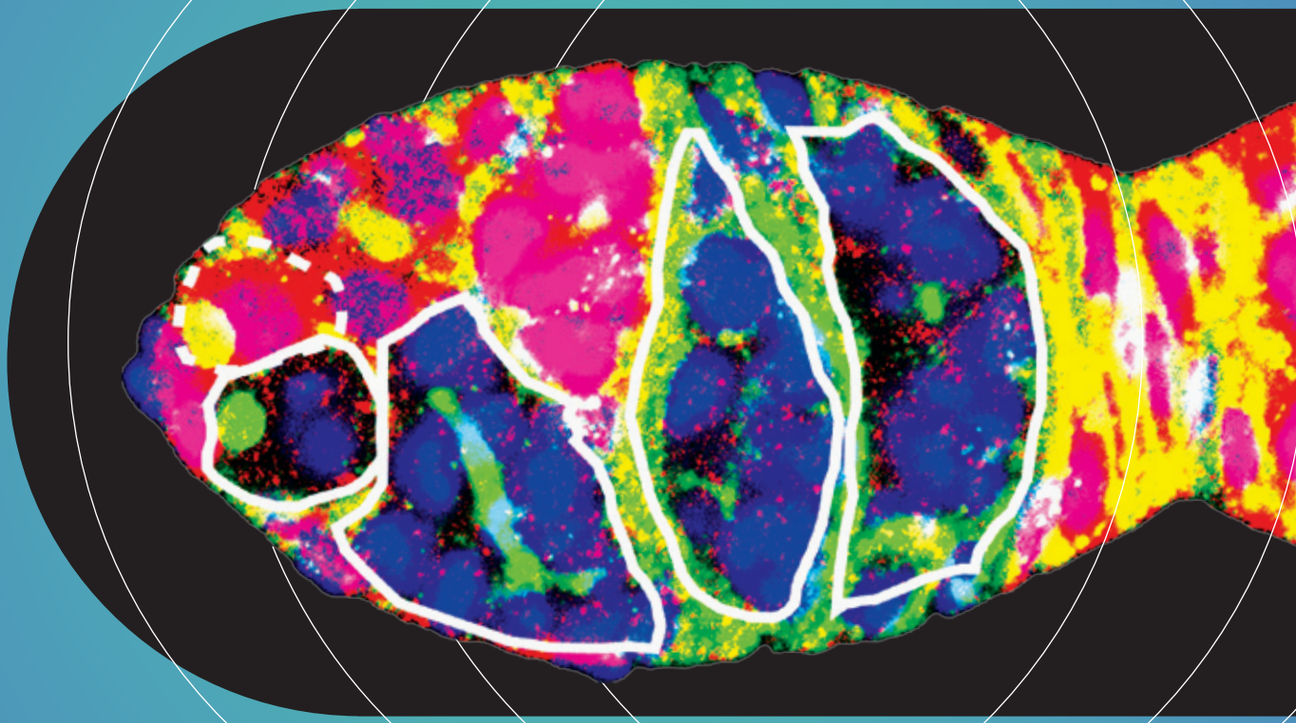
FALL 2007

Stowers REPORT

NEWS AND INSIGHT FROM
THE STOWERS INSTITUTE
FOR MEDICAL RESEARCH



STOWERS INSTITUTE RESEARCHERS SHED LIGHT ON THE UNIQUE CAPABILITIES OF STEM CELLS.

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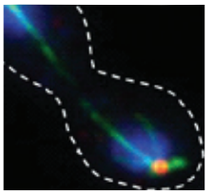

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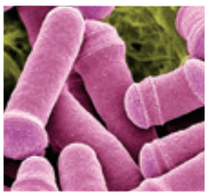
The Baumann and Gerton Labs investigate chromosome structure and its role in disease



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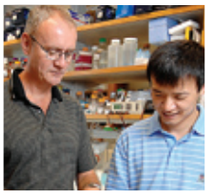

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Bringing You the New *Stowers Report*

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

The Stowers Report *will strive to make research at the Institute accessible to everyone while describing it with sufficient accuracy to earn credibility with scientists.*

You will notice the *Stowers Report* has a new format. The content has also changed to convey more of the results of research underway in laboratories at the Stowers Institute.

Research at the Institute centers on the theme of how genes regulate the behavior of cells – how cells divide, differentiate, migrate, die when appropriate, form patterns, coalesce into organs, and develop into whole organisms. The founders and members of the Institute believe that understanding the cellular and molecular biology of development will yield insights into things that go wrong with these finely tuned processes to cause disease.

By understanding how individual genes regulate the multiplication of intestinal stem cells, for example (see page 14), we begin to appreciate how changes in these genes can cause colon cancer. The quest to gain penetrating knowledge of how intestinal stem cells multiply cannot involve experiments with human beings, but it can be pursued ethically with animal models such as mice. Decades of research with simple animal models have shown time after time that insights gained from these studies point the way to practical improvements in the treatment of human disease.

We all appreciate the importance of seeking cures for diseases that afflict us and our families, but it is not easy to perceive the relevance of very basic research with yeast, round worms, fruit flies, frogs, and mice. The difficulty stems from inadequate efforts to explain this research to people who don't work in laboratories. As in many professional fields, the language used by specialists in cellular and molecular biology involves arcane terminology that has little meaning to those outside the field. It can be a daunting challenge to recognize the implications for human health by reading a paper from the Stowers Institute in an issue of *Science* or *Nature*, and this reality motivates the *Stowers Report* to explain such research more clearly to the larger constituency of individuals who are not scientists.

The challenge for the *Stowers Report* is the fact that its readers span the spectrum from cellular and molecular biologists who routinely communicate in the jargon of their field to people who never have and never will go near a laboratory. Those who work on the *Stowers Report* believe it should be as informative to the cancer survivors who aren't scientists as it is to the Nobel Prize winners on our mailing list.

The *Stowers Report* will strive to make research at the Institute accessible to everyone while describing it with sufficient accuracy to earn credibility with scientists. The Institute's laboratory leaders endorse this objective, and those whose work is described in this issue have taken time to ensure that the effort to explain their research in plain language does not compromise the integrity of the science itself. They deserve thanks both for conducting research with the potential to improve human health and for helping make it understandable.

I hope you will enjoy reading this issue of the *Stowers Report*. Please help us make it better by expressing your feelings about the new format, the focus on science, and the effort to let readers know what's happening in laboratories at the Stowers Institute.

The Stowers Institute is excited to launch the new *Stowers Report*, and we want to know what you think. Do you have a question about our research? Is there a topic you would like to see covered in a future issue of the *Stowers Report*? We welcome your feedback via e-mail to stowersreport@stowers-institute.org.

STRUCTURAL INTEGRITY

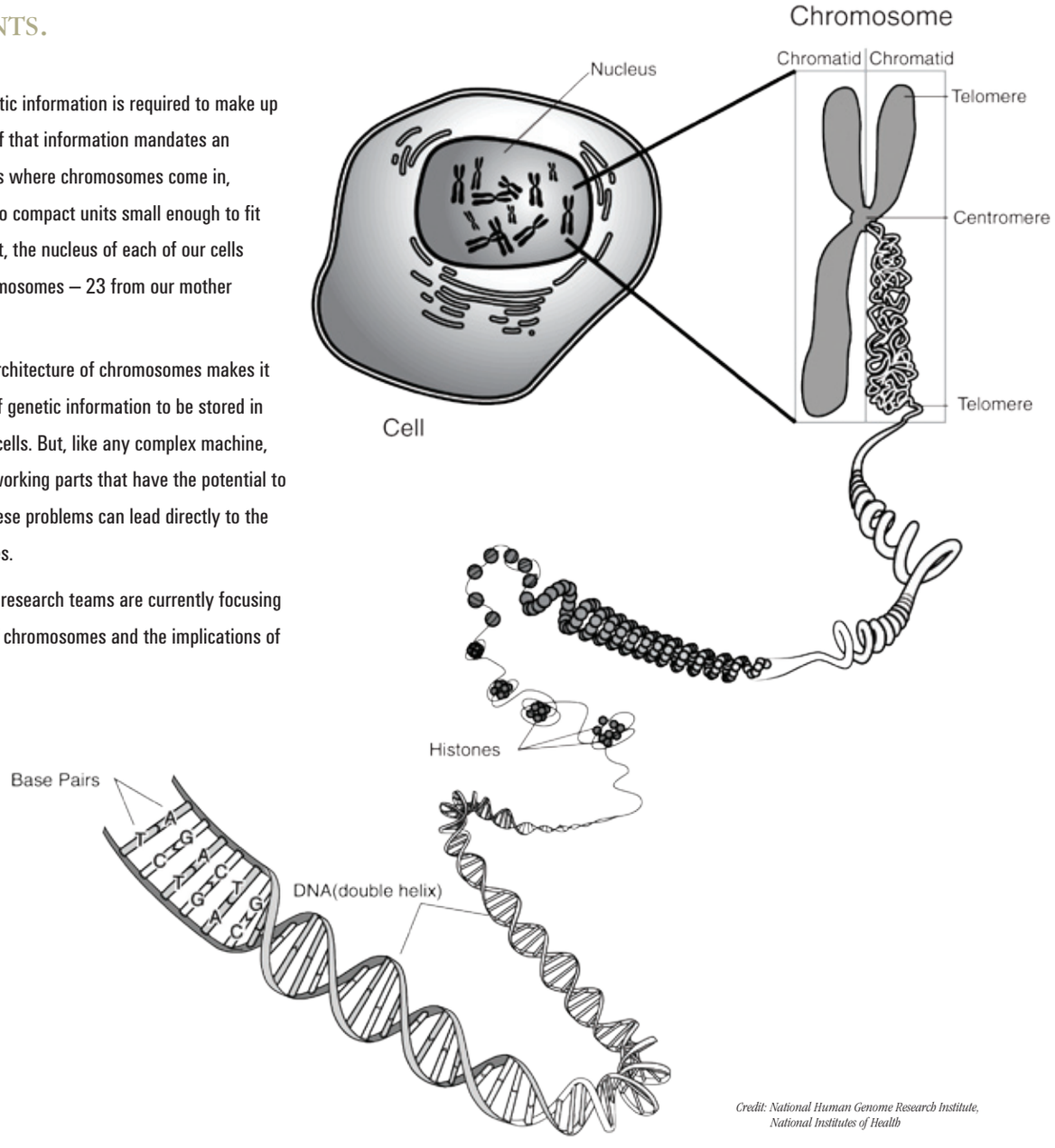
Investigating chromosome structure and its role in disease

Our genes set the course for much of our lives, determining everything from our hair color and height to our vulnerability to a variety of diseases. But when it comes to cancer, it is sometimes the packaging of our genes that counts.

An astounding amount of genetic information is required to make up the human body, and storing all of that information mandates an efficient packaging system. That's where chromosomes come in, packaging genetic information into compact units small enough to fit inside the nucleus of a cell. In fact, the nucleus of each of our cells normally accommodates 46 chromosomes – 23 from our mother and 23 from our father.

The amazingly sophisticated architecture of chromosomes makes it possible for enormous amounts of genetic information to be stored in the microscopic nuclei of human cells. But, like any complex machine, chromosomes rely on dozens of working parts that have the potential to break or malfunction. Many of these problems can lead directly to the onset of cancer and other diseases.

A number of Stowers Institute research teams are currently focusing their attention on the structure of chromosomes and the implications of structural problems in disease.



Credit: National Human Genome Research Institute, National Institutes of Health

Peter Baumann (left) and Nancy Bae (right) recently defined proteins that distinguish chromosome ends from DNA double-strand breaks in a publication in Molecular Cell.

Preventing Unnecessary Structural Repair

Occasionally, both strands of a DNA double helix are severed in a "double-strand break." These breaks subject the cell to significant risk because they can lead to harmful genome rearrangements. There are mechanisms for DNA to repair its own double-strand breaks, but to do so, the cell must recognize the break points as such. Cells are fairly successful at this self-diagnosis, except in rare occasions when improper repair efforts lead to genomic instability.

This begs several questions: How can a cell tell the difference between a break in the DNA and the end of the chromosome? Why don't cells make more misguided attempts to repair chromosome ends?

There is solid evidence to support the theory that chromosomes "cap" their ends – making them clearly discernable as ends rather than breaks – but specifically how that is done remains a mystery. Using a method to recreate DNA repair in the test tube, the Baumann Lab set out to characterize how chromosome ends are protected from unnecessary repair.

What they learned was surprising. Two possible factors in capping, long single-stranded overhangs and t-loop formations, were found to be unnecessary.

Instead, a short sequence of identical repeating DNA segments bound together by a protein complex called RAP1/TRF2 proved to be sufficient to protect the chromosome's ends from the initiation of double-strand break repair.

The Baumann Lab believes that the repeating DNA segments essentially serve as a code that confirms the location of the end of the chromosome to the cell. Any chromosome end lacking that code is identified as a break that requires repair. The presence or absence of RAP1/TRF2 is crucial in a cell's ability to distinguish between a double-strand break and a chromosome end.

The discovery represents an exciting new research direction for the Baumann Lab.

"By implicating the RAP1/TRF2 protein in this process, we've opened the door to new projects that will drill down on the specific mechanism by which the protein inhibits double-strand break repair at chromosome ends," explained Peter Baumann, Ph.D., Assistant Investigator and last author on the *Molecular Cell* paper detailing the findings. "Chromosomal rearrangements are a hallmark of cancer cells, so if we can learn more about why chromosome capping sometimes fails, we will better understand a significant cancer risk factor and its role in the onset of the disease."

PAPER: A RAP1/TRF2 Complex Inhibits Nonhomologous End-Joining at Human Telomeric DNA Ends

JOURNAL: *Molecular Cell*

ISSUE: May 11, 2007

AUTHORS*: **Nancy Bae, Ph.D.**, Postdoctoral Research Associate; **Peter Baumann, Ph.D.**, Assistant Investigator

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

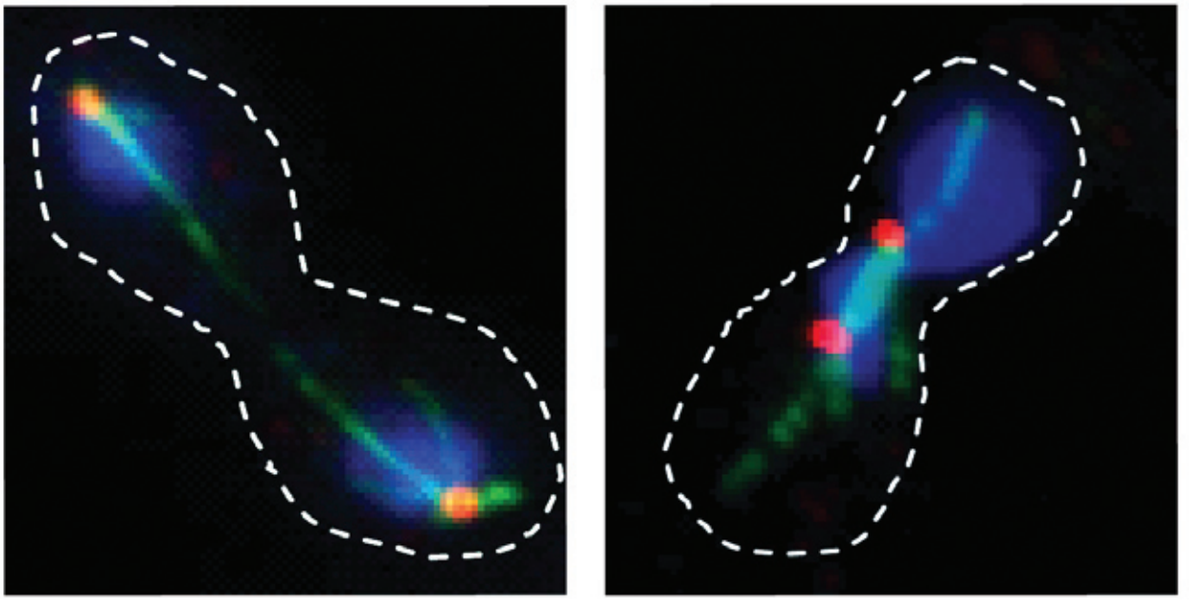
Peter Baumann, Ph.D., Assistant Investigator, also is an Assistant Professor in the Department of Biochemistry & Molecular Biology at The University of Kansas School of Medicine and a Pew Scholar in Biomedical Sciences. Learn more about his work at www.stowers-institute.org/labs/BaumannLab.asp.

Establishing a Solid Foundation for Chromosome Division

Cell division is a critical process for the human body. It is what allows us to change, grow, and heal. Successful cell division requires a cell to copy its own genetic information — via its chromosomes — and divide it evenly between the two new daughter cells. Errors in chromosome division can lead to cancer and developmental disorders including Down syndrome.

When cells divide, a specialized region on each chromosome known as the centromere ensures that chromosomes segregate properly to each newly formed cell. A structure known as the kinetochore forms within each centromere and serves as the specific site on the chromosome that attaches to the machinery responsible for moving each chromosome to a daughter cell during cell division. This machinery is the so-called spindle, and chromosomes are arranged along it during cell division to ensure proper distribution among the daughter cells.

Compared to the entire DNA genome, centromeres are very small DNA sequences. In order for chromosomes to segregate properly into the newly formed cell, the cell must specifically recognize the centromere and distinguish it from the rest of the DNA, allowing the kinetochore to form in the appropriate location. Proper positioning of the kinetochore is essential because improper formation can lead to incomplete or imprecise chromosome distribution — disastrous outcomes for the daughter cells.



Magnification shows the dramatic difference in how chromosomes behave in a dividing cell when the Scm3 gene is turned on (left) and off (right). In this image, DNA is stained blue, spindle pole bodies are stained red, and microtubules are stained green.

The Gerton Lab recently identified an inner kinetochore protein that is critical for the proper formation of the kinetochore. The protein Scm3 was discovered to serve as a marker, communicating to the cell where the kinetochore should be established. Without Scm3, cells cannot properly segregate chromosomes.

The team conducted this work using *Saccharomyces cerevisiae*, or budding yeast. It is a useful model in basic biomedical research because it is simple to grow in culture and it shares the complex internal cell structure found in plants and animals. Although the centromere in budding yeast cells is significantly less complicated than in human cells, the kinetochore is complex and can teach us much about human chromosome division.

"Identification of Scm3 is a promising step in understanding how kinetochore proteins find and recognize the DNA markers that ensure appropriate kinetochore development," said Jennifer Gerton, Ph.D., Assistant Investigator and last author on the *Molecular Cell* paper that detailed the findings. "We are moving forward with our work to develop the first comprehensive molecular understanding of how centromeric chromatin is formed and how the kinetochore is built. These are pivotal issues in the process of cell division, and we believe they will offer great insight into our understanding of diseases and disorders that are caused by errors in chromosome division."

PAPER: Scm3 Is Essential to Recruit the Histone H3 Variant Cse4 to Centromeres and to Maintain a Functional Kinetochore

JOURNAL: *Molecular Cell*

ISSUE: June 22, 2007

AUTHORS*: **Raymond Camahort**, Predoctoral Researcher; **Bing Li, Ph.D.**, Senior Research Associate; **Laurence Florens, Ph.D.**, Managing Director of Proteomics; **Selene Swanson**, Research Specialist II; **Michael Washburn, Ph.D.**, Director of Proteomics; **Jennifer Gerton, Ph.D.**, Assistant Investigator

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

Jennifer Gerton, 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-institute.org/labs/GertonLab.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-institute.org/labs/WashburnLab.asp.

2007 Hudson Prize Awarded to Jennifer Gerton

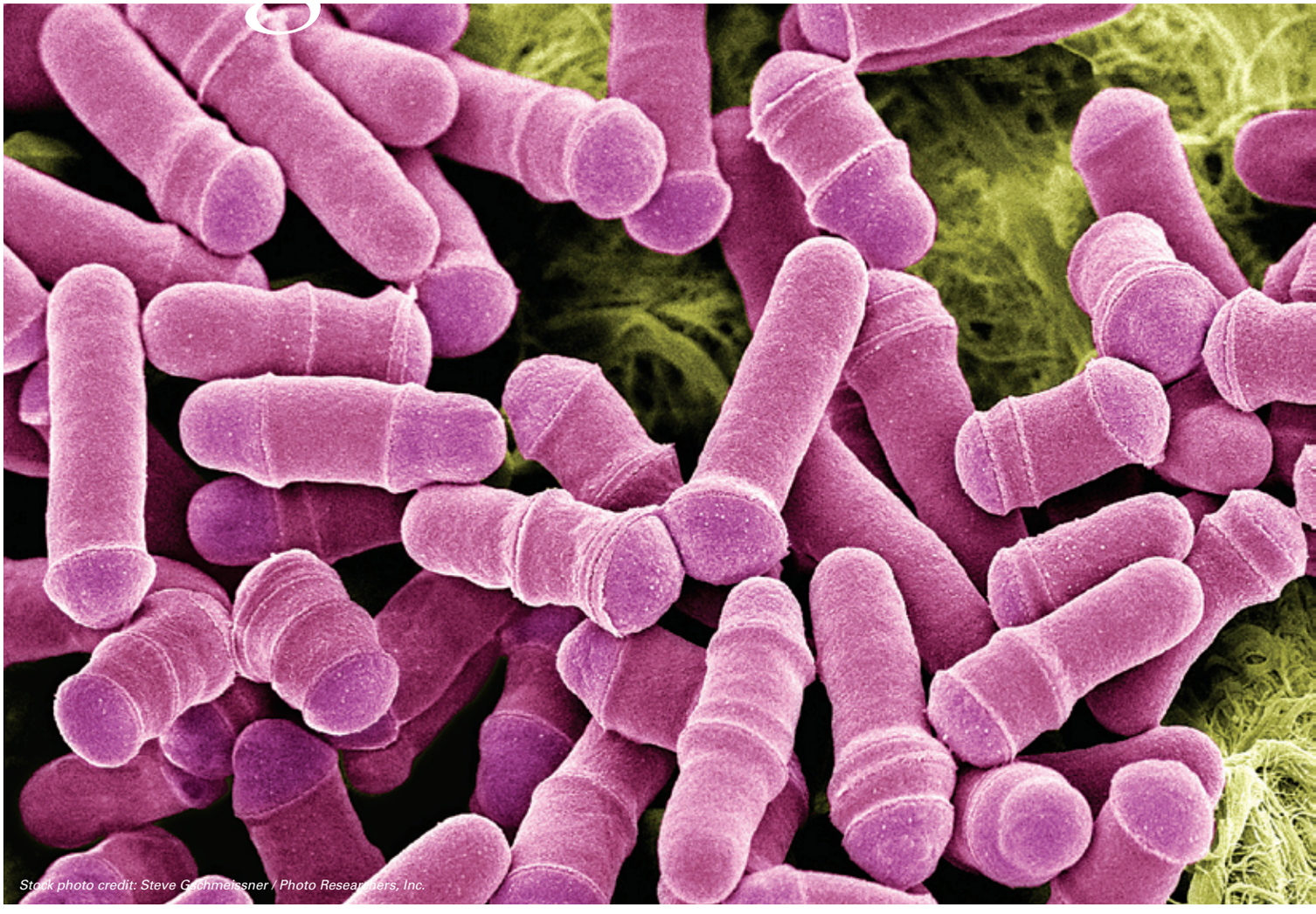
Jennifer Gerton, Ph.D., Assistant Investigator, has been named the 2007 Hudson Prize Recipient. Since 2003, the M.R. and Evelyn Hudson Foundation has recognized an early-career scientist at the Stowers Institute with a grant designed to accelerate the pace of laboratory experimentation. This year, the prize amount was increased to $75,000.

Dr. Gerton joined the Stowers Institute in 2002 from a postdoctoral fellowship in the laboratory of Joseph DeRisi, Ph.D., at the University of California at San Francisco. She holds a Ph.D. in microbiology and immunology from Stanford University.

Her research is focused on genomic and biochemical approaches aimed at understanding the mechanisms that ensure fidelity of chromosome distribution to the daughters of dividing cells. The survival of all living organisms depends on the pair of cells produced from the division of a single cell having the proper number of chromosomes. If this process fails, the resulting daughter cells contain either too few or too many chromosomes, and severe cellular abnormality or cell death typically ensues.

"I was absolutely thrilled to win the Hudson Prize," said Dr. Gerton. "It is an honor for me and the members of my lab. The prize increases the resources available to us to pursue our research on the relationship between chromosome cohesion and the human genetic disorder Cornelia de Lange syndrome, a genetic disorder that can lead to severe developmental anomalies. We will use the prize to add a new high-speed, high-density robot. As a result, we anticipate some great insights in the next year."

Taking on Leukemia



Stock photo credit: Steve Gschmeissner / Photo Researchers, Inc.

As unlikely as it may seem, yeast cells are being used by Stowers scientists to gain insight into mutations that lead to leukemia. Pictured above is a magnification of Schizosaccharomyces pombe*, or fission yeast.*

The Leukemia & Lymphoma Society estimates that 44,240 new cases of leukemia will be diagnosed in the United States in 2007. Leukemia is characterized by an abnormal increase in the number of white blood cells circulating in the body, a condition believed to result from DNA mutations that activate cancer-causing genes and deactivate tumor-suppressor genes in bone marrow stem cells. These genetic changes disrupt the normal proliferation and development of an individual stem cell in the lineage that leads to white blood cells and causes the cell to multiply uncontrollably.

Ali Shilatifard (center) completed a postdoctoral fellowship in the lab of Joan Conaway (left) and Ron Conaway (right) at the Oklahoma Medical Research Foundation a decade ago. Today, as colleagues at the Stowers Institute, the trio is contributing to an expanded understanding of leukemia.

The Stowers Institute is engaged in a variety of research that holds promise for a better understanding of leukemia. In fact, since 2003 Stowers Institute postdoctoral researchers have been awarded four fellowships by the Leukemia & Lymphoma Society in support of these projects; and Ali Shilatifard, Ph.D., Investigator, was a Scholar of the Leukemia & Lymphoma Society from 2001 until 2006 and currently serves on their Grant Review Subcommittee.

Researchers have identified four main types of leukemia, and though they share certain characteristics, each is unique. Recently, two Stowers Institute research teams completed projects that represent significant advances in understanding specific aspects of acute myeloid leukemia (AML), a form of the disease caused by acquired genetic damage to the DNA of a stem cell or one of its descendants in the bone marrow. This damage causes uncontrolled growth and a buildup of leukemic blast cells, which not only fail to function as normal blood cells but also block the production of normal marrow cells. AML is more likely to affect older people. It is considered one of the most difficult blood cancers to cure.

Model Behavior

Mutations that lead to leukemia commonly develop during the transcription process, when genetic information is transferred from DNA to RNA. AML is believed to be influenced by mutations that occur in the critical final stage of transcription, called elongation.

The stages of transcription are controlled by proteins called transcription factors. Research teams have paid special attention to one transcription factor, ELL/EAF, which is believed to control gene regulation by stimulating elongation of the RNA transcript. But how ELL/EAF does that remains a mystery: Does it regulate many genes or just a few? How is ELL/EAF targeted to the genes it regulates? How is the activity of ELL/EAF itself controlled?

For many years, pursuing these answers represented a daunting challenge. ELL/EAF was believed to be present only in multi-cellular organisms, necessitating the use of complex animal models such as fruit flies and mice.

Recently, a team of Stowers researchers including members of the Conaway Lab, the Bioinformatics Center, and the Proteomics Center discovered the presence of ELL/EAF in the very simple model organism *Schizosaccharomyces pombe*, or fission yeast. Of even greater significance, the ELL/EAF present in yeast demonstrated the properties one would expect from an elongation factor – inspiring confidence that insight gained through research with the yeast model will be useful in understanding transcription in humans.

"As different as humans are from yeast, we encode very similar proteins," explains Ron Conaway, Ph.D., Investigator and last author on *The Journal of Biological Chemistry* paper highlighting this discovery. "The discovery of ELL/EAF in yeast will allow our team to study its functions with relative ease and to address questions that have proved difficult to tackle using more complex model systems. Now, a number of very exciting research projects relating to ELL/EAF and its role in leukemia become not only possible but relatively simple to pursue."

PAPER: Identification and Characterization of a *Schizosaccharomyces pombe* RNA Polymerase II Elongation Factor with Similarity to the Metazoan Transcription Factor ELL

JOURNAL: *The Journal of Biological Chemistry*

ISSUE: Feb. 23, 2007

AUTHORS*: **Charles Banks**, Predoctoral Research Associate; **Stephanie Kong, Ph.D.**, Senior Research Associate; **Henrik Spahr, Ph.D.**, Stanford University School of Medicine; **Laurence Florens, Ph.D.**, Managing Director of Proteomics; **Skylar Martin-Brown**, Research Technician II; **Michael Washburn, Ph.D.**, Director of Proteomics; **Joan Conaway, Ph.D.**, Investigator; **Arcady Mushegian, Ph.D.**, Director of Bioinformatics; **Ronald 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-institute.org/labs/ConawayLab.asp.

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

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

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

Homing in on Treatment Targets

A topic of great interest to leukemia researchers is the identification of targets for potential treatment. These efforts require a detailed understanding of the cellular factors that contribute to leukemias, an essential prerequisite to devising interventions that might correct mutations responsible for the improper proliferation of white blood cells.

In work initiated at the Saint Louis University School of Medicine and continuing at the Stowers Institute, the Shilatifard Lab has made great strides in understanding the role of a histone protein involved in the development of childhood AML – the mixed lineage leukemia (MLL) complex.

The protein Histone H3 is an important component of chromatin, the packing material surrounding chromosomal DNA and preventing unwanted transcription of the message encoded in the DNA. Histone H3 can be altered by adding (methylating) or removing (demethylating) methyl groups from the histone protein. In a recent project, the Shilatifard Lab used fruit flies to examine the role of such H3 alterations in a leukemia-related complex – the fruit fly-equivalent of the human MLL protein – which has been established as an H3 methylase (an enzyme that methylates Histone H3). The team also worked with the fruit fly-equivalent of a known H3 demethylase (an enzyme that demethylates Histone H3).

The team discovered that a reduction in the MLL-equivalent resulted in an altered distribution of a chromatin binding protein believed to be involved in the regulation of gene expression, so the altered distribution pattern can result in altered transcriptional regulation, which may contribute to the onset of AML.

"The ultimate goal of this work is to pinpoint opportunities within the cell to reverse mutations that lead to the development of leukemia," said Dr. Shilatifard, last author on the *Nature Structural & Molecular Biology* publication that detailed the work. "Understanding the basic mechanics of the addition and removal of methyl groups on chromatin is an essential step in the process of identifying potential targets for the treatment of leukemias caused by MLL translocations."

PAPER: The trithorax-group gene in *Drosophila little imaginal discs* encodes a trimethylated histone H3 Lys4 demethylase

JOURNAL: *Nature Structural & Molecular Biology*

ISSUE: April 2007

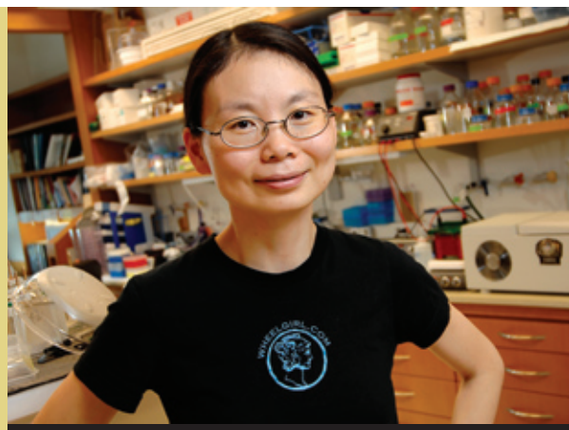
AUTHORS*: **Joel Eissenberg†, Ph.D.**, Saint Louis University School of Medicine; **Min Gyu Lee†, Ph.D.**, The Wistar Institute; **Jessica Schneider**, Saint Louis University School of Medicine; **Anne Ilvarsonn**, Saint Louis University School of Medicine; **Ramin Shiekhattar, Ph.D.**, The Wistar Institute; **Ali Shilatifard, Ph.D.**, Investigator

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

† Co-equal contributors to this publication.

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

The Leukemia & Lymphoma Society named Tingting Yao, Ph.D., a Postdoctoral Research Fellow in the lab of Investigators Joan Conaway, Ph.D., and Ron Conaway, Ph.D., a Special Fellow. The three-year appointment began on July 1 and provides $180,000 in funding for a project studying the enzyme UCH37, which is believed to play a significant role in gene expression and, therefore, a variety of cancers. The Leukemia & Lymphoma Society Special Fellowship is designed to permit the fellow to begin the transition to launching an independent research program. Dr. Yao joined the Conaway Lab in 2002. She received a Ph.D. in Biochemistry in 2002 from the University of Iowa and a B.S. in Biochemistry in 1996 from Wuhan University.



When Two Protein Domains are Better than One

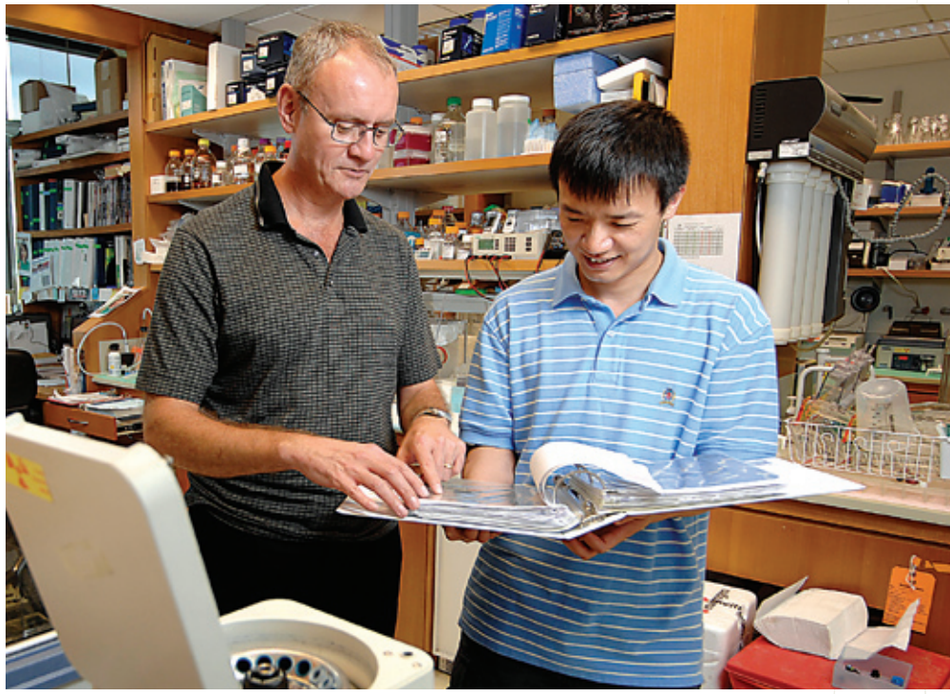
Evaluating how protein domain pairs can identify a specific histone modification

Each gene in the human body encodes a unique protein that performs a specialized function in the cell. Cells rely on the processes of transcription and translation to read each gene and produce the string of amino acids that make up the corresponding protein.

In transcription, genetic information is transferred from DNA into RNA. This requires unpacking a region of the chromosome to allow access of the transcription machinery. The exposed region needs to be repackaged following transcription. To that end, the transcribed region of the chromosome is notated chemically with a histone modification – the addition of a methyl group to its H3 histone that signals for repackaging.

Histone modifications can be read only by specific protein subunits. Like a secret code, this assures that the protein subunits, through specific protein domains, are attracted only to the appropriately transcribed region of the chromosome.

It was widely believed that a single protein domain would recognize a specific histone modification, as they were known to be required for recognition. However, sometimes the same protein domain is found in two or more protein complexes – only one of which is required at regions of transcription for repackaging. So, how can the cell direct only the appropriate protein complex to the area of transcription?



Jerry Workman (left) and Bing Li (right) demonstrated a mechanism for decoding histone modification marks in a recent Science *publication.*

The Workman Lab published a recent paper in *Science* that explained this complex function.

"Like so many of our colleagues around the world, we had generally accepted the idea that one domain could read a specific histone modification – a simple one-to-one ratio for effective communication," said Jerry Workman, Ph.D., Investigator and last author on the paper. "By measuring the protein complex binding to modified chromatin, we discovered that in some instances one domain on its own was insufficient to read the histone modification. But, when paired with the appropriate partner domain, the histone modification was easily identified and the process of

repackaging the chromosome after transcription occurred appropriately. Thus, in this instance, the histone code is read by a specific combination of protein domains."

Landmark modifications in chromosomes, such as H3 methylation, are of pivotal importance in cell growth and differentiation. The Workman Lab's discovery marks the beginning of the search for other domains that work in tandem to perform their transcription-related functions.

For another component of this project, the team studied an H3 methlyation, which is catalyzed by the human protein HYPB. HYPB interacts with the Huntington's disease protein huntingtin. In addition to changing the fundamental understanding of domain function, this work may assist in the design of therapeutic or preventative measures to fight Huntington's disease and related neurodegenerative disorders.

PAPER: Combined Action of PHD and Chromo Domains Directs the Rpd3S HDAC to Transcribed Chromatin

JOURNAL: *Science*

ISSUE: May 18, 2007

AUTHORS*: **Bing Li, Ph.D.**, Senior Research Associate; **Madelaine Gogol**, Programmer Analyst; **Mike Carey, Ph.D.**, Visiting Scientist from the David Geffen School of Medicine at UCLA; **Daeyoup Lee, Ph.D.**, formerly a Postdoctoral Research Associate; **Chris Seidel, Ph.D.**, Managing Director of Microarray; **Jerry Workman, Ph.D.**, Investigator

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

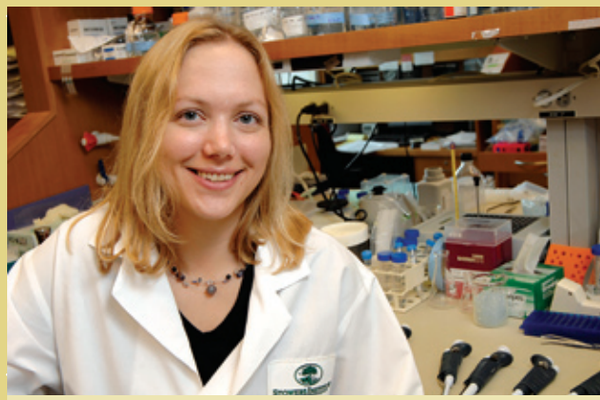
Jerry Workman, Ph.D., Investigator, joined the Stowers Institute in 2003 from The Pennsylvania State University where he was an associate investigator with the Howard Hughes Medical Institute. Learn more about his work at www.stowers-institute.org/labs/WorkmanLab.asp.

Karen Smith, Ph.D., Postdoctoral Research Associate in the Workman Lab, was selected for a Research Fellowship Award by the National Institute of Health's National Cancer Institute.

The award of nearly $150,000 over three years will support Dr. Smith's research into the role of novel histone deacetylase (HDAC)-interacting proteins that regulate cancer cell growth.

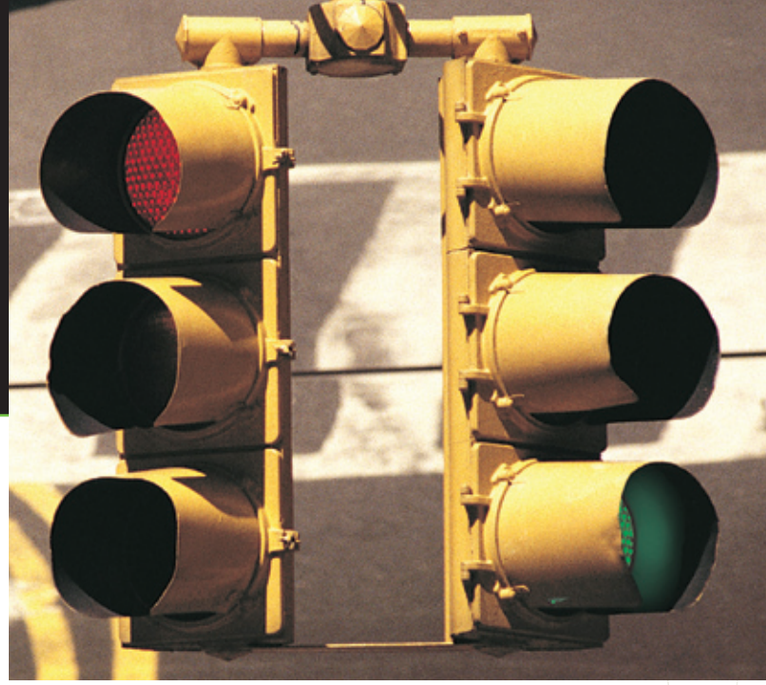
These proteins are the targets of a class of anti-cancer drugs called HDAC inhibitors that have been successful in treating a number of cancers, including breast cancer, in clinical trials. Despite clinical success, little is known about how inhibiting HDAC function can halt cancer cell growth.

Dr. Smith will be working to develop a more comprehensive understanding of how HDACs function in the cell to control gene expression and how this is connected to cancer cell growth in breast cancer. The aim of her work is to contribute to the development of HDAC inhibitors that are targeted to specifically inhibit proteins implicated in cancerous growth while bypassing unrelated proteins.



Red Light, Green Light

Demonstrating the role of INO80 in gene expression



Every cell in the human body has within its nucleus that person's complete genetic code. But each cell performs a specific function in a specific way. A cell knows what information in its genetic code is important based in large part on an internal traffic signal that determines which of its genes are turned "on" (functioning) and "off" (dormant). Genes that are turned on or off inappropriately can cause a cell to function improperly, leading to a variety of diseases.

For more than a decade, biomedical researchers have studied a transcription factor called YY1 because it is known to be important for turning on and off a variety of genes, including genes that control cell division, differentiation, and development.

The Conaway Lab has shown that YY1 works with a complex called INO80 that can remodel the structure of chromatin. In chromatin, chromosomal DNA is highly compacted by wrapping around a protein core. The degree of compaction plays an important role in determining whether or not a gene within a specific chromosomal region can be expressed.

Recently, the team's efforts to learn how YY1 and INO80 work together yielded a publication in *Nature Structural and Molecular Biology*.

"The data our team gathered for this paper suggests that one way YY1 controls gene expression is to bring the INO80 chromatin remodeling complex to the DNA sequences that determine when a gene is turned on or off," said Joan Conaway, Ph.D., Investigator and last author on the paper. "INO80 seems to control whether the gene is available to the machinery that copies DNA into messenger RNA and, therefore, whether the gene is expressed or not. In the end, this allows YY1 to direct the cell to make specific proteins that function in various processes, including cell cycle control."

Because of their contributions to cell cycle control, YY1 and INO80 have been suggested as eventual targets for cancer therapy. That will be possible, however, only when researchers have established a more comprehensive understanding of their functional mechanism.

Researchers hope to be able to eventually manipulate transcription factors and chromatin remodeling complexes to turn genes on or off to prevent or fight disease. The Conaway Lab's discovery about the role of INO80 in gene expression is an important step toward this goal.

PAPER: YY1 functions with INO80 to activate transcription

JOURNAL: *Nature Structural and Molecular Biology*

ISSUE: September 2007

AUTHORS*: **Yong Cai†, Ph.D.**, Research Specialist I; **Jingji Jin†, Ph.D.**, Senior Research Associate; **Tingting Yao, Ph.D.**, Postdoctoral Research Fellow; **Aaron Gottschalk**, Predoctoral Researcher; **Selene Swanson**, Research Specialist II; **Su Wu**, Harvard Medical School; **Yang Shi, Ph.D.**, Harvard Medical School; **Michael Washburn, Ph.D.**, Director of Proteomics; **Laurence Florens, Ph.D.**, Managing Director of Proteomics; **Ronald Conaway, Ph.D.**, Investigator; **Joan Conaway, Ph.D.**, Investigator

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

† Co-equal contributors to this publication.

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

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

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-institute.org/labs/WashburnLab.asp.

What Makes Stem Cells Special

Understanding the mechanism of self renewal

SINCE THEIR DISCOVERY MORE THAN 40 YEARS AGO, THE UNIQUE PROPERTIES OF STEM CELLS HAVE CAPTIVATED BIOMEDICAL RESEARCHERS.

Stem cells are undifferentiated, meaning their specific function in the tissues and organs in which they reside has not yet been determined. Unlike normal cells, stem cells can renew themselves. And, they have a limited ability to change themselves into related specialized cell types. For example, a stem cell in the blood can become a red or white blood cell (but not a heart or brain cell).

These qualities of flexibility make stem cells an interesting target for research – research that may one day allow us to coax stem cells to replace the damaged or failing cells that cause a variety of diseases.

The Xie Lab has dedicated the last several years to studying how stem cell self-renewal is controlled and which factors contribute to self-renewal.

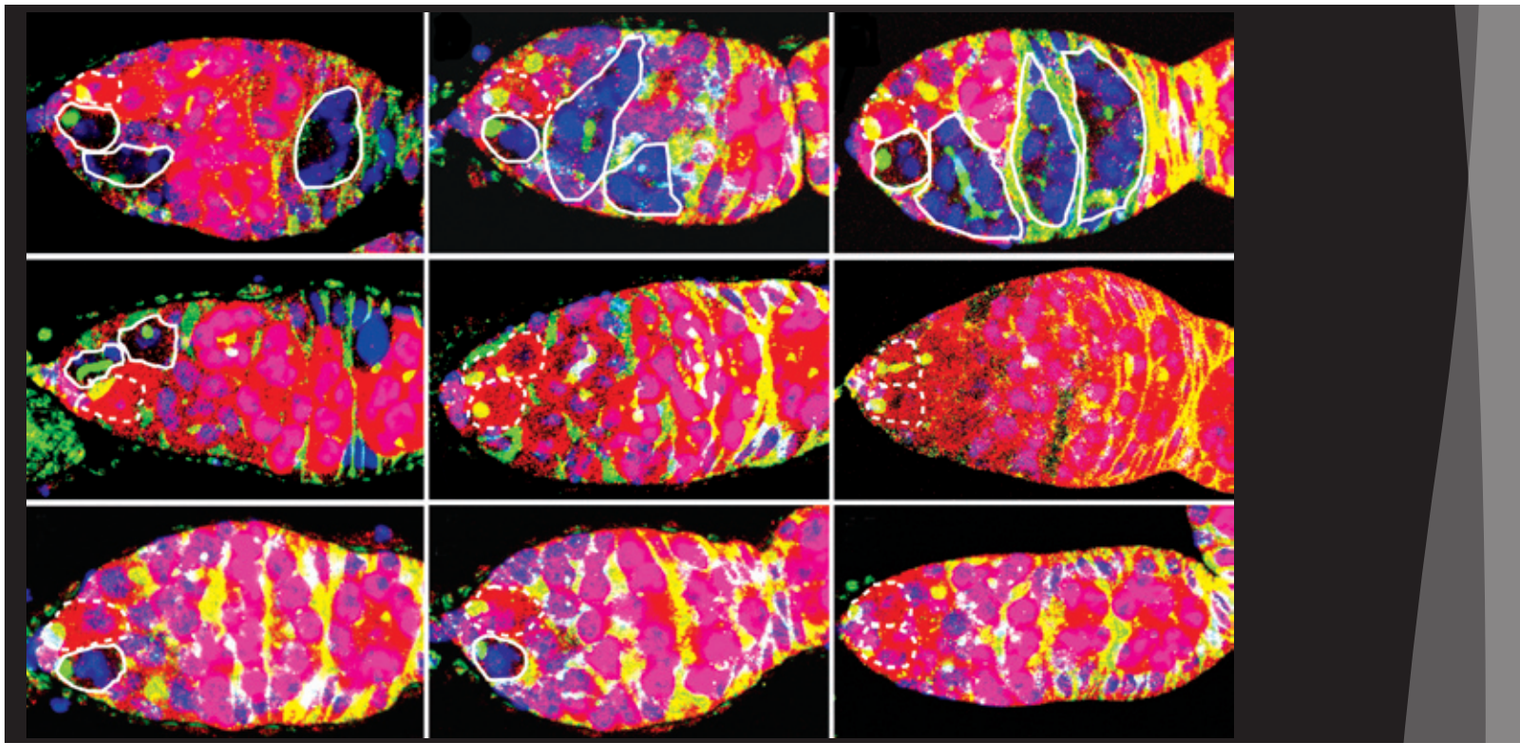
"Stem cells have been heralded as a promising potential treatment for human degenerative diseases," said Ting Xie, Ph.D., Associate Investigator. "One of the barriers to using stem cells to treat disease is the difficulty in expanding stem cell populations to levels that could effectively treat disease. To address this challenge, our team is attempting to understand how stem cell self-renewal is controlled. When we understand that better, we believe we will be able to mimic those properties and expand stem cell populations either in a lab dish for transplantation or directly in the human body to repair damaged tissues and fight disease."

The Xie Lab recently identified a key element for controlling self-renewal. Examining the stem cell populations found in the fruit fly ovary, the team established that a single gene, Dcr-1, which was previously associated with stem cell division, also plays a pivotal role in the self-renewal of ovarian stem cells.

The findings, published in *Current Biology*, established that Dcr-1, which is essential for the production of single-stranded microRNAs that regulate the expression of genes with different functions, controls self-renewal of ovarian stem cells. By eliminating Dcr-1 function from the stem cells, the Xie Lab demonstrated that without Dcr-1 the ovarian stem cells failed to be maintained or to multiply.

"We expect that there are a number of microRNAs involved in the renewal of stem cells," said Dr. Xie. "Now, we will turn our attention toward identifying them and establishing a better understanding of their function in stem cell regulation. These findings have sent us down an exciting path toward a more comprehensive understanding of stem cells and their promise."

Magnified images of fruit fly ovaries demonstrate the difference in ovarian stem cell maintenance when the Dcr -1 gene is turned on (top row) or off (bottom two rows).Without Dcr -1, the stem cell population, shown in blue, is unable to proliferate or to be maintained.



PAPER: Dcr-1 Maintains *Drosophila* Ovarian Stem Cells

JOURNAL: *Current Biology*

ISSUE: March 20, 2007

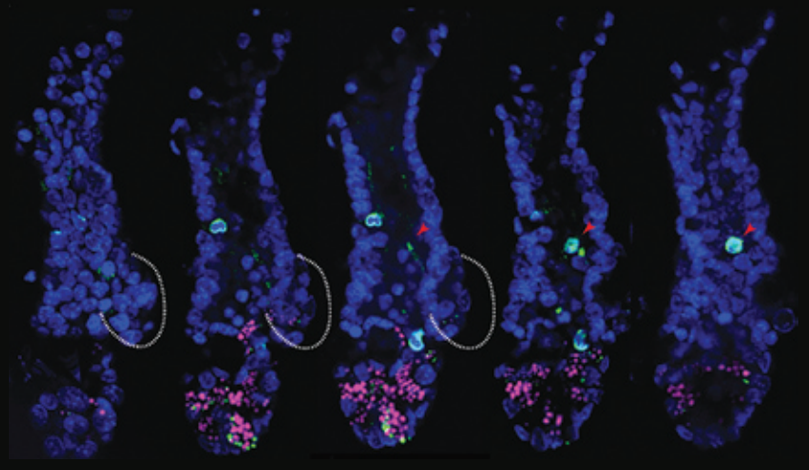
AUTHORS*: **Zhigang Jin, Ph.D.**, Postdoctoral Research Associate; **Ting Xie, Ph.D.**, Associate Investigator

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

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

RETHINKING THE ORIGINS OF CANCER

Exploring how stem cells impact the formation of tumors



A magnification of an intestinal section shows a correlation between the presence of stem cells (marked by red arrows) and the formation of additional crypts, which can lead to tumors.

Though cancer has been studied for decades, scientists continue to make discoveries that revolutionize our most fundamental understanding of the disease. The most recent paradigm shift has come from the theory that cancer is a stem cell-driven disease — that cancer arises from cells that share the properties of self-renewal and developmental flexibility found in adult stem cells.

The Linheng Li Lab has spent several years studying stem cells and making landmark discoveries related to their biology. Most recently, the team turned its attention to the process by which normal stem cells become cancer stem cells and how cancer stem cells initiate the development of tumors.

The work was conducted using intestinal polyposis in mice as a model. Intestinal polyposis is a precancerous, abnormal growth of cells that causes polyps to form in the lining of the intestine. It is associated with an increase in the number of crypts, the depressions in the wall of the intestine where intestinal stem cells reside. Too many crypts in one area of the intestine can lead to the formation of polyps and, eventually, to intestinal cancer.

Mutations in a tumor suppressor gene, PTEN, are associated with Cowden syndrome in humans. Cowden syndrome is an inherited disorder characterized by multiple tumor-like growths and an increased risk of certain forms of cancer. One of the abnormalities of Cowden syndrome is intestinal polyposis.

An abnormal increase in the number of stem cells within the intestinal crypts had been proposed to be the cause of an increase in the number of crypts. To test this theory, the team studied mice in which the PTEN gene had been conditionally knocked out. Deleting the expression of PTEN in both intestinal epithelial (intrinsic changes) and stromal cells (environmental changes) makes the intestine more susceptible to the development of tumors, mimicking the conditions found in human patients with Cowden syndrome.

The work, primarily carried out by Xi He, M.D., Research Specialist II, found that the loss of PTEN led both to an increase in the number of stem cells and to a change in their position. These changes were the hallmarks of the conversion of normal stem cells to cancer stem cells that initiate multiple crypt growth and form polyps.

"We observed a direct relationship between abnormal proliferation of cancer stem cells and the initiation of precancerous growth. The loss of this one tumor-suppressor gene makes normal stem/progenitor cells more susceptible to convert to cancer stem cells," said Linheng Li, Ph.D., Associate Investigator and last author on the *Nature Genetics* publication detailing the results. "We have now gained an insight into a process of how cancer stem cells initiate tumorigenesis in the intestinal system and documented some of the basic features of cancer stem cells. I believe this work will contribute to the development of treatments that target cancer stem cells at both the cellular and molecular levels — a very exciting prospect for the future of cancer therapy."

PAPER: PTEN-deficient intestinal stem cells initiate intestinal polyposis

JOURNAL: *Nature Genetics*

ISSUE: February 2007

AUTHORS*: **Xi He, M.D.**, Research Specialist II; **Tong Yin, Ph.D.**, Postdoctoral Research Associate; **Justin Grindley, Ph.D.**, Senior Research Associate; **Qiang Tian, M.D., Ph.D.**, Institute for Systems Biology; **Toshiro Sato, M.D., Ph.D.**, formerly a Postdoctoral Research Associate; **W. Andy Tao, Ph.D.**, Purdue University; **Ramanarao Dirisina, Ph.D.**, Northwestern University Medical School; **Kimberly Porter-Westpfahl**, Research Technician I; **Mark Hembree**, Laboratory Manager I; **Teri Johnson, Ph.D.**, Managing Director - Histology Facility; **Leanne Wiedemann, Ph.D.**, Staff Scientist; **Terrence Barrett, M.D.**, Northwestern University Medical School; **Leroy Hood, M.D., Ph.D.**, Institute for Systems Biology; **Hong Wu, M.D., Ph.D.**, University of California, Los Angeles, School of Medicine; **Linheng Li, Ph.D.**, Associate Investigator

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

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

Attacking Vitamin A

Identifying mutations that interfere with Vitamin A metabolism to cause birth defects

Vitamin A is found naturally in a variety of foods, including squash, carrots, liver, and eggs. It is also found in high quantities in some pharmaceuticals, including acne medications.

An important nutrient for embryonic development, Vitamin A contributes to proper cell growth; development of the eyes, heart, limbs, and ears; the formation of healthy skin and mucous membranes; resistance to infection; growth of bone; and metabolism of fat.

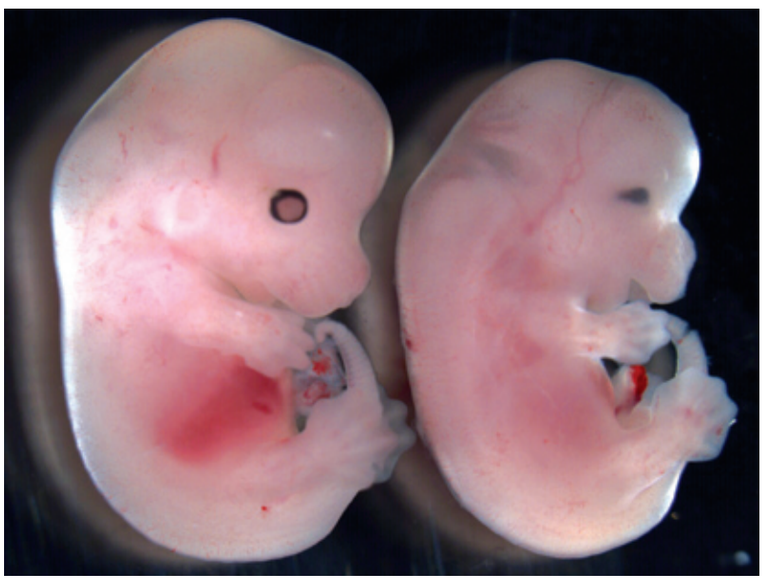
When ingested, the body metabolizes Vitamin A into retinoic acid. Retinoic acid is responsible for regulating the formation and differentiation of tissues and organs. Problems at any stage of the metabolism of Vitamin A can lead to a deficit of retinoic acid and a variety of birth defects.

While working on a project unrelated to Vitamin A, the Trainor Lab discovered a mouse mutant called *trex*, which exhibited head, face, limb, and organ abnormalities so severe they caused the death of the gestating mouse embryo.

"These types of developmental anomalies represent a major focus of our work, so we followed the trail of this mutation." said Paul Trainor, Ph.D., Assistant Investigator and last author on the *Genes and Development* publication of the resulting discovery. "We discovered that the *trex* mouse contained a mutation in a gene called RDH10 that prevented the normal metabolism of Vitamin A to retinoic acid. The disruption of Vitamin A metabolism led to a deficit of retinoic acid and improper embryonic development."

The Trainor Lab's discovery identified RDH10 as a key regulator of Vitamin A metabolism and indicated that mutations to RDH10 may be responsible for a number of congenital birth defects associated with low levels of Vitamin A.

"It is very encouraging to identify new genetic factors that can cause Vitamin A deficiencies," said Dr. Trainor. "Anything that helps us to understand how Vitamin A imbalances occur represents great progress for better understanding birth defects."



A healthy mouse embryo (left) contrasts a malformed mouse embryo of the same age (right). The mutant embryo resulted from improper Vitamin A metabolism caused by mutations to the RDH10 protein.

PAPER: RDH10 is essential for synthesis of embryonic retinoic acid and is required for limb, craniofacial, and organ development

JOURNAL: *Genes and Development*

ISSUE: May 1, 2007

AUTHORS*: **Lisa Sandell, Ph.D.**, Senior Research Associate; **Brian Sanderson**, Laboratory Manager II; **Gennadiy Moiseyev, Ph.D.**, University of Oklahoma Health Sciences Center; **Teri Johnson, Ph.D.**, Managing Director – Histology Facility; **Arcady Mushegian, Ph.D.**, Director of Bioinformatics Center; **Kendra Young**, Research Technician II; **Jean-Philippe Rey**, Research Specialist I; **Jian-xing Ma, M.D., Ph.D.**, University of Oklahoma Health Sciences Center; **Karen Staehling-Hampton, Ph.D.**, Managing Director of Molecular Biology; **Paul Trainor, Ph.D.**, Assistant Investigator

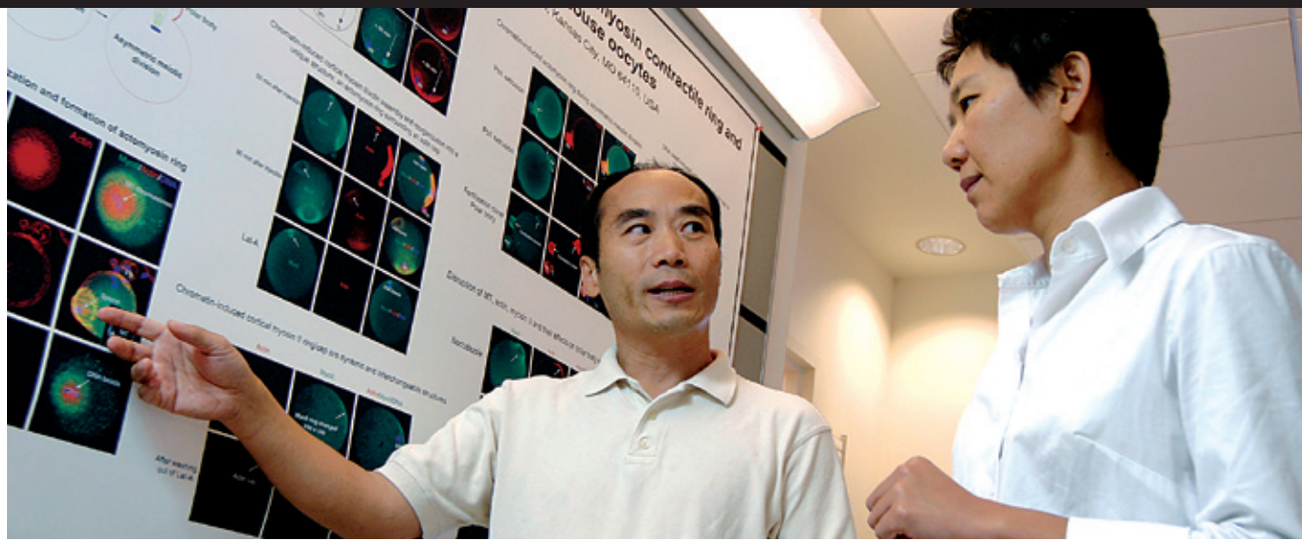
**Authors' primary appointments are with the Stowers Institute for Medical Research unless otherwise noted.*

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

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

Asymmetric Perfection

Understanding how asymmetric cell division is specified during female meiosis



Rong Li (right) and Manqi Deng (left) recently demonstrated the process of mammalian egg maturation through asymmetric cell division in a publication in Developmental Cell.

PAPER: The Ran GTPase Mediates Chromatin Signaling to Control Cortical Polarity during Polar Body Extrusion in Mouse Oocytes

JOURNAL: *Developmental Cell*

ISSUE: February 2007

AUTHORS*: **Manqi Deng, Ph.D.**, Senior Research Associate; **Praveen Suraneni**, Research Technician II; **Richard Schultz, Ph.D.**, University of Pennsylvania; **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-institute.org/labs/RongLiLab.asp.

Female mammals are born with ovaries containing most, if not all, of the eggs they will ever have. But, for one of these eggs to be fertilized by a sperm, it must first complete a maturation process in the ovary known as oogenesis. Incomplete oogenesis can result in infertility and developmental abnormalities.

During oogenesis, an egg goes through a form of asymmetric cell division called female meiosis. Unlike normal cell division, in which cellular material is evenly divided to produce two identical daughter cells, female meiosis involves two successive divisions that produce two different cell types – an egg and so-called polar bodies. After completing meiosis, the egg contains only half the number of chromosomes found in ordinary body cells but retains almost all of the cellular material (cytoplasm), leaving the polar bodies to die and be extruded from the cell. Female meiosis enables the egg to eliminate the excess chromosomes in the polar bodies while retaining the cellular material required to sustain the earliest stages of development.

The Rong Li Lab recently examined this process and discovered a novel pathway involving a chromatin-associated protein known as Ran GTPase that may define the site for polar body extrusion.

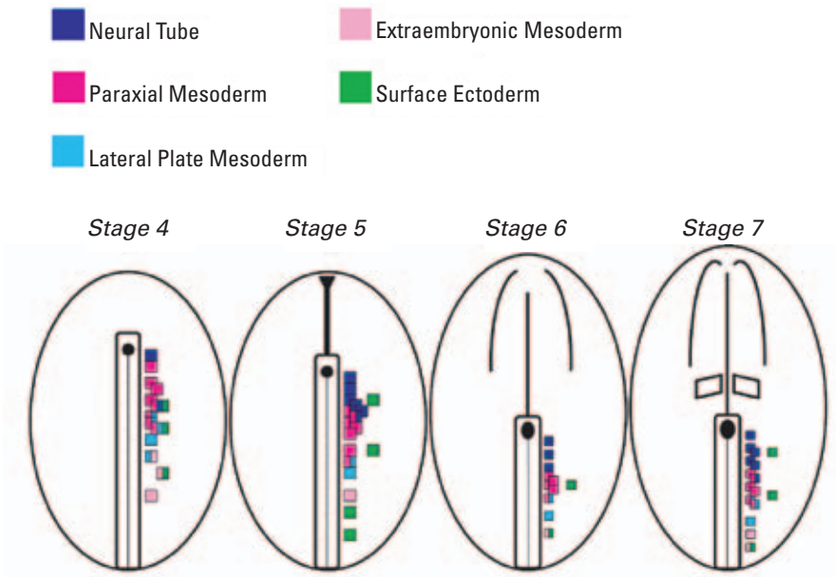
"This study provides important clues to the molecular signals used by the meiotic chromosomes to communicate with the cell membrane in order for the machinery of cell division to be assembled at the right place," said Rong Li, Ph.D., Investigator and last author on the *Developmental Cell* publication reporting the results.

Additionally, the team established that there are significant differences between the process of cell division in germ cells (eggs and sperm) and somatic cells (any ordinary cell in the body). For that reason, female meiosis provides a unique paradigm for understanding the basic strategies that mammalian cells use to complete specialized cell divisions.

"For our team, this is the first step toward understanding the molecular basis of cell division during egg maturation in mammals," said Dr. Li. "It will allow us to use a collection of experimental approaches to achieve a more detailed understanding of this process."

The Ties that Bind Us

Understanding common themes in the spinal formation of higher and lower vertebrates



Fate mapping allows researchers to mark specific cells and monitor where they migrate during embryonic development. Above is an illustration of the epiblast fate mapping during the stages encompassing gastrulation in a chick embryo.

PAPER: Dual mode of paraxial mesoderm formation during chick gastrulation

JOURNAL: *Proceedings of the National Academy of Sciences*

ISSUE: February 20, 2007

AUTHORS*: **Tadahiro Iimura, Ph.D.**, Senior Research Associate; **Xuesong Yang, Ph.D.**, University of Dundee; **Cornelis Weijer, Ph.D.**, University of Dundee; **Olivier Pourquié, Ph.D.**, Investigator

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

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

One way that taxonomists have traditionally classified vertebrates relied on what was known about how their spines form. For many years, it was believed that the spines of higher vertebrates, such as reptiles, birds, and mammals, formed in a fundamentally different way compared to the spines of lower vertebrates, such as fish.

The Pourquié Lab recently published work in *Proceedings of the National Academy of Sciences (PNAS)* showing that a single fundamental process of spine development is consistent across all vertebrates.

The mechanisms of spine formation are the major focus of the Pourquié Lab. The team uses a variety of animal models to understand the complicated process of vertebral column formation and developmental problems that lead to serious disorders like congenital scoliosis.

The team's recent findings focus on the formation of an embryonic tissue known as the paraxial mesoderm. Mesoderm is the name given to the middle layer of the three cell layers that form an early embryo. It is the source of bone, muscle, and connective tissue. The paraxial mesoderm forms along the sides of the primitive precursor of the brain and spinal cord, called the neural tube.

In vertebrates, the earliest stage of embryonic body formation is known as gastrulation. This process includes the formation of the primitive streak – a long band of cells that forms along the axis of an embryo – and the tail bud – a knob of tissue that contributes to the formation of the lower part of the spine. In primitive vertebrates, the process of gastrulation leads directly to the development of the paraxial mesoderm.

Conventional wisdom held that this was not true in higher vertebrates: that the posterior paraxial mesoderm did not form as a result of gastrulation; instead, it resulted from stem cells repositioning the primordium of the spine.

"Working with chick embryos, we were able to demonstrate that both of these mechanisms are actually at work in the formation of the spine in higher vertebrates," said Olivier Pourquié, Ph.D., Investigator and last author on the *PNAS* publication. "It is true that the center of the spine forms from cells present in the primitive streak and tail bud, but it is also true that the lateral parts of the spine are derived from the continuation of the gastrulation process. The surprise here is that the mechanisms responsible for paraxial mesoderm formation are largely consistent across vertebrates."

Stowers Investigators Leave Legacy of Knowledge by Publishing Scientific Books

The life of a Principal Investigator (PI) at the Stowers Institute is far from leisurely. Add up the hours spent at the lab bench, mentoring lab members, collaborating with colleagues, preparing papers for publication, attending scientific meetings, teaching and advising at area universities, writing grant applications, and completing myriad other tasks each day, and it is difficult to imagine how anyone could find the time to write a book.

But during their time at the Stowers Institute, two PIs have done just that. Since joining the Stowers Institute in 2001, Scott Hawley, Ph.D., Investigator, has co-authored three books: one about the basic principles that underlie genetic analysis, an introductory textbook regarding human genetics and the human genome, and an encyclopedic text covering the genetics of his primary research model, *Drosophila*. And this year, Arcady Mushegian, Ph.D., Director of Bioinformatics, published his first book, *Foundations of Comparative Genomics*.

Squeezing in writing time late at night and on weekends, both authors are inspired by the opportunity to communicate about their work in a format that offers a significant amount of flexibility.

"In the primary journal articles, in reviews, and even in opinion papers, one is usually trying to present the evidence and make the most convincing case on a relatively narrow subject in the most concise way," Dr. Mushegian said. "In a book, one can experiment with the writing style and with the choice of the subject matter, and can also pay attention to interesting themes like the history of science or the logic of the scientific argument."

Dr. Hawley has written books both for scientists and for non-scientists, and his inspirations to do so have come from two very different places.

"Many scientists see genetics as a tool, rather than the highly refined, constantly evolving field that it is," said Dr. Hawley. "The goal of my books for scientists is to help researchers who use genetics to understand how geneticists think – to codify a platform on which to build ideas about genetics.

"In writing *The Human Genome, A User's Guide*, the motivation was very different. I wanted to make human genetics accessible to people who haven't ever had a biology course in college. Many families who are affected by a genetic disease come to understand the symptoms and treatments, but there aren't many resources for understanding the origins of the disease. I wanted to change that."

But these authors don't just write for their readers. Their own research benefits from the constant reevaluation of the basic concepts of their work.

"Each time I work on a new book, I have to relearn the fundamentals of the science of genetics," explained Dr. Hawley. "I have to rethink the tools that we use and how we use them, and that encourages me to apply fundamental concepts to the challenging problems in my lab – often with very rewarding results."

Counting published book authors among its faculty also is a boon to the Stowers Institute.

"Leading scientists like Drs. Hawley and Mushegian have much to contribute to their respective fields," said William B. Neaves, Ph.D., President and CEO. "It is important for the maturation of any field for its thought leaders to share their experience and knowledge by recording them in books. It is an enormous undertaking, but by authoring influential books, Drs. Hawley and Mushegian have become Stowers Institute ambassadors to readers around the world."

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

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

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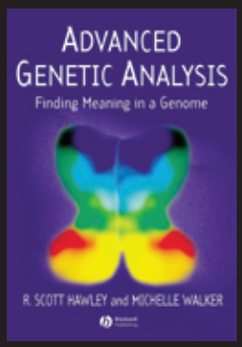

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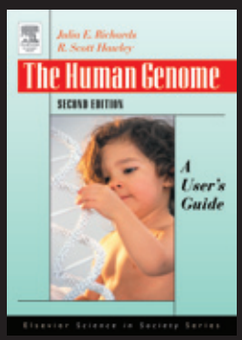

Richards JE, Hawley RS. *The Human Genome: A User's Guide*. 2nd ed. San Diego, CA: Elsevier Academic Press; 2005.

Stowers Institute Welcomes Julia Zeitlinger

Julia Zeitlinger, Ph.D., Assistant Investigator, has established the latest independent research program at the Stowers Institute. She joined the Institute in September 2007 from a postdoctoral fellowship in the lab of Richard Young, Ph.D., at the Whitehead Institute for Biomedical Research at Massachusetts Institute of Technology.

"I have been very impressed with the scientific environment and the strong values of the Institute," said Dr. Zeitlinger. "The people here are smart and do top-notch science in an incredibly supportive and collegial environment. I am very fortunate that my research area is complementary to existing research programs in transcription, development, and genomics. The potential for collaborations is tremendous and I have no doubt that my research will benefit from the scientific environment of the Stowers Institute."

Dr. Zeitlinger's research uses the fruit fly *Drosophila melanogaster* to understand the gene regulatory networks that underlie cellular differentiation. One of the fundamental methods in her research is ChIP-chip technology, a method that detects all genomic binding sites for a particular protein in one experiment. Using this technology, she has demonstrated that gene regulatory networks are often context-dependent and integrated with other networks. She hopes to build predictive models of gene regulation that could help in the diagnosis and treatment of diseased cells in humans.

"We are delighted to welcome Dr. Zeitlinger to the Stowers Institute," said William B. Neaves, Ph.D., President and CEO. "She has already performed outstanding research showing how the genes that control early differentiation of cells are regulated. This topic holds immediate interest for many scientists at the Institute."

"Dr Zeitlinger is a pioneer in investigating the nature of interactions between regulatory proteins and chromosomes," said Robb Krumlauf, Ph.D., Scientific Director. "Her work is providing important insight into the detailed organization of events associated with how cells make decisions in development, differentiation, and disease. She will share many creative ideas with her new colleagues at the Stowers Institute."

Dr. Zeitlinger earned a B.Sc. in Human Biology from King's College London, U.K., and a Ph.D. in Molecular Biology for her work with Dirk Bohmann, Ph.D., at the European Molecular Biology Laboratory in Heidelberg, Germany. She was awarded an undergraduate scholarship from the German National Merit Foundation and a long-term postdoctoral fellowship from the Human Frontier Science Program.

This appointment brings the Stowers Institute to a total of 22 independent research programs in cellular and molecular biology, complemented by three technology centers devoted to bioinformatics, imaging, and proteomics.

Consortium Creates Opportunity for Scoliosis Researchers

The Stowers Institute supports basic biomedical research in its laboratories. Institute scientists use model organisms like yeast, fruit flies, and mice to understand how genetic mutations lead to a variety of diseases and disorders. Research involving animal models is a vital first step in any biomedical research project, but even basic researchers sometimes benefit from access to clinical data and information from real-world patients.

Members of the Pourquié Lab have solved this problem by organizing the International Consortium for Vertebral Anomalies and Scoliosis (ICVAS).

The mission of ICVAS is to better understand the cause of scoliosis and other abnormalities of the spine in humans. In order to achieve this mission, ICVAS is developing a cell repository that will contain samples from patients with scoliosis. The samples in the ICVAS repository will be collected by ICVAS members through blood samples from consenting patients. Blood samples are de-identified and "transformed" into a cell line, which can divide and grow indefinitely, providing a continual source of DNA for research by ICVAS members.

In addition, ICVAS has also created a database that contains anonymous clinical data on the patients who have submitted samples. The database allows members to determine which patient samples they would like to study. It may also eventually be used to study trends in the clinical features and outcomes of patients with scoliosis.

Oliver Pourquié, Ph.D., Investigator, is the President of ICVAS. Members of his lab including Holly Welsh, Certified Genetic Counselor, and Olivier Tassy, Ph.D., Howard Hughes Medical Institute Research Specialist II, have been integral in developing the consortium and the database.

"The system provides an efficient method for basic researchers to gain access to clinical data; for clinical researchers to acquire more diverse data; and for patients to contribute to the research that will impact our understanding of scoliosis in important ways," said Dr. Pourquié. "The founding members of ICVAS have come together to address a frustrating challenge in an innovative way. I believe the consortium will allow each of us to advance our research significantly."

Olivier Pourquié (seated), Holly Welsh (right), and Olivier Tassy (left) have worked with colleagues around the world to establish the International Consortium for Vertebral Anomalies and Scoliosis.

ICVAS members include physicians and researchers at institutions around the world. Membership in ICVAS is limited to researchers and clinicians with an interest in studying or treating vertebral malformations. In order to become a member, clinicians are obligated to contribute samples from patients with vertebral anomalies or skeletal defects, and basic researchers are required to share novel research ideas. Together, these two types of members provide the samples and the scientific direction necessary to achieve the mission of the consortium.

More information about ICVAS is available at www.icvas.org.

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

March of Dimes Recognizes Two Additional Stowers Researchers

The March of Dimes named two additional Stowers researchers to the ranks of Basil O'Connor Starter Scholar award recipients. Sue Jaspersen, Ph.D., and Kausik Si, Ph.D., Assistant Investigators, each were awarded $150,000 over two years to support research projects that offer insight into the cause of human birth defects. They are the fifth and sixth Stowers researchers to receive the honor.

Dr. Jaspersen joined the Stowers Institute from the University of Colorado at Boulder where she was a Helen Hay Whitney Fellow in the laboratory of Dr. Mark Winey. With this funding, she is studying the role of a group of proteins, called SUN proteins, in chromosome positioning and transcriptional regulation. Chromosome positioning has powerful effects on the regulation and timing of gene expression as well as the epigenetic control of transcription programs, all of which are critical to normal human development and the prevention of birth defects.

Dr. Si joined the Stowers Institute from the Columbia University Center for Neurobiology and Behavior where he conducted postdoctoral research with Dr. Eric Kandel, winner of the 2000 Nobel Prize in Physiology or Medicine. Dr. Si's laboratory concentrates on information storage and memory retention in the brain. A better understanding of this process may lead to insight about the basis of birth defects that affect brain function.

"The March of Dimes' recognition of the potential of early career scientists at the Stowers Institute to contribute to the field of birth defects research is gratifying," said William B. Neaves, Ph.D., President and CEO. "We recruit researchers like Drs. Jaspersen and Si because we believe their work will be highly relevant to improving human health. We are pleased to have organizations like the March of Dimes join us in expressing confidence in these young scientists."

The March of Dimes named Kausik Si (left) and Sue Jaspersen (right) Basil O'Connor Starter Scholars.

Sue Jaspersen, 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-institute.org/labs/JaspersenLab.asp.

Kausik Si, Ph.D., Assistant Investigator, also is an Assistant Professor in the Department of Physiology at The University of Kansas School of Medicine. Learn more about his work at www.stowers-institute.org/labs/SiLab.asp.

Susan G. Komen for the Cure Awards First Stowers Grant

Chunying Du became the first Stowers Institute researcher to receive funding from Susan G. Komen for the Cure.

Susan G. Komen for the Cure awarded Chunying Du, Ph.D., Assistant Investigator, a grant in the amount of $300,000 over three years. The award will support her research into the possibility of treating chemotherapy-resistant breast cancer by reducing the level of a protein (BRUCE) that is believed to contribute to chemotherapy-resistance in cancerous cells.

Susan G. Komen for the Cure awarded nearly $82 million in scientific research grants this year. Dr. Du is the first Stowers researcher the organization has funded.

"I am honored to receive this grant from Susan G. Komen for the Cure," said Dr. Du. "This funding will allow my lab to give special attention to the exciting possibility that reducing the levels of the BRUCE protein will improve the effectiveness of chemotherapy in cases of breast cancer that demonstrate a resistance to treatment."

Dr. Du joined the Stowers Institute from a Howard Hughes Medical Institute postdoctoral fellowship in the lab of Dr. Xiaodong Wang at the University of Texas Southwestern Medical Center at Dallas. She has a Ph.D. in molecular, cellular, and developmental biology from Iowa State University.

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-institute.org/labs/DuLab.asp.

2007 Stowers Scholars

2007 STOWERS SCHOLARS:
(back row from left) Stephen Gradwohl, Steven Scoville, Timothy Hutson, *(middle row from left)* Nicole Schweppe, Jamie Bernard, Jonathan Scrafford, *(front row)* Laura Schaefer, Bethany Harris.

Each summer, college students from around the country apply to participate in the Stowers Scholars Program. This year, eight Stowers Scholars were selected from among 73 applicants. These students conduct research at the Institute under the supervision of Stowers researchers and conclude their summer experience with a presentation of their findings. To learn more about the Stowers Scholars program, visit www.stowers-institute.org/ScientistsSought/training/scholarsprogram.asp.

Student Scholar	Lab	School	Project
Jamie Bernard	Microarray	University of Kansas	"Gene Synthesis, a Synthetic Approach"
Stephen Gradwohl	Yu Lab	Washington University	"Olfactometer Odorants: Delivery Analysis and Characterization"
Bethany Harris	Proteomics	University of Kansas	"Proteomic Analysis of RNAPII-Associated Proteins"
Timothy Hutson	Shilatifard Lab	Saint Louis University	"Detecting Cross-Talk Between Histone Modifications"
Laura Schaefer	Rong Li Lab	William Jewell College	"Screen for Mutations that Affect the Localization of a Polyamine Transporter in *Saccharomyces cerevisiae*"
Nicole Schweppe	Hawley Lab	Rockhurst University	"Spontaneous Nondisjunction in Natural Populations of *Drosophila*"
Steven Scoville	Cytometry	Brigham Young University	"Highly Purified Stem Cell Identification by Microarray and QPCR"
Jonathan Scrafford	Baumann Lab	Stanford University	"Roles of Rap1 in Non-Homologous End-Joining Inhibition at Telomeres"

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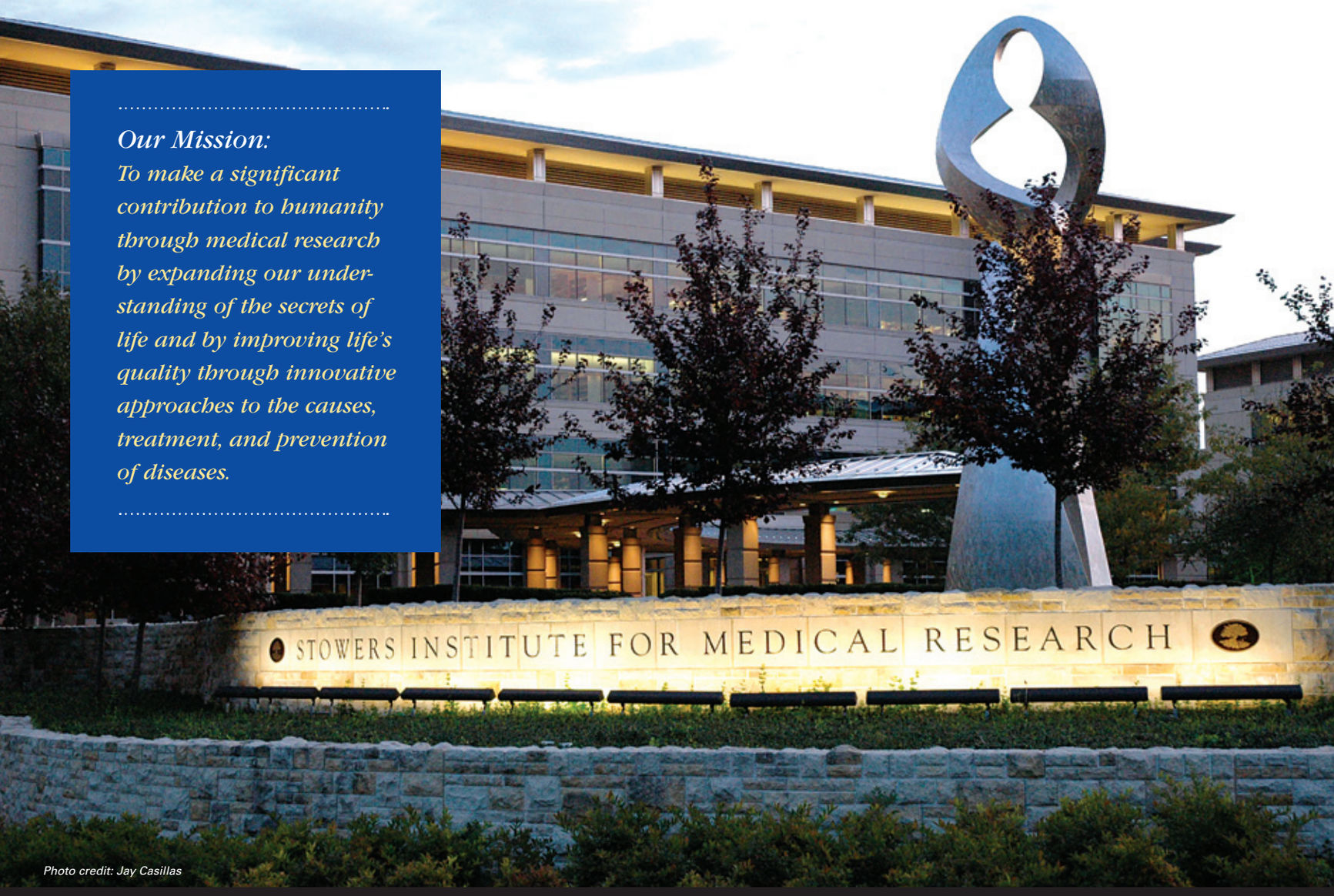

Our Mission:
To make a significant contribution to humanity through medical research by expanding our understanding of the secrets of life and by improving life's quality through innovative approaches to the causes, treatment, and prevention of diseases.

Photo credit: Jay Casillas

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FOR MEDICAL RESEARCH

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