FALL 2008

Stowers REPORT

NEWS AND INSIGHT FROM
THE STOWERS INSTITUTE
FOR MEDICAL RESEARCH

STOWERS RESEARCH UNRAVELS THE MYSTERIES OF THE FORMATION OF THE SPINE. PAGE 2

FALL 2008

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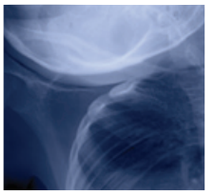

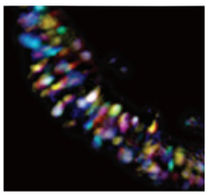

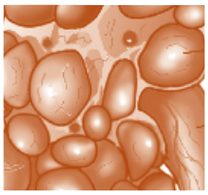

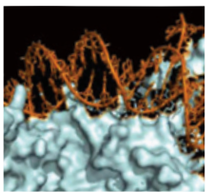

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Basic Research to Improve Human Health

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

All of us who have the privilege of working here every day believe you will appreciate the Institute's progress toward Jim and Virginia Stowers' goal of improving human health through basic research of the highest quality.

Jim and Virginia Stowers have faith in the power of basic research to improve human health. They know how ultimate solutions come from meticulous probing of normal molecular and cellular processes in animal models, building over many years of hard work a detailed understanding of what can go wrong to cause disease and how to prevent it. When asked years ago why they planned to give their fortune to the Stowers Institute, Jim and Virginia answered, "So that our grandchildren will have better options if diagnosed with a serious illness decades from now." This issue of the *Stowers Report* describes more discoveries emerging from the Institute's labs and the hope they offer for everyone's children and grandchildren.

Chronic kidney failure imposes a dreadful burden on patients whose lives depend on regular dialysis, and the most common cause is a gene-based illness known as polycystic kidney disease (PKD). Until a few months ago, no one expected the Rong Li Lab, a team of scientists focused on understanding the regulation of cell division, to discover a potential pharmacological means of preventing PKD. In fact, Rong and her team have shown that a commonly prescribed treatment for rheumatoid arthritis can prevent cyst formation in the kidneys of mice carrying a gene mutation that would otherwise cause the disease. If the drug exerts the same influence in people with PKD, clinical application could be accelerated by its proven safety in arthritic patients (see page 8).

Using additional funds from his appointment as an investigator of the Howard Hughes Medical Institute three years ago, Olivier Pourquié and his research team began searching for mutated human genes that cause malformations of the spine. Olivier expected that genes controlling spinal development in chick and mouse embryos would play similar roles in human development — a reasonable possibility due to the conservation of genes across species as revealed in genome sequences of laboratory animals and human beings. The search led to the discovery of mutated genes in children with severe scoliosis, an important step in relating basic research with animal models to the genetics of human developmental anomalies (see page 2).

Because of the complexity of the brain compared to other organs, deep insight into neurological diseases such as Alzheimer's and Parkinson's depends heavily on basic laboratory research aimed at revealing the details of normal brain functions. Earlier this year, the Yu Lab completed a landmark study of how the mouse brain processes and integrates sensory information. The Yu team showed how a small number of dedicated neurons processes olfactory information to discern gender while combinatorial action of a larger number of neurons determines individual identity. Although people depend far less on olfactory information than mice, the principles of how the brain handles sensory information are likely to be similar in both (see page 6).

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.

Among the most medically relevant research at the Institute is Ali Shilatifard's study of how gene expression is normally regulated and how mistakes in gene regulation cause cancer. Gene expression depends on transcription of information encoded in DNA, and the Shilatifard Lab recently showed that strategic pauses in the process are controlled by an elongation factor that interrupts the synthesis of the transcript, messenger RNA. Defects in the molecular machinery responsible for DNA transcription are known to cause some leukemias, and the Shilatifard team strives to understand the details so that more effective therapies can be found (see page 10).

As you read this issue of the *Stowers Report*, I hope you enjoy learning more about what's happening in laboratories at the Stowers Institute. All of us who have the privilege of working here every day believe you will appreciate the Institute's progress toward Jim and Virginia Stowers' goal of improving human health through basic research of the highest quality.

BIT BY BIT

Utilizing Diverse Methodologies to Understand Vertebral Formation and Congenital Spinal Abnormalities

When the Stowers Institute set out to recruit Olivier Pourquié, Ph.D., Investigator, from the Developmental Biology Institute of Marseille, France, colleagues around the United States warned that it couldn't be done — that Dr. Pourquié would never leave his native France. They were wrong.

Impressed by the research opportunities at the Stowers Institute and the quality of life in Kansas City, Dr. Pourquié established his laboratory at the Stowers Institute in 2002. From the very beginning, his work proceeded quickly as his team published one discovery after another – each shedding new light on the poorly understood process of the formation of the early spine. In 2005, Dr. Pourquié received one of the most prestigious designations in basic biomedical research when he was awarded an appointment with the Howard Hughes Medical Institute (HHMI).

Today, generously funded by the Stowers Institute and HHMI, and supported by a team of more than 20 talented lab members, Dr. Pourquié takes advantage of a broad range of tools to help understand precisely how the early spine is formed and why that process sometimes goes awry. In recent months, the Pourquié Lab has collaborated with scientists from around the world to use new tools and analytical methods to make exciting advancements in his work.

"When studying a system as complicated as the spine, we must constantly push ourselves to find new tools and new perspectives," said Dr. Pourquié. "We are very fortunate to be doing this work at the Stowers Institute where collaboration is embraced and we have the freedom to pursue new ideas – even if they are considered 'risky' within the field. Being able to be creative and to take some risks in our research has led us to very exciting discoveries. There is no better way to do science."

Knowing When to Say When

What makes a snake a snake? In part, it is the length of its spine, made up of approximately 300 vertebrae. All vertebrate embryos form in a head-to-tail manner. As the body elongates over time, vertebral precursors called somites are formed from the presomitic mesoderm, the middle layer of the three cell layers that form an early embryo. In previous work, the Pourquié Lab established that the periodicity of somite formation is controlled by a cellular signaling system called the "clock and wavefront."

Recently, the team turned its attention to identifying how the body regulates the clock and wavefront system to ensure that the appropriate number of vertebrae is formed. Their findings appeared in the July 17 issue of *Nature*.

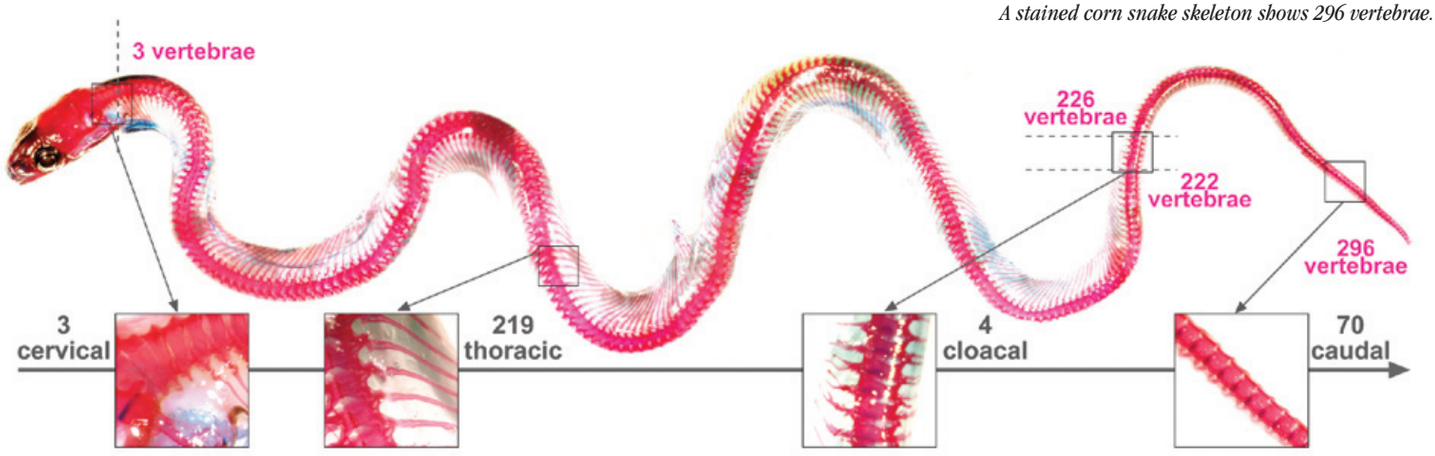
"Virtually nothing was known about this process," said Dr. Pourquié, "so we set out to understand how these very important steps in embryonic development are regulated. It is important because any error in this process can lead to significant spinal malformations."

As the signaling molecules of the "clock" build up and dissipate in rhythmic oscillations, new somites are formed. It is the job of the "wavefront," a second set of signaling molecules, to move the somites along the developing spine. The spine lengthens, and with it, so does the presomitic mesoderm – but only for a limited period of time. At a set point, the presomitic mesoderm begins to shrink and continues to shrink until there is too little remaining to create any more somites.

Although the clock and wavefront mechanism produces nearly 300 somites in snakes, mice form just 65, and humans just 33. How can the same process have such varied results?

"What influences the number of somites in each species is the rate of somite formation," explained Dr. Pourquié. "In snake embryos, somites form much more quickly than in mice or humans, relative to the developmental pace. As a result, there are more somites, but they are smaller."

A stained corn snake skeleton shows 296 vertebrae.



Gomez et al. Control of Segment Number in Vertebrate Embryos. Nature. *2008;454:335-339*

Understanding the mechanism of vertebral column development in animals offers insight into how the spine forms in humans. In the long term, a better understanding of the process may aid in the prevention or treatment of disorders like congenital scoliosis or caudal agenesis. In the short term, the Pourquié Lab has satisfied the curiosity of those who have wondered how the body knows when to stop making vertebrae.

Bridging the Clinical Divide

For many years, the Pourquié Lab studied the process of vertebral formation and vertebral anomalies exclusively in animal models like chicks, mice, and snakes. But there is a limit to what animals can tell us about human health. Recently, the team established a consortium of spinal researchers to facilitate collaboration with clinical colleagues around the world. Among consortium members, physician researchers share blood samples from patients being treated for spinal disorders. Basic researchers like Dr. Pourquié can analyze those samples to determine if their findings in animal models hold true for human health.

When the process of spinal formation in humans goes wrong, one of the consequences can be a rare genetic disorder called Spondylothoracic Dysostosis. Also known as Jarcho-Levin Syndrome, it is characterized by distinctive malformations of the vertebrae and ribs, respiratory problems, and other abnormalities. Infants born with

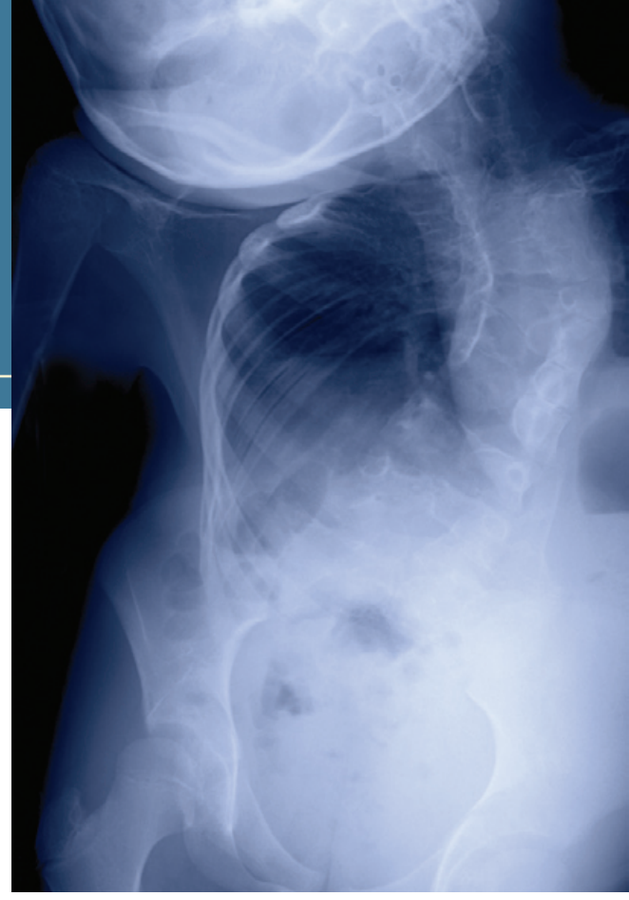
PAPER: Control of Segment Number in Vertebrate Embryos

JOURNAL: *Nature*

ISSUE: July 17, 2008

AUTHORS*: **Céline Gomez, Ph.D.**, formerly a Postdoctoral Research Associate; **Ertuğrul Özbudak, Ph.D.**, Postdoctoral Research Associate; **Joshua Wunderlich**, Cytometry Research Technician III; **Diana Baumann**, Managing Director; **Julian Lewis, Ph.D.**, Vertebrate Development Laboratory, Cancer Research U.K.; **Oliver Pourquié, Ph.D.**, Investigator

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



An antero-posterior view of rib and vertebral abnormalities in a patient with Spondylothoracic Dysostosis.

PAPER: Mutations in the MESP2 Gene Cause Spondylothoracic Dysostosis/Jarcho-Levin Syndrome

JOURNAL: *The American Journal of Human Genetics*

ISSUE: June 2008

AUTHORS*: **Alberto Cornier†, M.D.**, Department of Molecular Medicine, La Concepción Hospital, and Department of Biochemistry, Ponce School of Medicine; **Karen Staehling-Hampton†, Ph.D.**, Managing Director, Molecular Biology; **Kym Delventhal**, Laboratory Manager I; **Yumiko Saga, Ph.D.**, Division of Mammalian Development, National Institute of Genetics; **Jean-Francois Caubet, M.D.**, Department of Orthopedic Surgery, Children's Hospital Boston; **Nobuo Sasaki, M.D.**, Division of Mammalian Development, National Institute of Genetics; **Sian Ellard, Ph.D., M.R.C.Path**, Department of Molecular Genetics, Royal Devon and Exeter Hospital; **Elizabeth Young, M.D.**, Department of Molecular Genetics, Royal Devon and Exeter Hospital; **Norman Ramirez, M.D.**, Department of Orthopedics, La Concepción Hospital; **Simon Carlo, M.D.**, Department of Molecular Medicine, La Concepción Hospital, and Department of Genetics, San Juan Bautista School of Medicine; **Jose Torres, M.D.**, Department of Biochemistry, Ponce School of Medicine; **John Emans, M.D.**, Department of Orthopedic Surgery, Children's Hospital Boston; **Peter Turnpenny, M.D.**, Clinical Genetics Department, Royal Devon and Exeter Hospital; **Olivier Pourquié, Ph.D.**, Investigator

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

†Co-equal contributors to this publication.

Spondylothoracic Dysostosis have short necks and limited neck motion, and they are short in stature. Spondylothoracic Dysostosis was first characterized in the Puerto Rican population 70 years ago and is especially prevalent in people of Puerto Rican ethnicity.

Dr. Pourquié recently collaborated with the Institute's Molecular Biology Facility and clinical colleagues around the world to sequence five genes thought to be involved in various congenital vertebral abnormalities. Working with DNA samples from 31 patients at Boston Children's Hospital, the team discovered a single patient with a mutation in the MESP2 gene that completely disrupted the function of the gene and seemed to be implicated in the patient's case of Spondylothoracic Dysostosis.

Cornier et al. Mutations in the MESP2 Gene Cause Spondylothoracic Dysostosis/Jarcho-Levin Syndrome. Am J Hum Genet. *2008;82:1334-1341*

Following that lead, the team sequenced additional DNA samples from patients of Puerto Rican ethnicity with Spondylothoracic Dysostosis and discovered the same mutation in the MESP2 gene. Identification of the gene carrying the Spondylothoracic Dysostosis mutation is particularly important for people who have a family history of the disease. The mutation can be detected by a simple test, allowing individuals to determine whether they are at risk of passing the disorder on to future generations. The work appeared in the June issue of the *American Journal of Human Genetics*.

"For many years, my team has worked with animal models, studying the intricacies of spinal formation in chicks or mice," said Dr. Pourquié. "But all the while, we've been building toward a better understanding of human health. It is very rewarding to have an opportunity to examine human cells and to make meaningful contributions to the clinical understanding of serious spinal abnormalities."

Continuing their collaborations with the Molecular Biology Facility and with colleagues outside of the Institute, the Pourquié Lab will continue sequencing genes from patients with congenital vertebral anomalies in an effort to pinpoint causal mutations. Additionally, they plan to sequence MESP2 in a larger collection of DNA samples from Puerto Rico to determine the carrier frequency of the mutation in the general Puerto Rican population.

The Power of Numbers

When it comes to drawing conclusions about how the early spine is formed, the Pourquié Lab has another trick up its sleeve – computational biology. Working with the Institute's Bioinformatics Center and outside colleagues who conduct research at the intersection of mathematics and biology, the Pourquié Lab led the effort to apply a novel mathematical approach to large-scale data analysis of the formation of the spine in the early embryo. Their results appeared in the journal *PLoS ONE*.

Analyzing data previously generated by the Pourquié Lab (Dequeant et al., *Science* 2006), the team developed a sophisticated mathematical model that pointed toward a role for unexpected genes in the segmentation clock. The project was funded by the

Fundamental Laws of Biology Program sponsored by the Defense Advanced Research Project Agency, an initiative to engage mathematicians, physicists, and biologists to evaluate novel mathematical approaches for large-scale analysis of biological data.

To confirm the mathematical results, the team conducted subsequent experiments with the newly identified genes and found that they did, in fact, play a role in the function of the segmentation clock.

"The computational approach of this collaboration allowed us to find another layer of information within previously collected data," said Dr. Pourquié. "It is a wonderful complement to our other methods because it helps us to identify rich targets for fruitful experimentation. This was a particularly rewarding collaboration."

PAPER: Comparison of Pattern Detection Methods in Microarray Time Series of the Segmentation Clock

JOURNAL: *PLoS ONE*

ISSUE: August 6, 2008

AUTHORS*: **Mary-Lee Dequeant, Ph.D.**, Postdoctoral Research Associate; **Sebastian Ahnert, Ph.D.**, Cavendish Laboratory; **Herbert Edelsbrunner, Ph.D.**, Duke University and Geomagic; **Thomas Fink, Ph.D.**, National Center for Scientific Research and Curie Institute; **Earl Glynn**, Scientific Programmer; **Gaye Hattem**, Programmer Analyst II; **Andrzej Kudlicki, Ph.D.**, University of Texas Southwestern Medical Center; **Yuriy Mileyko, Ph.D.**, Duke University; **Jason Morton, Ph.D.**, University of California Berkeley; **Arcady Mushegian, Ph.D.**, Director of Bioinformatics Center; **Lior Pachter, Ph.D.**, University of California Berkeley; **Maga Rowicka, Ph.D.**, University of Texas Southwestern Medical Center; **Bernd Sturmfels, Ph.D.**, University of California Berkeley; **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 and Cell Biology at The University of Kansas School of Medicine. Learn more about his work at www.stowers-institute.org/labs/PourquieLab.asp.

Julia Zeitlinger

JULIA ZEITLINGER NAMED PEW SCHOLAR

Each year, the Pew Charitable Trust names a class of 15 Pew Scholars in Biomedical Sciences. The prestigious appointment is based on performance during education and training and demonstration of outstanding promise as a contributor in science relevant to human health. The Pew Charitable Trusts seek particularly creative and innovative approaches and encourage risk-taking in research. Each year, Pew Scholars meet to present their research and engage in scientific collaboration and exchange with other Pew Scholars.

This year, Julia Zeitlinger, Ph.D., Assistant Investigator, was selected for the honor, which carries an award of $240,000 over four years.

Dr. Zeitlinger joined the Stowers Institute in September 2007 from a postdoctoral fellowship in the lab of Richard Young, Ph.D., at the Whitehead Institute for Biomedical Research.

Her research uses the fruit fly *Drosophila melanogaster* to understand the gene regulatory networks that underlie cellular differentiation. One of the key 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 treatment of human disease.

"I am very grateful to be selected for this award," said Dr. Zeitlinger. "In addition to the financial support, the Pew Scholars Program will help stimulate my research by providing regular opportunities to meet with some of the most creative scientists in this country."

DO I KNOW YOU?

PHEROMONES AND INTRASPECIES RECOGNITION

Perfume makers would have you believe that pheromones hold the key to attracting a mate. And that may be true — if you are a mouse.

Many mammals rely on these chemical signals to communicate with other members of their species about their sexual, social, and reproductive status. New research from the Stowers Institute suggests some intriguing ways that members of a species identify different signals to recognize one another.

Pheromones and the olfactory organ that detects them – the vomeronasal organ (VNO) – are of special interest to Ron Yu, Ph.D., Assistant Investigator, and researchers in his lab who study the brain's methods of processing sensory information. Among the team's topics of interest is how pheromones trigger innate behaviors such as mating rituals, territorial aggression, and neuroendocrine responses.

"The 'big picture' for our work is trying to understand how the nervous system processes sensory information and how that information generates meaningful perceptions and behaviors," said Dr. Yu. "We can learn a lot about these systems by studying pheromone processing in mice because mice integrate sensory information from pheromones in a robust and stereotyped way."

In April, the Yu Lab published in *Science* the results of large-scale imaging experiments that help to explain how pheromone information is processed by the sensory system.

The work was made possible by a newly developed line of transgenic mice that express the genetic calcium indicator G-CaMP2 in the lab. Calcium indicators are molecules that respond differently to light when calcium levels increase. Since the activation of pheromone receptors elevates the calcium level inside the cell, the new strain of mice allowed the team to visually track pheromone reception with significantly improved sensitivity and resolution.

Using highly sophisticated imaging techniques, the team characterized two distinct pheromone processing functions at work: the use of a small number of dedicated neurons to communicate gender; and the combinatorial action of a larger number of neurons to communicate individual identity.

The team estimated that information about gender is encoded by just ten of the VNO's 250 dedicated receptors, which function explicitly to detect sex-specific cues in the urine. Interestingly, identification of a male requires use of just two to three receptors while identification of a female requires more. The difference in the number of gender-specific cells may reflect the more complex physiology and hormonal regulation of female animals.

Conversely, information about identity, which allows members of a species to recognize one another, is encoded by the combinatorial activation of VNO neurons – the cumulative effect of signals from multiple neurons processed together. The process is a bit like the human ability to recognize an acquaintance by assimilating information from a number of cues, including height, hair color, voice, etc.

"The mammalian pheromones are a complex mixture of molecules about which we understand little. Our understanding could benefit a lot by studying how natural pheromones activate the VNO at the systems level," said Dr. Yu. "We got a glimpse of how social information is recognized by the sensory system – in this case, through the VNO. Our findings reveal an extraordinary richness of pheromone cues, along with some striking features of pheromone representation in the VNO. Important social information such as gender is likely processed by a dedicated neural circuit, and, based on our results, we will be able to map out this

A slice of the vomeronasal organ (VNO) expressing the calcium sensor, G-CaMP2, was exposed to urine samples from individual mice of different sex and strain. Individual urine elicited distinct patterns of activation of the VNO neurons. The patterns of activation by six different urine samples are color-coded and shown in this merged picture.

He et al. Encoding Gender and Individual Information in the Mouse Vomeronasal Organ. Science. *2008;320:535-538*

circuit. In this sense, our current work provides the basis for our future research into the mechanism of sensory processing and our efforts to shed light on how social signals are passed between animals."

Although humans lack the VNO that processes pheromones, understanding how the VNO integrates pheromone information may shed light on how humans integrate information from our senses. The neural circuitry in the human brain underlies complex human behaviors. Proper formation of the neural circuitry and seamless processing of sensory information are essential for mental health. Alterations in either can lead to devastating psychiatric and neurological diseases such as schizophrenia, autism, Parkinson's disease, and Alzheimer's disease. Using animal models to dissect the neural circuitry and to reveal the molecular and cellular mechanism behind these important functions of the brain may lead to a better understanding of how the brain works and to possible treatments for neurological diseases.

"Dr. Yu joined the Institute just over three years ago from a postdoctoral fellowship at Columbia University," said William B. Neaves, Ph.D., President and CEO. "It is gratifying to see his work lead to a publication in a journal as rigorous and prestigious as *Science* so early in his career. The caliber of his work is precisely what Jim and Virginia Stowers intended when they founded the Stowers Institute with the mission of conducting the highest quality basic research with the potential to improve human health."

PAPER: Encoding Gender and Individual Information in the Mouse Vomeronasal Organ
JOURNAL: *Science*

ISSUE: April 25, 2008

AUTHORS*: **Jie He, Ph.D.**, Postdoctoral Research Associate; **Limei Ma, Ph.D.**, Research Specialist II; **SangSeong Kim, Ph.D.**, Postdoctoral Research Associate; **Junichi Nakai, M.D.**, Laboratory for Memory and Learning, RIKEN Brain Science Institute; **Ron Yu, Ph.D.**, Assistant Investigator

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

A COMMON DISEASE YIELDS TO AN UNCOMMON ADVANCE

Basic Research Opens the Door to a Long-Sought Treatment for a Kidney Disease

POLYCYSTIC KIDNEY DISEASE (PKD) IS ONE OF THE WORLD'S MOST COMMON LIFE-THREATENING GENETIC DISEASES, AFFECTING MORE THAN 12 MILLION PEOPLE WORLDWIDE.

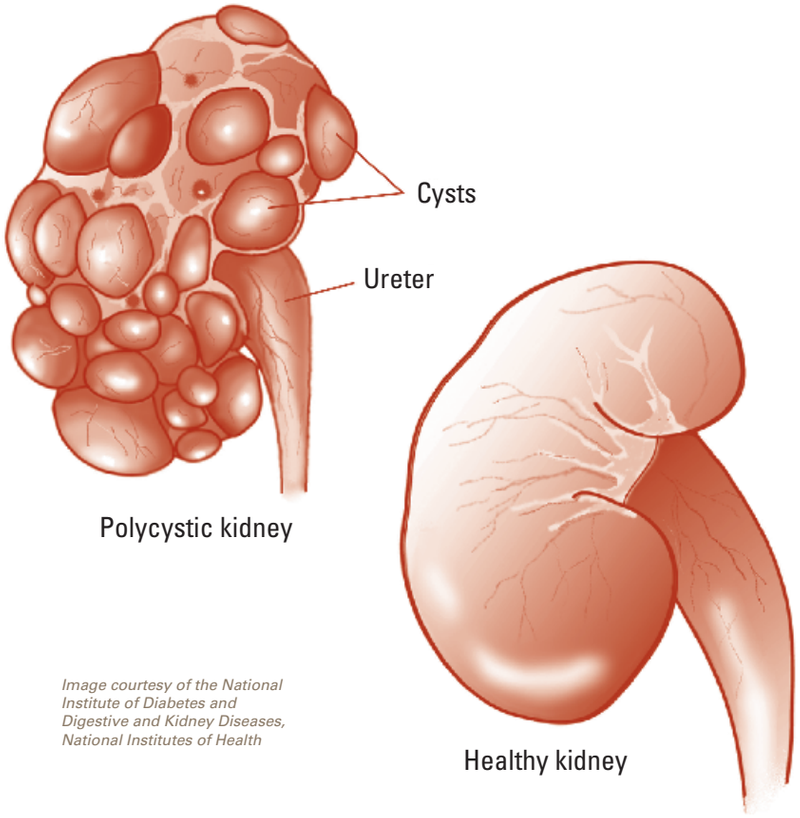

Image courtesy of the National Institute of Diabetes and Digestive and Kidney Diseases, National Institutes of Health

A polycystic kidney (left) is overtaken by fluid-filled cysts.

PKD causes fluid-filled cysts to grow in the kidneys. Over decades, these cysts multiply and grow and result in pain, urinary tract infections, and ultimately kidney failure. Despite much research, dialysis and kidney transplantation are the only treatments currently available to patients suffering from this disease. The most common form of the disease is called Autosomal Dominant PKD (ADPKD). In families where one parent suffers from ADPKD, each child has a 50 percent chance of inheriting the disease.

ADPKD is caused by mutations to the PKD1 or PKD2 genes, which encode proteins called polycystins. Evidence suggests that polycystins normally work together to act as a molecular sensor of the fluid flow outside of kidney cells. In ADPKD, one of the polycystins is mutated so that the sensor is partially inactivated. It is thought that the malfunctioning sensor leads to aberrant cellular changes that ultimately result in the formation of the kidney cysts.

Recently, the Stowers Institute's Rong Li Lab made a critical discovery related to ADPKD. Working in mice, they established that Tumor Necrosis Factor-α (TNF-α), a signaling protein that triggers inflammation, can disrupt the delivery of one of the polycystin proteins to the cell surface where it normally acts. By further reducing the effectiveness of the already malfunctioning sensor in ADPKD patients, TNF-α signaling promotes the formation of cysts. This new insight into the origin of ADPKD cysts is an important advancement in its own right, but it is especially exciting because it may open the door to a treatment option for people suffering from ADPKD.

In the same publication, the team established that treatment with a drug called entanercept (tradename: Enbrel®) prevented the formation of cysts in a mouse model of ADPKD. Etanercept is a recombinant protein drug that binds to and inhibits TNF-α and has been approved for the treatment of inflammatory diseases like rheumatoid arthritis, psoriasis, and ulcerative colitis.

"As with any new treatment option, the use of etanercept in ADPKD will have to be carefully tested and extensively vetted before it can be a viable treatment option for people living with ADPKD," said Rong Li, Ph.D., Investigator. "But, preliminary findings in animal studies are encouraging. This was an exciting discovery for Xiaogang Li and the other members of our team."

BioMed Valley Discoveries, the Stowers Institute's affiliated translational research and development organization, is pursuing further development of the discovery to determine if it is an appropriate treatment for ADPKD and how it can best be brought to market.

The work was the result of collaboration with the Institute's Histology Facility, led by Teri Johnson, Ph.D., and with a team of researchers at The University of Kansas Medical Center.

Xiaogang Li, Ph.D., Senior Research Associate in the Rong Li Lab, was the first author on the publication of these findings in the journal *Nature Medicine*. He received a grant from the PKD Foundation earlier this year that provides $150,000 to support his efforts to understand the origins of PKD.

For more information about PKD or the PKD Foundation, visit www.PKDCure.org.

PAPER: A Tumor Necrosis Factor-α–Mediated Pathway Promoting Autosomal Dominant Polycystic Kidney Disease

JOURNAL: *Nature Medicine*

ISSUE: June 15, 2008

AUTHORS*: **Xiaogang Li, Ph.D.**, Senior Research Associate; **Brenda Magenheimer**, University of Kansas Medical Center; **Sheng Xia, Ph.D.**, Postdoctoral Research Associate; **Teri Johnson, Ph.D.**, Managing Director, Histology Facility; **James Calvet, Ph.D.**, University of Kansas Medical Center; **Darren Wallace, Ph.D.**, University of Kansas Medical Center; **Rong Li, Ph.D.**, Investigator

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

2008 HUDSON PRIZE AWARDED TO RON YU

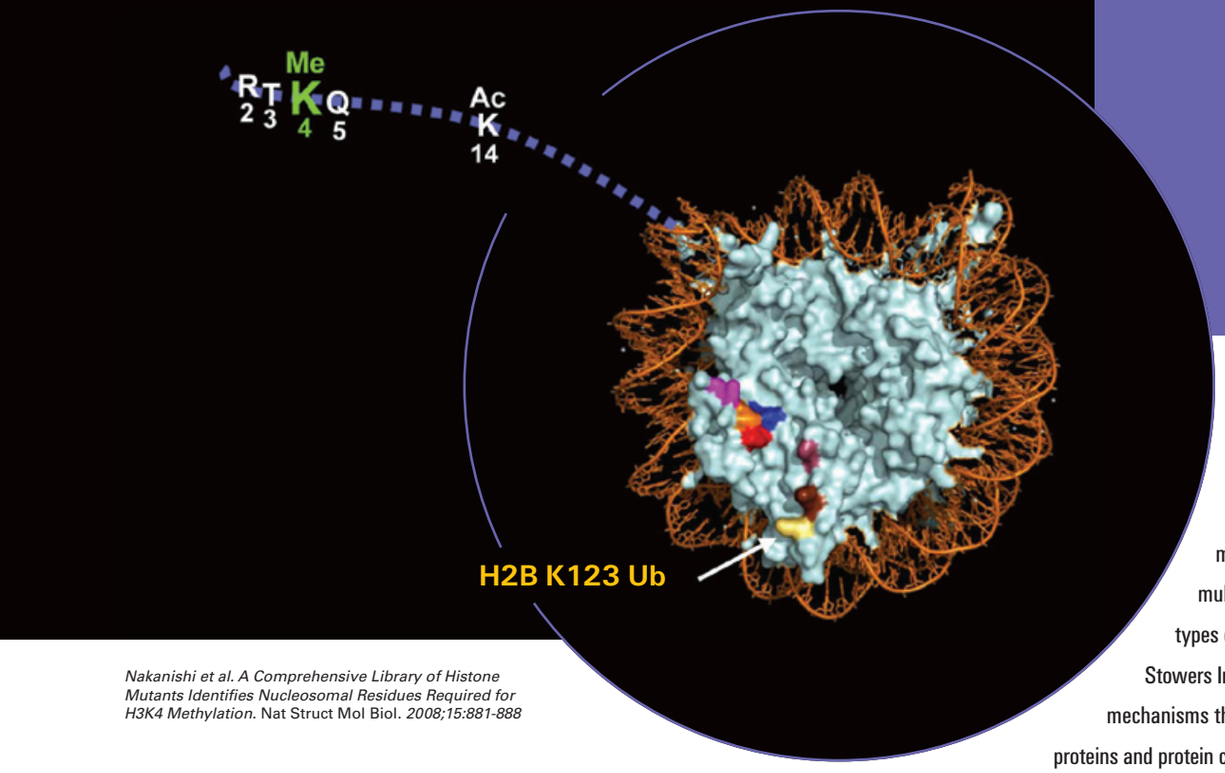
Ron Yu

Ron Yu, Ph.D., Assistant Investigator, has been named the 2008 Hudson Prize winner. Since 2003, the M.R. and Evelyn Hudson Foundation has recognized an early-career scientist at the Stowers Institute with a grant intended to accelerate the pace of laboratory experimentation. Dr. Yu received $75,000 from the Hudson Foundation.

Dr. Yu joined the Stowers Institute in 2005 from the Columbia University Center for Neurobiology and Behavior where he completed postdoctoral studies with Dr. Richard Axel, winner of the Nobel Prize in Physiology or Medicine in 2004. Ron Yu earned a Ph.D. in Molecular, Cellular, and Biophysical Studies at Columbia University.

Research in the Yu Lab concerns the sensory systems and how the senses influence specific innate behaviors. In particular, the lab studies the neural circuits and their physiological functions in the mouse olfactory and vomeronasal systems to reveal how the nervous system detects, parses, and integrates sensory information and generates meaningful behaviors.

"Being recognized by the Hudson Foundation was a distinct honor," said Dr. Yu. "I greatly admire the work of previous Hudson Prize winners, and joining their ranks gives me greater confidence in performing cutting-edge science. With the generous support from the Hudson Foundation, I plan to recruit an additional postdoctoral scientist to initiate a series of experiments linking two sensory systems — the olfactory system and the auditory system — to mammalian innate behaviors. These studies will provide insight into how sensory systems function in the brain."



The locations of residues required for normal levels of H3K4 methylation mapped onto the crystal structure of the yeast nucleosome.

Nakanishi et al. A Comprehensive Library of Histone Mutants Identifies Nucleosomal Residues Required for H3K4 Methylation. Nat Struct Mol Biol. *2008;15:881-888*

ONE GENE AT A TIME

Establishing a Role of the MLL Gene and its Translocation Partners in Leukemia

Leukemia, a cancer of the blood or bone marrow, is characterized by an abnormal multiplication of blood cells. There are many types of leukemia and nearly as many causes. The Stowers Institute's Shilatifard Lab studies the molecular mechanisms that underlie leukemia — particularly the proteins and protein complexes that regulate critical steps in the pathogenesis of this devastating disease. Their work aims to identify potential targets for more effective leukemia treatments.

The mixed-lineage leukemia (MLL) gene holds special interest because mutations that cause the exchange of parts between MLL and other chromosomes, known as translocations, are associated with childhood leukemia. In recent months, the Shilatifard Lab has made notable progress in answering questions about the MLL gene product and its translocation partners.

Investigating MLL's Partner in Crime

When genes are expressed, a transcription elongation factor known as ELL plays a critical role in the transcription of the information contained in that gene. ELL is found in translocations with MLL in children suffering from Acute Myeloid Leukemia (AML). The Shilatifard Lab recently expanded their understanding of ELL's function by demonstrating that it plays a role in the transcription of genes containing a paused RNA polymerase II (Pol II). Elongation is the second of three stages in the process of transcription. It must be completed at precisely the right time and place within the cell to ensure proper cellular development. In this work, the team established that ELL regulates strategic interruptions (pauses) in the function of Pol II to regulate its synthesis of messenger RNA (mRNA) — the transcript containing the information encoded in a gene.

"The pausing by Pol II is a common biological mechanism for regulating gene expression," said Ali Shilatifard, Ph.D., Investigator. "So this doesn't come as a surprise, but it is very useful for us to understand that ELL regulates the interruption of Pol II to ensure appropriate synthesis of mRNA. We are working backwards from mRNA synthesis to understand each previous step in the intricate process. The better we understand ELL and its function, the better chance we have to understand leukemia."

Advancing Technology to Advance Results

Genes are contained on chromosomes, which are made up of chromatin – a complex of DNA and proteins (such as histones). Histones play a role in turning genes on and off through an ongoing process of modification by methyl groups or small proteins, such as ubiquitin. These molecules serve as markers that signal the cell to turn genes on or off at the appropriate time.

In earlier work using yeast as a model, the Shilatifard Lab demonstrated that one such chemical modification, the addition of a methyl group to the histone H3K4 by COMPASS (the yeast equivalent of MLL) required a vital enzyme to be inactivated by attaching a ubiquitin protein to the histone. This delicate balance of chemical modifications is possible only with the aid of sophisticated communication among the histones – a process called "histone crosstalk."

The histone crosstalk mechanism of yeast shares much in common with that of humans. Through work with yeast cells, the Shilatifard Lab has made great strides in understanding histone crosstalk, specifically as it applies to the human MLL complex, which is linked to AML – an aggressive childhood form of leukemia.

The team has made impressive strides in studying histone crosstalk, but they were slowed by the limited research tools available. To solve the problem, the Shilatifard Lab collaborated with the Institute's Molecular Biology Facility to build a comprehensive library of histone mutants to study the fundamental mechanism of how genes are turned on and off. Development of the library allowed the team to identify previously unknown components of histones that are required for proper histone methylation and may be relevant to the development of leukemia.

"We are excited to have the histone mutant library as a resource for our lab and also for the chromatin/transcription community," said Dr. Shilatifard. "This library will not only advance our efforts, but we believe it will enhance the efforts of colleagues around the world. This is an important resource for our field."

The 13-member team of the Molecular Biology Facility led by Karen Staehling-Hampton, Ph.D., Managing Director, provides technologically based collaborations including DNA sequencing, site-directed mutagenesis, riboprobe synthesis, plasmid preps, and distribution of clones/vectors from in-house collections.

"This work is another gratifying example of how creative ideas from our research groups in combination with the Institute's commitment to world-class research facilities continue to raise the bar on what is possible," said Robb Krumlauf, Ph.D., Scientific Director. "Our research facilities are led and staffed by scientists who are gifted in their own right, and who constantly exploit the best currently available technology to develop new, cutting-edge techniques that fundamentally change the way our research teams approach their work. This kind of effective partnership between research and technology is a huge part of what makes the Stowers Institute such a rewarding place to conduct research."

PAPER: Regulation of the Transcriptional Activity of Poised RNA Polymerase II by the Elongation Factor ELL

JOURNAL: *Proceedings of the National Academy of Sciences*

ISSUE: June 24, 2008

AUTHORS*: **Edwin Smith, Ph.D.**, Research Scientist; **Benjamin Winter**, Research Technician I; **Joel Eissenberg, Ph.D.**, Saint Louis University; **Ali Shilatifard, Ph.D.**, Investigator

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

PAPER: A Comprehensive Library of Histone Mutants Identifies Nucleosomal Residues Required for H3K4 Methylation

JOURNAL: *Nature Structural & Molecular Biology*

ISSUE: August 2008

AUTHORS*: **Shima Nakanishi, Ph.D.**, Postdoctoral Research Associate; **Brian Sanderson**, Senior Laboratory Manager; **Kym Delventhal**, Laboratory Manager I; **William Bradford**, Research Specialist I; **Karen Staehling-Hampton, Ph.D.**, Managing Director, Molecular Biology; **Ali Shilatifard, Ph.D.**, Investigator

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

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

MIKE WASHBURN HONORED BY ALMA MATER

Dr. John Boezi was a distinguished faculty member in the Department of Biochemistry and Molecular Biology at Michigan State University (MSU) whose dedication to teaching and uncompromising principles of integrity and performance were respected by students and colleagues alike. Upon his death in 1980, the department established an annual award in his honor recognizing a graduate who has gone on to a distinguished career reflecting the qualities personified by Dr. Boezi.

In April, Michael Washburn, Ph.D., Director of Proteomics, traveled to East Lansing, Michigan to receive the John A. Boezi Alumnus Award. Dr. Washburn received a doctorate in Biochemistry and Environmental Toxicology from MSU in 1998. While on campus to accept the award, he delivered the John A. Boezi Memorial Lecture entitled "Using Normalized Spectral Abundance Factors to Visualize Protein Complexes and Protein Interaction Networks."

"Though I never met Dr. Boezi, I believe that his approach to science is one to which we can all aspire," said Dr. Washburn. "It was an honor to be selected for this award and a privilege to have an opportunity to talk about my current work. My time at Michigan State University had a lasting impact on my career, and I always enjoy returning to campus."

Mike Washburn

KAUSIK SI AWARDED NEUROSCIENCE FELLOWSHIP

Kausik Si

Esther A. & Joseph Klingenstein Fund, Inc. has selected Kausik Si, Ph.D., Assistant Investigator, for the Klingenstein Fellowship in the Neurosciences. The award of $150,000 over three years is intended to support early-career scientists engaged in innovative research in the neurosciences.

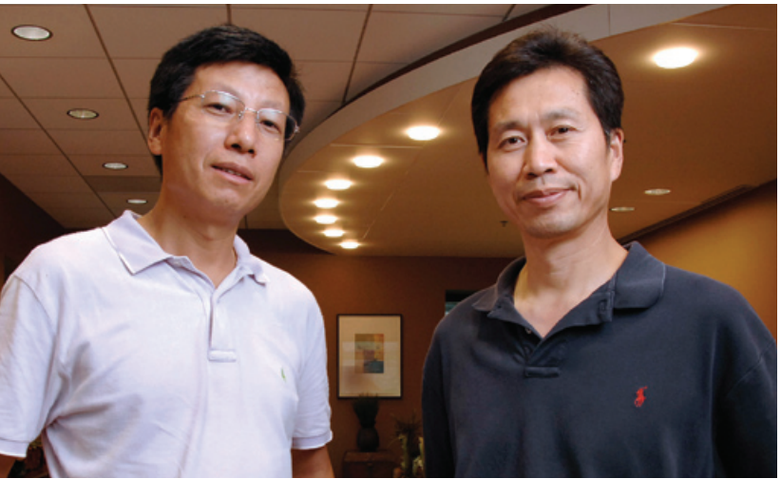
Dr. Si's laboratory concentrates on how information is acquired via learning and stored over time as memories in the brain. He devotes special attention to the role of synapses in memory.

"We are interested in understanding how long-lasting memories are formed," said Dr. Si. "Our team has discovered unique properties of a neuronal protein that might explain part of this process, but the idea is in its infancy and is somewhat controversial. Support from the Klingenstein Fund will help us to probe this very intriguing question further."

Dr. Si joined the Institute in June 2005 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.

Four Stowers Principal Investigators Promoted

CLIMBING THE SCIENTIFIC LADDER



Ting Xie (left) and Linheng Li (right) have been promoted to the position of Investigator.

Peter Baumann (left) and Jennifer Gerton (right) have been promoted to the position of Associate Investigator.

Principal Investigators (PIs) at the Stowers Institute enjoy generous funding and unparalleled support. The Institute strives to provide each research team with everything they need to conduct innovative, ground breaking research. In exchange, the Institute expects nothing less than scientific excellence.

There is no tenure at the Stowers Institute. Instead, PIs are appointed to six- to seven-year terms. Near the end of each term, they are evaluated by the Institute's Scientific Advisory Board (SAB), a group of seven members of the National Academy of Sciences who are internationally recognized leaders of research programs at other institutions. It is the job of the SAB to determine if the Stowers PI has met the lofty goal of the Institute – to make discoveries of such importance that they change the way experts in the field think about their own work.

Applying the rigor of that standard, the SAB recommended four Stowers Institute PIs for renewal at their annual meeting in Kansas City in April 2008.

Investigators

Linheng Li, Ph.D., was promoted from Associate Investigator to Investigator. He joined the Institute as an Assistant Investigator in 2000 from the University of Washington Medical Center where he held a faculty appointment after completing postdoctoral training in the laboratory directed by Leroy Hood, Ph.D. Dr. Li earned his Ph.D. in Molecular and Cellular Biology from New York University Medical School.

Dr. Li's research focuses on understanding the molecular mechanisms and genetic pathways that regulate adult stem cell development. Using the mouse model system to study the molecular mechanisms controlling hematopoietic (blood) stem cell behavior, Dr. Li works to gain insight into the causes of leukemias, lymphomas, and autoimmune diseases that may point the way to better treatments.

Dr. Li has published a number of significant discoveries since joining the Institute, including a 2003 publication in *Nature* that resolved the quarter-century search for the bone marrow stem cell niche and demonstrated how the bone marrow stem cell population could be doubled in size. These findings created new opportunities for research on the stem cell niche, and could eventually lead to more effective bone marrow transplants. More recently, he has published papers that identified an intrinsic pathway involving controls of the transitions that stem cells make between the quiescent and active states and clarified how normal stem cells become cancer stem cells and how cancer stem cells can cause the formation of tumors.

Dr. Li was the recipient of the 2004 Hudson Prize from the M.R. and Evelyn Hudson Foundation and a 2005 Basil O'Connor Starter Scholar Award from the March of Dimes. He holds a faculty appointment as an Associate Professor in the Department of Pathology and Laboratory Medicine at the University of Kansas School of Medicine.

Ting Xie, Ph.D., was promoted from Associate Investigator to Investigator. Dr. Xie joined the Institute as an Assistant Investigator in 2000 after completing a postdoctoral fellowship in the laboratory of Allan Spralding, Ph.D., 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.

Dr. Xie's research focuses on the genetic and molecular analysis of stem cells and germ cell development. Working with fruit flies, he strives to uncover principles of stem cell biology that offer insight for human health. Recently, he has published papers showing that the microRNA pathway is essential for controlling self-renewal of germline stem cells and somatic stem cells and demonstrating that an increase in BMP signaling can prolong the lifespan of stem cells and promote proliferation.

Dr. Xie was the recipient of the 2003 Hudson Prize from the M.R. and Evelyn Hudson Foundation. He holds a faculty appointment as an Associate Professor in the Department of Anatomy and Cell Biology at the University of Kansas School of Medicine.

"Drs. Li and Xie were among the first researchers at the Stowers Institute, joining as early-career Assistant Investigators," said William B. Neaves, President and CEO. "In both cases, their exceptional work has accelerated their advancement, making them eligible for promotion twice in just eight years. This is a testament to Dr. Li's and Dr. Xie's innovative research in stem cell biology. Their careers have flourished while at the Institute, and their promotions to full Investigators are well deserved."

Associate Investigators

Peter Baumann, Ph.D., has been promoted from Assistant Investigator to Associate Investigator, effective January 1, 2009. He joined the Stowers Institute in 2002 after completing a Howard Hughes Medical Institute postdoctoral fellowship in the laboratory of Thomas Cech, Ph.D., 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.

Dr. Baumann's 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. The goal of his research is to understand the dynamics of telomere length regulation and to use this knowledge to influence the life span of specific cell populations. His research has significant relevance both for attempting to limit the infinite potential of cancer cells to divide and for seeking ways to prevent premature aging of tissues. Recent publications from the Baumann Lab have defined proteins that distinguish chromosome ends from DNA double-strand breaks and identified the elusive telomere RNA subunit in a single-cell model.

In 2003, Dr. Baumann was named a Pew Scholar by the Pew Charitable Trusts, and in 2004 he was awarded a Basil O'Connor Starter Scholar Award from the March of Dimes. He holds a faculty appointment as an Assistant Professor in the Department of Molecular and Integrative Physiology at the University of Kansas School of Medicine.

Jennifer Gerton, Ph.D., has been promoted from Assistant Investigator to Associate Investigator, effective January 1, 2009. She joined the Stowers Institute in 2002 from a postdoctoral fellowship in the laboratory of Joseph DeRisi, Ph.D., 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. 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 abnormality or death ensues. Recent publications from the Gerton Lab have mapped the cohesin complex in yeast and identified a factor responsible for specification of centromeres.

Dr. Gerton was the recipient of the 2006 Hudson Prize from the M.R. and Evelyn Hudson Foundation and a 2003 Basil O'Connor Starter Scholar Research Award from the March of Dimes. In addition to her primary appointment at the Stowers Institute, Dr. Gerton holds a faculty appointment as an Assistant Professor in the Department of Biochemistry and Molecular Biology at The University of Kansas School of Medicine.

"Drs. Gerton and Baumann started their careers as laboratory leaders at the Stowers Institute, and each has thrived in that role," said Dr. Neaves. "Over the past six years, they have built strong laboratory teams and led innovative research projects. They are making important contributions in their fields, and the Stowers Institute is fortunate to have them on its team."

GERTON LAB AWARDED $1.5 MILLION FROM NIH

Jennifer Gerton

Jennifer Gerton, Ph.D., Assistant Investigator, has been awarded a grant worth more than $1.5 million from the National Institutes of Health. The award, which will be distributed over a five-year period, will fund the Gerton Lab's efforts to shed light on the mechanisms ensuring that cells produced from mitotic and meiotic division contain the proper number of chromosomes. Errors that result in an incomplete chromosome complement are highly correlated with cancer and can cause spontaneous miscarriage, Down's syndrome, and other developmental disorders.

The Gerton team uses the budding yeast *S. cerevisiae* as a model to understand the molecular mechanisms that contribute to the fidelity of chromosome distribution, paying special attention to the parts of chromosomes that control their movement during cell division – the centromeres and kinetochores. 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.

"Our ultimate goal is to reconstruct centromeric chromatin and the inner kinetochore in the lab," explained Dr. Gerton. "Doing so will help us to build the first detailed molecular model of centromeric chromatin and inner kinetochore formation. It will allow us to evaluate our current understanding of the function of centromeres and kinetochores in chromosome segregation, and may help us to better understand the origins of cancer and new avenues for therapy."

POSTDOCTORAL FELLOW AWARDED NIH NATIONAL RESEARCH SERVICE AWARD

Kimberly Inman

Kimberly Inman, Ph.D., a Postdoctoral Research Fellow in the laboratory of Associate Investigator Paul Trainor, Ph.D., has received a Ruth L. Kirschstein National Research Service Award (NRSA) from the National Institutes of Health. The award provides more than $150,000 in funding over three years.

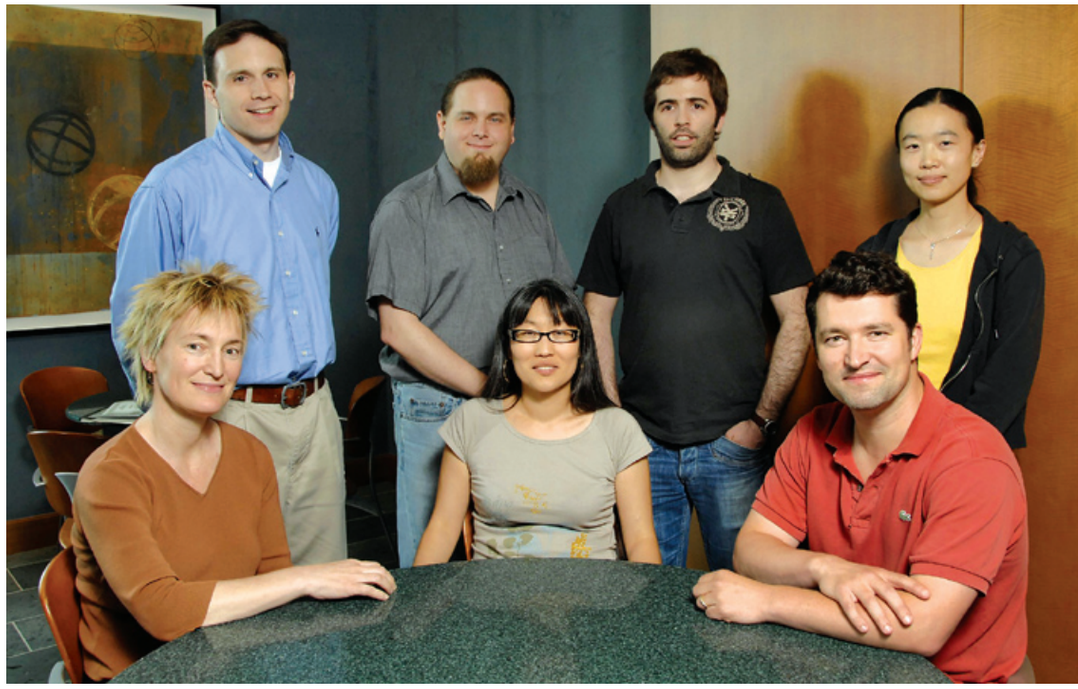
The Kirschstein NRSA helps ensure that highly trained scientists will be available in adequate numbers and in appropriate research areas to carry out the national biomedical, behavioral, and clinical research agenda.

Dr. Inman joined the Stowers Institute in 2006 after receiving a Ph.D. in Cellular and Molecular Biology from the University of Wisconsin-Madison. She will use the award to investigate the role of a pair of transcription factors, FoxC1 and FoxC2, in the embryonic development of the head and face.

"Most of the tissues that form the head are derived from neural crest cells, but recent studies have shown that the environment surrounding neural crest cells also influences the patterning and development of cranial tissues," said Dr. Inman. "With the help of the Kirschstein NRSA, I will work to identify the external factors that play a role in craniofacial development and to explain the susceptibility of neural crest cells to malformation and the high incidence of congenital birth defects of the head and face."

2008 Young Investigator Research Day

Each spring, the Stowers Institute offers its graduate students and postdoctoral researchers an opportunity to present their work at Young Investigator Research Day (YIRD). This year, more than 85 scientists made oral presentations or presented research posters. Stowers Institute Principal Investigators scored the presentations and posters, and awarded prizes to those ranked highest. YIRD 2008 was coordinated by Nancy Bae, Ph.D., Postdoctoral Research Associate in the Baumann Lab, and featured talks by Paul Russell, Ph.D., Professor of Molecular Biology at the Scripps Research Institute, and Beverly Purnell, Ph.D., Senior Editor at *Science*.



2008 Young Investigator Research Day award winners include (back row from left) David Scoville, William Gilliland, Goncalo Vilhais-Neto, Shuyi Chen, (front row from left) Lisa Sandell, Mary-Lee Dequeant, Alexander Aulehla, and (not pictured) Rebecca McLennan.

Runners-up — Best Poster		
Shuyi Chen	Xie Lab	FGF-Signaling Controls the Retinal Fissure Closure by Orchestrating Cell Proliferation, Morphological Changes and Fate Switches
Rebecca McLennan	Imaging Center	The Role of Neuropilins in Cranial Neural Crest Cell Migration
Lisa Sandell	Trainor Lab	Roles for Retinoids in Embryonic Development of Heart, Pharyngeal Organs and CNS Revealed by Retinoid-deficient Mutant Mice
Winner — Best Poster		
Mary-Lee Dequeant	Pourquié Lab	Comparison of the Segmentation Clock Networks in Fish, Chick, and Mouse
Runner-up — Best Oral Presentation by a Graduate Student		
David Scoville	Linheng Li Lab	Functional Characterization of Intestinal Stem Cells
Winner — Best Oral Presentation by a Graduate Student		
Goncalo Vilhais-Neto	Pourquié Lab	Atrophin2 Controls the Left-Right Synchronization of Somitogenesis
Winner — Best Oral Presentation by a Postdoctoral Researcher (tie)		
Alexander Aulehla	Pourquié Lab	A ß-catenin Gradient Links the Clock and Wavefront Systems in Mouse Embryo Segmentation
William Gilliland	Hawley Lab	Hypoxia Transiently Sequesters Mps1 and Polo to Filaments in *Drosophila* Oocytes

2008 Stowers Scholars

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 more than 50 applicants. Scholars 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.

2008 Stowers Scholars include (back row from left) Megan Rogge, Brent Stutzman, Varian Bailey, Kinjal Majumder, Justin Ryder, (front row from left) Nathan Droz, Jennifer Harness, and Maxie Darke.

Student Scholar	Lab	School	Project
Varian Bailey	Linheng Li Lab	Howard University (2008 B.S.)	Characterizing Some Novel PTEN-interacting Factors
Maxie Darke	Xie Lab	Emory University	Use of Wing Phenotypes to Study Genetic Interactions in *Drosophila*
Nathan Droz	Shilatifard Lab	Rockhurst University	Functions of Elongation Factors in Transcription Regulation
Jennifer Harness	Proteomics Center	University of Kansas	Preparation of a RNAPII Mutant Library to Study the Effects of Ubiquitination on the Transcription Cycle
Kinjal Majumder	Baumann Lab	Drury University	Characterization of Subnuclear Organelles in *Xenopus* Oocytes
Megan Rogge	Jaspersen Lab	Rockhurst University	Characterizing SLP1
Justin Ryder	Yu Lab	Truman State University	Mating Calls: Determining the Sensory Triggers of Ultrasonic Vocalization in Male Mice
Brent Stutzman	Proteomics Center	Bethel College	Using Quantitative Proteomics to Investigate YDL156w: A Protein of Unknown Function in *Saccharomyces Cerevisiae*

ANIMAL CARE PROGRAM COMMENDED BY NATIONAL ACCREDITATION BODY

Among research institutions that rely on animal models to conduct their work, one group's accreditation is a sure sign of quality: the Association for Assessment and Accreditation of Laboratory Animal Care (AAALAC) International. AAALAC International is a private, nonprofit organization that promotes the humane treatment of animals in science through voluntary accreditation and assessment programs.

The Stowers Institute's animal care program was first accredited by AAALAC in 2002 and has maintained its accreditation since that time based on regular and thorough site inspections by teams that include top animal care professionals and researchers from around the nation. AAALAC conducted its most recent inspection at the Institute in February and enthusiastically re-accredited the Institute's animal care program.

In its notification letter, the AAALAC Accreditation Council recognized the Institute for excellence in a number of areas, writing, "The Council commends you and the staff for providing and maintaining an exemplary program of laboratory animal care and use. Especially noteworthy were the administration's commitment to a superior program of animal care; the quality of the facilities and equiptment; the dedicated staff; the engaged Institutional Animal Care and Use Committee and their thorough post-approval mentoring program; the institution's exemplary animal care practices; the excellent husbandry records; the detailed medical records; and the well-written standard operating procedures."

Since its inception, the Institute has cultivated an innovative animal care program that puts state-of-the-art technology into the hands of skilled animal care professionals. The caliber of the animal care program is a testament to the professionalism of its dedicated staff, whose effort is crucial to the quality and consistency of Stowers Institute research.

Recognizing Recent Hope Shares® Donations

Between March 1 and September 15, 2008, contributions of at least $1,000, the minimum for establishing a Hope Shares account in the endowments of the Stowers Institute, were received from, in memory of, or in honor of the following:

$10,000 or More

American Century Employees

Landon Rowland, Kansas City Impact Fund

$5,000 or More

Clay Blair Family Foundation

Gilmore and Bell, PC

Webb R. Gilmore

$1,000 or More

From Lauren and Ryan Contillo and Kathleen Stowers-Potter in Memory of Lawrence Joseph Contillo

Marshall and Jill Dean

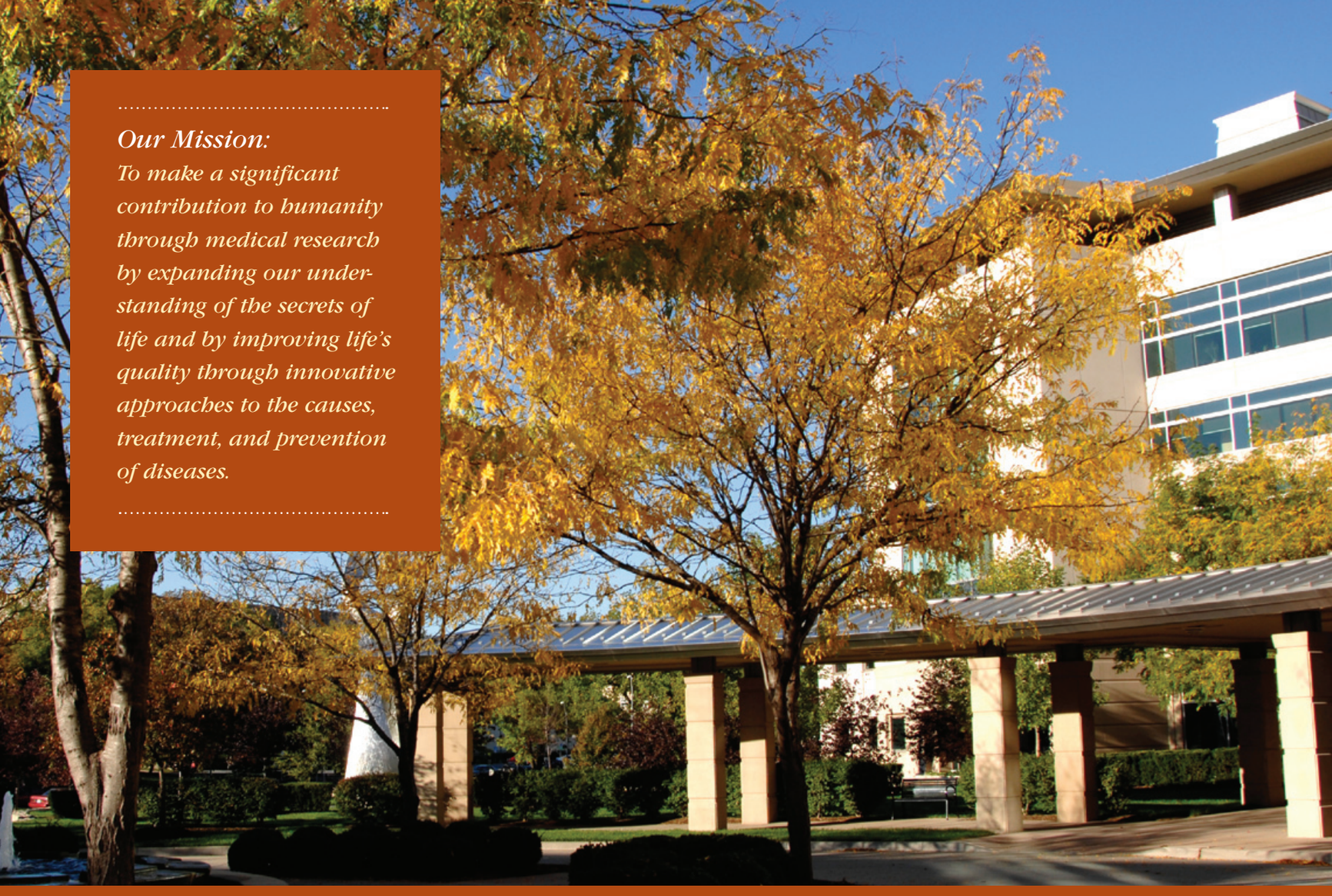
From Herbert and Estelle Adler in Memory of Caryn Lisnek O'Connell

From Jim and Alex Potter, Lauren and Ryan Contillo, and Kathleen Stowers-Potter in Memory of James William Potter

THESE DONORS AND THOSE THEY HONOR WILL NEVER BE FORGOTTEN.

Hope Shares donations are invested with the Institute's endowments. To establish a Hope Shares account, visit www.stowers-institute.org or call (816) 926-4000.

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



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.

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