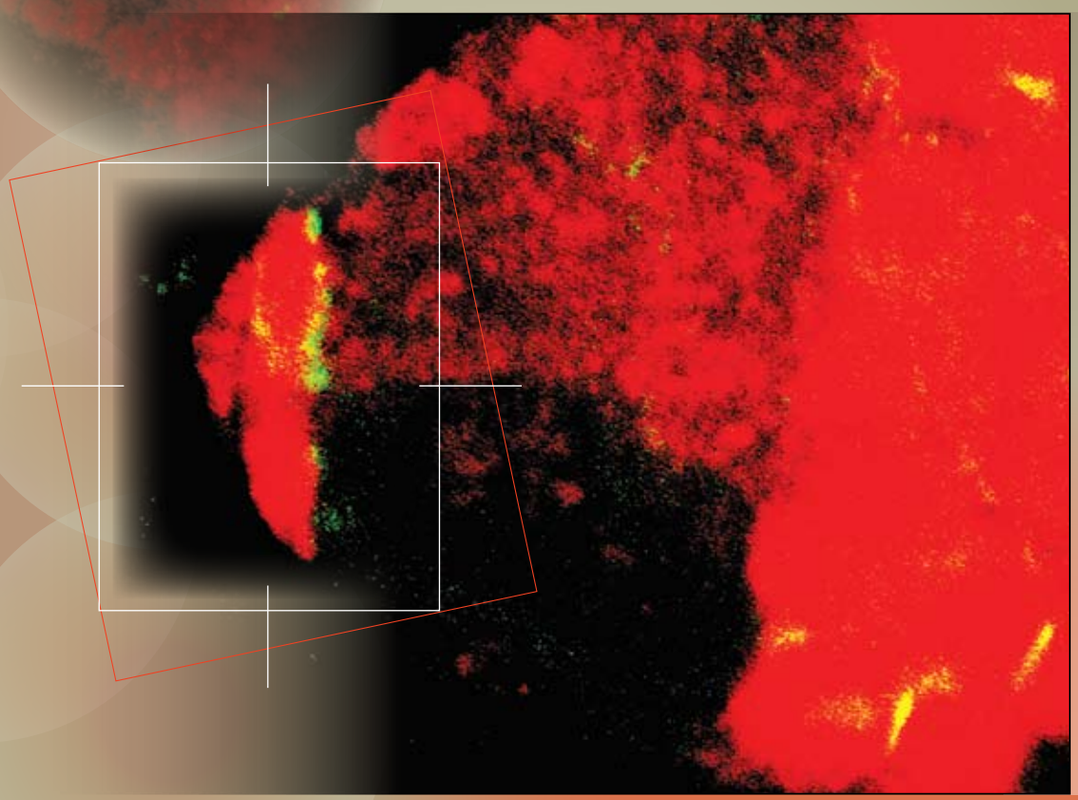
FALL 2009

Stowers REPORT

NEWS AND INSIGHT FROM
THE STOWERS INSTITUTE
FOR MEDICAL RESEARCH

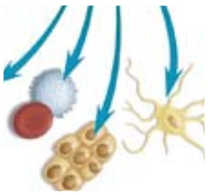


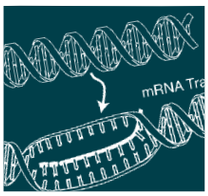
STOWERS RESEARCHERS EXAMINE THE BALANCE OF STEM CELL SELF-RENEWAL AND DIFFERENTIATION. PAGE 2

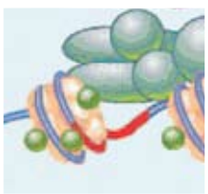
FALL 2009

Stowers REPORT

PUBLISHED BY THE STOWERS INSTITUTE FOR MEDICAL RESEARCH







ALSO IN THIS ISSUE

STOWERS REPORT

FALL 2009
PUBLISHED BY THE STOWERS INSTITUTE FOR MEDICAL RESEARCH

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

CONTRIBUTORS:

PHOTOS:
DON IPOCK
WRITING:
MARIE FARRELL JENNINGS
DESIGN AND LAYOUT:
KUHN & WITTENBORN ADVERTISING

PRESIDENT'S LETTER

BY DAVID CHAO, PH.D., PRESIDENT

This is my first letter to you as the Stowers Institute's President, and I'd like to take this opportunity to share some of the reasons why I am delighted to take on this new role.

First, I am excited to be a part of an incredibly productive period in the life sciences. Biologists today have a complete parts list for organisms with sequenced genomes and can now puzzle over how the pieces fit together. At the same time, it has become increasingly clear that these parts are organized into conserved pathways that are used and reused in different contexts and organisms. Pathways can therefore be studied in the most tractable organism with insights quickly extended to other areas (for example, see the articles on the Xie, Shilatifard, and Abmayr Labs' recent discoveries on pages 2, 6, and 8, respectively). Meanwhile, the development of high throughput, high resolution and genomic scale technologies promises the generation of data at a rate, scale, and depth that could hardly have been imagined only a few years ago (for example, see the article on the Hawley Lab's and Molecular Biology Facility's recent work on page 8). The convergence of these forces promises a time of rapid progress, filled with surprises and insights into the underlying mechanisms of life.

Second, I look forward to leading the next phase of the Institute's development by building upon the successful research model that Bill Neaves and Robb Krumlauf have developed and refined over the last decade. We have grown from a few dozen members in 2000 to almost 500 today. We have published over 600 papers that have been cited over 14,000 times. We have won more than $50 million dollars in some of the scientific world's most rigorous competitions. For an organization that is less than a decade old, these are impressive accomplishments. Our ramp-up puts us on par with some of the best new research institutions in the world, and, as the Institute's infrastructure and programs mature, we are poised to have an even greater impact in science and health.

Finally, I am honored to belong to a extraordinary organization that is bound together by a compelling vision and enduring values. We are privileged to be members of a magnificent team. There are only a few times in life when hope, hard work, and fate converge to achieve something sublime. On these rare occasions the results are remarkable and something to be savored. I consider myself incredibly fortunate and privileged to be a part of these extraordinary times at the Stowers Institute.

What makes the Institute's team work so well together? First, I believe that the foundation of our team starts with enduring values. Every day, I am reminded of Jim and Virginia Stowers' message to all of us and the importance of living up to their values. Like many members of the Institute, I have on my desk a framed description of Jim and Virginia's guiding principles for the Institute. Their purity of purpose, commitment to excellence and selflessness are simultaneously humbling and inspiring. Second, I believe that the Institute has been fortunate to have wise stewards and guides. Through their integrity, high standards, and unwavering commitment to excellence and collegiality, the Board, the Scientific Advisory Board, Robb and Bill have all ensured that we adhere to Jim and Virginia's guiding principles. Finally, and most importantly, I believe that our team succeeds because we have team members who are pursuing Jim and Virginia's vision with a special, uncommon quality.

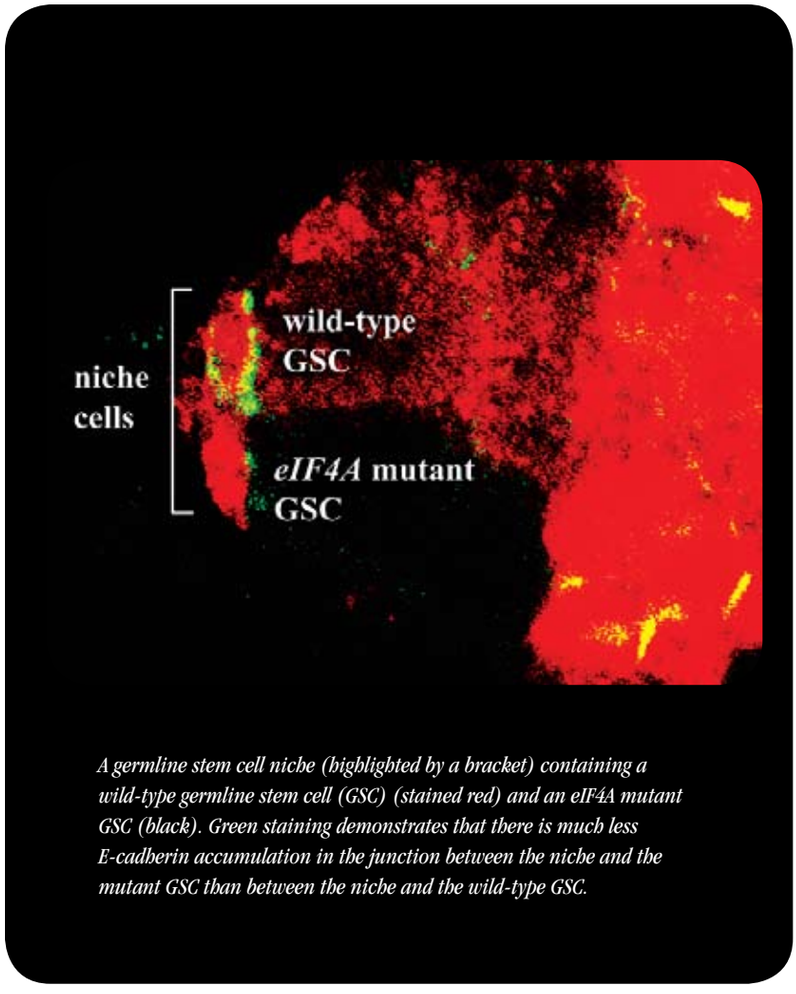
When I first visited Kansas City, my wife Julia and I enjoyed a dinner with Bill and his wife Priscilla. Midway through dinner, Bill leaned forward and looked over his glasses in the way that I have since learned is the prelude to a provocative question. After a short pause for dramatic effect, Bill shot out in his West Texas drawl, "Well, Dave, do you think you want to be a pioneer here?" I was surprised at the time, but I suppose Bill's question is one that all of us have considered at some point in one form or another and one that all of us have answered in the affirmative. All of us have chosen to be a part of this grand adventure called the Stowers Institute. We have chosen to defy skeptics, evaluate the opportunity at the Institute with an open mind, and take on the challenge of trying something new. As a consequence, all of us share a "pioneering spirit" – a mix of self-reliance, self-confidence and optimism that compels us to set out on a journey of exploration. We are a group that is striking in its diversity but is bound together by this common ethos. This "pioneering spirit" is, I believe, the underlying force that makes our team so special and drives us to strive together to achieve Jim and Virginia's vision of "Hope for Life."

I hope all of you share my excitement as our pioneering team enters an exciting period of discovery and rapid progress. Please enjoy the following pages as another installment describing our shared adventure.

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

GIVE & TAKE

Examining the Balance of



A germline stem cell niche (highlighted by a bracket) containing a wild-type germline stem cell (GSC) (stained red) and an eIF4A mutant GSC (black). Green staining demonstrates that there is much less E-cadherin accumulation in the junction between the niche and the mutant GSC than between the niche and the wild-type GSC.

THE LONG AND WINDING PATH OF BIOLOGICAL DEVELOPMENT OFTEN BEGINS WITH THE MEETING OF TWO GAMETES (A SPERM AND AN EGG) THAT COME TOGETHER TO CREATE A SINGLE CELL — DESTINED TO DIVIDE AND MULTIPLY TO FORM ALL OF THE SPECIALIZED CELLS THAT WILL MAKE UP AN ENTIRE ORGANISM.

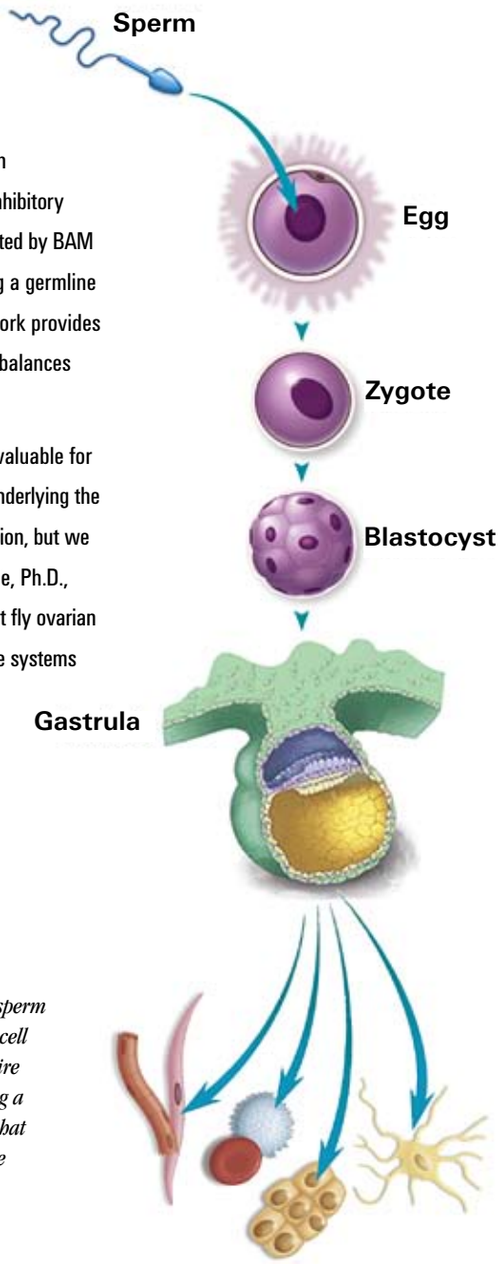
The division and multiplication of cells to maintain a population of the same type is known as self-renewal. The formation of specialized cells from less specialized cells is known as differentiation and is triggered by highly controlled modifications in the expression of genes. These two processes repeat throughout the life cycle and must operate in equilibrium to maintain an organism's fitness. Imbalances can lead to tissue degeneration or to the generation of excess tissue in the form of tumors. Studies on germline stem cells, which are responsible for the generation of gametes, will not only help understand how gametes are produced but also will provide a better understanding of stem cell regulation in general.

In recent work, the Stowers Institute's Xie Lab has revealed how the BAM protein, a differentiation factor, is involved in regulating the differentiation/self-renewal balance. Scientists had long believed that BAM was necessary for germline stem cell differentiation, but it had been unclear how it contributed to the larger issues of the balance.

Stem Cell Self-Renewal and Differentiation

The Xie Lab demonstrated that BAM can act as an inhibitor of protein synthesis and that a translation initiation factor called eIF4A can counteract BAM's inhibitory effect. One of the proteins whose translation is inhibited by BAM is E-cadherin, a protein that is critical to maintaining a germline stem cell's attachment to its niche. The Xie Lab's work provides insight into how a molecular system of checks and balances serves to regulate differentiation and self-renewal.

"This new information about the role of BAM is valuable for the insight it offers into the molecular mechanisms underlying the control of the balance of self-renewal and differentiation, but we also believe it will apply more broadly," said Ting Xie, Ph.D., Investigator and senior author on the paper. "The fruit fly ovarian stem cell system has been one of the most productive systems for identifying the factors controlling self-renewal, so the experimental approaches developed for this project represent exciting opportunities to further elucidate the factors involved in the delicate balance of stem cell self-renewal and differentiation."



Human development begins when a sperm fertilizes an egg and creates a single cell that has the potential to form an entire organism. This cell divides, launching a cycle of division and specialization that ultimately forms every cell type of the human body.

PAPER: eIF4A Controls Germline Stem Cell Self-Renewal by Directly Inhibiting BAM Function in the *Drosophila* Ovary

JOURNAL: *Proceedings of the National Academy of Sciences*

ISSUE: July 14, 2009

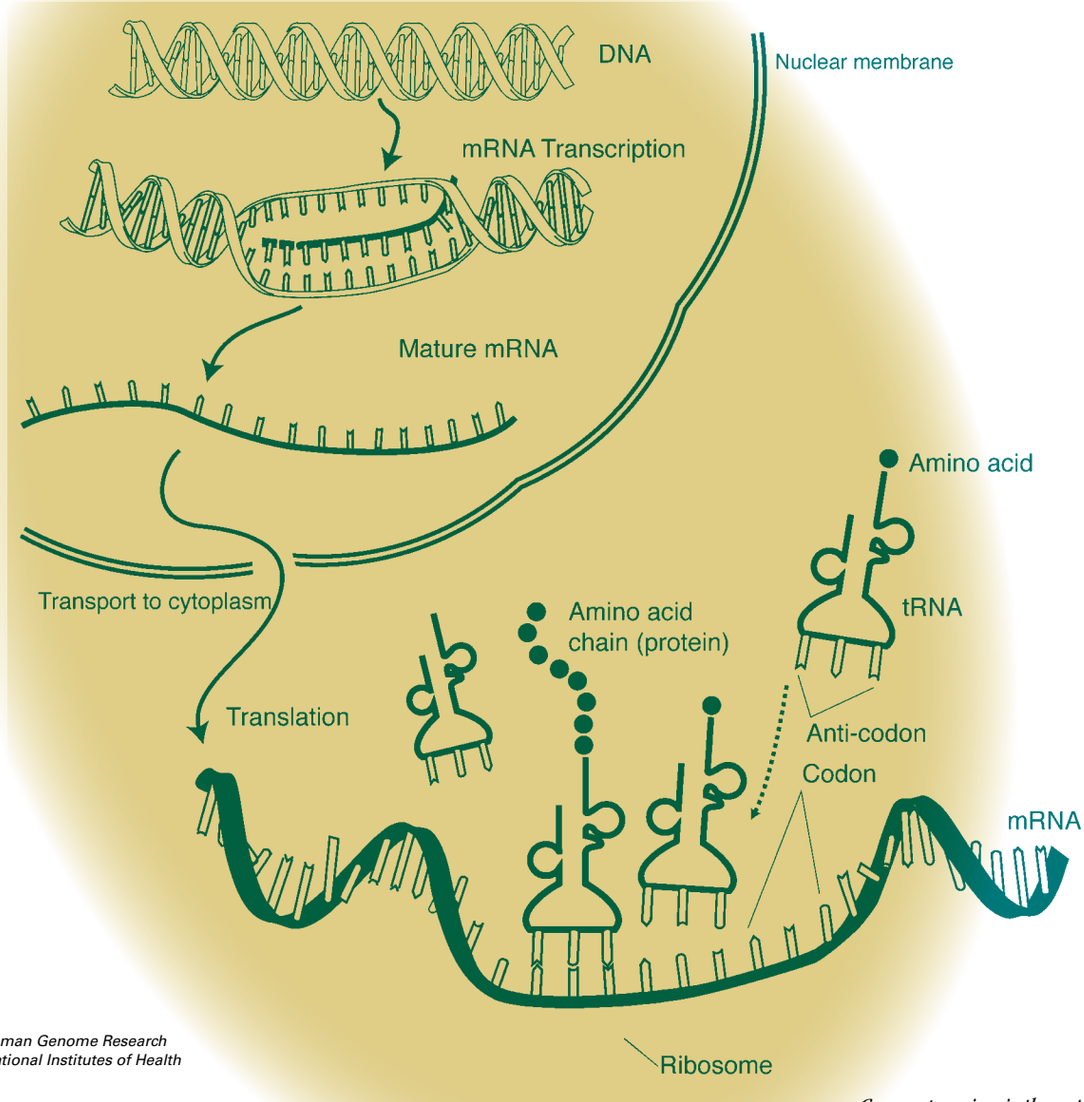
AUTHORS*: **Run Shen**†, **Ph.D.**, Postdoctoral Research Associate; **Changjiang Weng**†, **Ph.D.**, formerly a Postdoctoral Research Associate; **Junujing Yu**, Predoctoral Researcher; and **Ting Xie**, **Ph.D.**, Investigator

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

† *Co-equal contributors to this publication.*

Ting Xie, Ph.D., Investigator, also is 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.org/labs/XieLab.asp.

EXPRESS YOURSELF



National Human Genome Research Institute, National Institutes of Health

Gene expression is the entire process that takes the information contained in genes on DNA and turns that information into proteins. It requires two phases: transcription, which is the copying of DNA into messenger RNA; and translation, which is the production of proteins by decoding the mRNA produced in transcription.

Elucidating the Role of the Rtr1 Protein in Transcription and Gene Expression

Many research projects at the Stowers Institute investigate the mechanics of gene expression, the process by which the information in genes is converted into the proteins that form the cell's building blocks.

The first step in gene expression is transcription, which is the production of an RNA molecule using a gene's DNA as a template. RNA Polymerase II (Pol II) is the RNA-producing enzyme that is responsible for the transcription of messenger RNA (mRNA), which is subsequently processed and translated into protein by other enzymes.

Recently, the Stowers Institute's Washburn and Workman Labs collaborated to shed light on the role of a protein, Rtr1, in the regulation of Pol II during transcription. Pol II is an enzyme composed of many different proteins that work together. One of these proteins, Rpb1, has one unique end made up of a repeating chain of amino acids called the carboxy-terminal domain (CTD). The CTD is involved in the initiation of transcription and the regulation of mRNA processing. The addition of phosphate groups (phosphorylation) and removal of phosphate groups (dephosphorylation) to the CTD are thought to be key mechanisms for regulating Pol II's activity.

Rtr1 was previously known to interact with Pol II, but until now, its specific role in regulating transcription had not been described. This work has shown that Rtr1 regulates the phosphorylation of Pol II during the early stages of the transcription cycle when phosphorylation of the amino acid serine 5 on the CTD is normally high.

To study the impact of Rtr1, the team deleted the protein from yeast cells. They observed an increase in the levels of serine 5 phosphorylation, especially toward one end of the gene – the 3′ end – which suggests that Rtr1 regulates the removal of phosphate groups from serine 5.

Dephosphorylation of serine 5 is an essential step in the elongation stage of transcription, but until the Washburn Lab published this work, no proteins were known to specifically target serine 5 for dephosphorylation in the coding region of genes.

The process of transcription and the interaction between Rtr1 and Pol II is very similar across species – even from yeast to humans. Based on this work, the team believes that Rtr1 also likely plays a role in the regulation of the Pol II transcription cycle in higher organisms.

"Understanding the function of Rtr1 will allow us to further examine its role in the phosphorylation of Pol II and to understand the biological effects of serine 5 CTD hyperphosphorylation," said Michael Washburn, Ph.D., Director of Proteomics Center and senior author on the publication. "This was an excellent collaboration with the laboratory of Jerry Workman – it was our work together that made this discovery possible."

PAPER: Rtr1 is a CTD Phosphatase that Regulates RNA Polymerase II during the Transition from Serine 5 to Serine 2 Phosphorylation

JOURNAL: *Molecular Cell*

ISSUE: April 24, 2009

AUTHORS*: **Amber Mosley, Ph.D.**, Senior Research Associate; **Samantha Pattenden, Ph.D.**, Senior Research Associate; **Michael Carey, Ph.D.**, University of California, Los Angeles; **Swaminathan Venkatesh, Ph.D.**, Postdoctoral Research Associate; **Joshua Gilmore, Ph.D.**, Postdoctoral Research Associate; **Laurence Florens, Ph.D.**, Managing Director of Proteomics; **Jerry Workman, Ph.D.**, Investigator; **Michael Washburn, Ph.D.**, Director of Proteomics

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

Michael Washburn, Ph.D., Director of Proteomics, holds a faculty appointment as an Associate Professor in the Department of Pathology & Laboratory Medicine at The University of Kansas School of Medicine. Learn more about his work at www.stowers.org/labs/WashburnLab.asp.

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

SEARCHING FOR THE MISSING PIECES

Illustration by Julia Schulze, co-equal lead author on the Molecular Cell *publication.*

PAPER: Linking Cell Cycle to Histone Modifications: SBF and H2B Monoubiquitination Machinery and Cell-Cycle Regulation of H3K79 Dimethylation

JOURNAL: *Molecular Cell*

ISSUE: September 11, 2009

AUTHORS*: **Julia Schulze**†, University of British Columbia; **Jessica Jackson**†, Washington University School of Medicine; **Shima Nakanishi, Ph.D.**, Postdoctoral Research Fellow; **Jennifer Gardner**, Research Technician II; **Thomas Hentrich**, Simon Fraser University; **Jeff Haug**, Managing Director, Cytometry Facility; **Mark Johnston, Ph.D.**, Washington University School of Medicine; **Sue Jaspersen, Ph.D.**, Assistant Investigator; **Michael Kobor, Ph.D.**, Child and Family Research 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.*

EACH CELL IN THE HUMAN BODY CONTAINS APPROXIMATELY SIX FEET OF DNA. THAT IS A LOT OF GENETIC INFORMATION TO FIT INSIDE OF THE NUCLEUS OF A CELL, BUT A PACKAGING PROTEIN MAKES IT ALL POSSIBLE: THE HISTONE.

Histones serve as spools around which DNA can coil tightly to neatly package a complete genetic code in each and every cell.

But histones are more than just hardware. In the process of gene expression, histones undergo molecular changes that can alter their interaction with DNA and nuclear proteins in ways that ultimately affect the regulation of genes.

The Stowers Institute's Shilatifard Lab is making strides in examining the impact of histone modifications on human health and, especially, their role in the onset of leukemias.

When Histone Signals Cross

One way that a histone can be modified is through the addition of a methyl group in a process known as methylation. The Shilatifard Lab has provided new insight into the molecular basis for the methylation of the histone H3K4, which has been associated with an aggressive form of childhood leukemia known as Mixed Lineage Leukemia (MLL). The MLL protein is often found when a genetic error causes a portion of one chromosome to break and fuse with another in a chromosomal translocation. These chromosomal errors can lead to MLL, whose patients have low survival rates and limited treatment options.

Working in yeast, the Shilatifard Lab observed that the addition of three methyl groups (a process known as trimethylation) on the fourth lysine of H3K4 is regulated by the active site of the yeast equivalent of the MLL protein complex, known as COMPASS. They also demonstrated that a single residue (Tyr1052) functions with a known subunit of COMPASS (Cps40) to regulate the trimethylation of H3K4.

By specifying the detailed molecular changes that launch the complicated process that ends in chromosomal translocation, the team hopes eventually to identify opportunities to intervene to treat or cure MLL.

The Universal Language of Histones

One aspect of the molecular machinery required for proper H3K4 methylation by COMPASS is the modification of histone H2B through the attachment of a single ubiquitin molecule by the RAD6/Bre1 complex. Like methylation, the addition of ubiquitin is another modification that can regulate the function of histones.

The interplay of methylation and ubiquitination in regulating histone function is called "histone crosstalk." In recent work, the Shilatifard Lab demonstrated that human RAD6/Bre1 functions in human histone crosstalk, just as it had previously been demonstrated to function in yeast.

"This study demonstrates the awesome power of simple genetic and biochemical model systems, such as yeast, in deciphering molecular machinery involved in chromatin biology and how yeast can play a role as a template in identifying the human counterparts of these proteins," said Dr. Shilatifard.

Uncovering the Mechanisms of Histone Modifications, One Step at a Time

"Human RAD6 can functionally replace yeast RAD6, and H2B monoubiquitination in humans functions by the same histone crosstalk mechanism as it does in yeast, demonstrating the conservation in this system from yeast to humans."

Novel Tools Bring Novel Results

Most recently, the Shilatifard Lab collaborated with Michael Kobor, Ph.D., University of British Columbia, and Sue Jaspersen, Ph.D., Stowers Institute Assistant Investigator, to apply a novel screen to improve their understanding of the molecular machinery required for the modification of histone H3K79.

The team investigated the function of the enzyme Disruptor-of-Telomeric-Silencing-1 (Dot1). Dot1 is capable of methylating histone H3 on lysine 79 (H3K79). Abnormal H3K79 methylation has been linked to the onset of blood-related cancers.

PAPER: Regulation of H3K4 Trimethylation via Cps40 (Spp1) of COMPASS is Monoubiquitination-Independent: Implication for a Phe/Tyr Switch by the Catalytic Domain of Set1

JOURNAL: *Molecular and Cellular Biology*

ISSUE: July 29, 2009

AUTHORS*: **Yoh-hei Takahashi, Ph.D.**, Postdoctoral Research Associate; **Jung-Shin Lee, Ph.D.**, Postdoctoral Research Associate; **Selene Swanson**, Research Specialist II; **Anita Saraf, M.D., Ph.D.**, Senior Proteomics Scientist; **Laurence Florens, Ph.D.**, Managing Director of Proteomics; **Michael Washburn, Ph.D.**, Director of Proteomics Center; **Raymond Trievel, Ph.D.**, University of Michigan; **Ali Shilatifard, Ph.D.**, Investigator

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

Several residues within the histone tails and some within the histone core can be altered by molecular modifications, including methylation. Although the link between histone methylation by Dot1 and blood-related cancers is well established, very little is known about the molecular machinery required for H3K79 methylation.

The project is the first to establish a connection between chromatin modification and the cell cycle, and may ultimately contribute to better treatments for blood-related cancers.

"With the help of a novel screen developed in our lab, we were able to dissect the molecular machinery required for Dot1's function," said Dr. Shilatifard. "The result may ultimately contribute to better treatments for blood-related cancers because H3K79 methylation is associated with the pathogenesis of Acute Myeloid Leukemia."

Aiming for Targeted Treatments

"Each of these three papers represents exciting findings because each is a significant step toward establishing precisely how histone modifications contribute to leukemia and how we might develop treatments that better target and treat the disease," said Dr. Shilatifard. "Problems in histone modification are capable of setting off chain reactions that have devastating consequences, but until we truly understand each step of the process, it will be difficult – if not impossible – to develop any effective, targeted treatments for leukemia. Each discovery we make about the mechanics of histone modifications brings us closer to better outcomes for patients and their loved ones."

PAPER: RAD6-Mediated Transcription-Coupled H2B Ubiquitylation Directly Stimulates H3K4 Methylation in Human Cells

JOURNAL: *Cell*

ISSUE: May 2009

AUTHORS*: **Jaehoon Kim, Ph.D.**, The Rockefeller University; **Mohamed Guermah**, The Rockefeller University; **Robert McGinty**, The Rockefeller University; **Jung-Shin Lee, Ph.D.**, Postdoctoral Research Associate; **Zhanyun Tang, Ph.D.**, The Rockefeller University; **Thomas Milne, Ph.D.**, The Rockefeller University; **Ali Shilatifard, Ph.D.**, Investigator; **Tom Muir, Ph.D.**, The Rockefeller University; **Robert Roeder, Ph.D.**, The Rockefeller University

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

Sue Jaspersen, Ph.D., Assistant Investigator, also is an Assistant Professor in the Department of Molecular & Integrative Physiology at The University of Kansas School of Medicine. Learn more about her work at www.stowers.org/labs/JaspersenLab.asp.

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

Michael Washburn, Ph.D., Director of Proteomics, holds a faculty appointment as an Associate Professor in the Department of Pathology & Laboratory Medicine at The University of Kansas School of Medicine. Learn more about his work at www.stowers.org/labs/WashburnLab.asp.

A MODEL SUBJECT

Advances in Fruit Fly Biology Promise Insight

THE PESKY AGRARIAN FRUIT FLIES — MEMBERS OF THE *TEPHRITIDAE* FAMILY — THAT OCCASIONALLY ACCOMPANY FRESH PRODUCE MIGHT BE A NUISANCE, BUT DON'T HOLD IT AGAINST THEIR BIOLOGICAL COUSINS — THE *DROSOPHILA MELANOGASTER*.

This smaller species of fruit fly is a critically important model organism that allows researchers to study normal biological processes and shed light on genetic factors that may contribute to human disease.

Fruit flies and humans share most of their genes, including 70 percent of all known human disease genes. They are a popular model organism because genes can be inserted, deleted, or modified; and large numbers of flies can be randomly mutated to generate genetic characteristics (phenotypes) relevant to human disease. Fruit flies are such an influential research model that new discoveries about their biological makeup garner significant attention, and many such discoveries ultimately provide important insights into human health. In recent months, two Stowers teams have made notable advancements in fruit fly biology.

PAPER: Identification of EMS-Induced Mutations in *Drosophila melanogaster* by Whole-Genome Sequencing

JOURNAL: *GENETICS*

ISSUE: May 2009

AUTHORS*: **Justin Blumenstiel, Ph.D.**, formerly a Postdoctoral Research Fellow; **Aaron Noll**, Bioinformatics Programmer Analyst III; **Jennifer Griffiths**, Research Technician III; **Anoja Perera**, Laboratory Manager II; **Kendra Walton**, Research Technician III; **William Gilliland, Ph.D.**, Senior Research Associate; **Scott Hawley, Ph.D.**, Investigator; and **Karen Staehling-Hampton, Ph.D.**, Managing Director of Molecular Biology

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

The Big Picture

R. Scott Hawley, Ph.D., Investigator, is among the world's leading experts in fruit fly genetics. His team recently collaborated with the Institute's Molecular Biology Facility to develop a "whole-genome sequencing approach" to mapping mutations in fruit flies – an advancement that promises to change the way that fruit fly genetics is conducted.

Finding the mutated gene responsible for potentially significant phenotypes is labor intensive and time consuming, and many mutations that cause medically relevant phenotypes remain undiscovered.

The new approach developed by the Hawley Lab and Molecular Biology Facility lowers the barrier to finding mutations and greatly accelerates the discovery of genes important for human health by reducing the time and effort required to identify mutations of biological interest.

The team validated the whole-genome approach by mapping a fruit-fly mutation caused by the compound ethyl methanesulfonate (EMS) and determining the DNA sequence of the mutant fly's entire genome. The results provided insight into the mechanism of EMS mutagenesis and into gene conversion events involving balancer chromosomes – genetic tools used to prevent genetic recombination between homologous chromosomes during meiosis.

"This new whole-genome sequencing approach is fast and cost effective," said Dr. Hawley, co-equal senior author on the publication. "Among other uses, it also carries the potential to pinpoint inheritable molecular characteristics that are controlled by several genes at once – a particularly exciting new resource for genetic researchers."

"The traditional mapping method could take months to years depending on the complexity of the phenotype," said Karen Staehling-Hampton, Ph.D., Managing Director of Molecular Biology and co-equal senior author

into Human Health

Drosophila melanogaster *is a popular research model for basic scientists.*

on the paper. "This advance will allow us to map mutations of interest in just a few weeks. The next-generation sequencing technology used for this project is extremely exciting. It will allow researchers to sequence genomes for a few thousand dollars, a cost unheard of just a few years ago. It will also enable them to take their science in new directions and answer new questions that were not possible with traditional sequencing technology."

Apples to Apples

The Stowers Institute's Abmayr Lab studies the development of multicellular organisms: how differentiating cells acquire specific properties and capabilities associated with their ultimate purpose in the body, and how different cell types must coordinate to organize themselves into functional structures. The team utilizes the fruit fly to study how organs develop.

In the course of this work, the Abmayr Lab has demonstrated that a fruit fly structure similar to the human site where components in the blood filter into the urine for excretion (the podocyte slit diaphragm) is present in the cells that detoxify the equivalent of blood in fruit flies.

The team was working to determine whether structurally related proteins in flies and humans played similar roles. They focused on whether the removal of unwanted components of fly blood by proteins in nephrocytes – specialized arthropod cells whose function involves the accumulation or formation of waste or excretory products – is related to the process of filtration through the slit diaphragm of human kidneys by similar proteins.

"Similar molecules in flies and humans are responsible for forming these structures," said Susan Abmayr, Ph.D., Associate Investigator and senior author on the paper. "While these findings have also been reported by another group, we have gone on to show that small changes in the structure of the Sns protein – the protein necessary for the proper functioning of the renal filtration barrier in fruit flies – lead to major structural disruptions in the nephrocyte diaphragm. Moreover, elimination of the fly protein Pyd, another conserved slit diaphragm protein, also causes major structural problems."

The discovery that the fly equivalents of mammalian kidney proteins function in these cells, and that even modest changes in the nephrin-like Sns protein perturb the nephrocyte diaphragm, confirms that fruit flies are useful models for the mammalian slit diaphragm in the human kidney.

On the basis of these studies, the team is currently carrying out structure and function studies with Sns in the fly nephrocytes, since structural requirements for Sns are likely to be conserved in nephrin. They are also conducting genetic screens in flies to identify novel molecules associated with nephrocytes and the nephrocyte diaphragm with the hope that these molecules, like those described in this paper, will have human equivalents that are critical in the kidney.

PAPER: Sns and Kirre, the *Drosophila* Orthologs of Nephrin and Neph1, Direct Adhesion, Fusion and Formation of a Slit Diaphragm-Like Structure in Insect Nephrocytes

JOURNAL: *Development*

ISSUE: July 15, 2009

AUTHORS*: **Shufei Zhuang, Ph.D.**, Postdoctoral Research Associate; **Huanjie Shao, Ph.D.**, formerly a Postdoctoral Research Associate; **Fengli Guo**, Senior Electron Microscopy Specialist; **Rhonda Trimble**, Electron Microscopy Specialist; **Elspeth Pearce**, Research Technician II; **Susan Abmayr, Ph.D.**, Associate Investigator

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

Susan Abmayr, Ph.D., Associate Investigator, also is Associate Professor, Department of Anatomy & Cell Biology at The University of Kansas School of Medicine. Learn more about her work at www.stowers.org/labs/AbmayrLab.asp.

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

MOVING RIGHT ALONG

Demonstrating how a Trio of Compounds Make Room for Gene Expression and DNA Repair

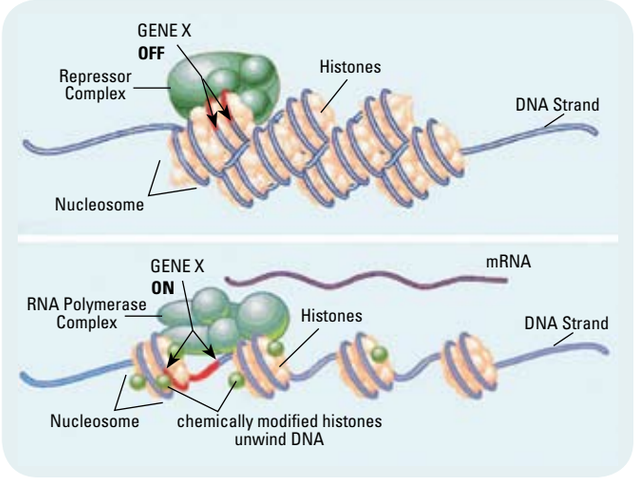
Chromosomes, the repositories of genetic information, are packaged in a complex combination of DNA, RNA, and protein called chromatin. Throughout a cell's life cycle, chromatin undergoes a series of structural changes known as chromatin remodeling. During the remodeling process, histone proteins – key components of chromatin – are rearranged in a process that exposes segments of DNA allowing them to interact with gene expression or DNA repair machinery.

The Stowers Institute's Conaway Lab recently discovered a previously unknown chromatin remodeling function of an enzyme called Amplified in Liver Cancer 1 (Alc1). The Alc1 protein is encoded by a gene that is associated with cancer of the liver when mutated or expressed at high levels. By itself, the Alc1 protein does not have any detectable effect on nucleosomes (the fundamental repeating units of chromatin), but, in the presence of a compound called NAD and another enzyme called poly(ADP-ribose) polymerase 1 (Parp1), Alc1 has the ability to move nucleosomes along strands of DNA and to expose specific segments of DNA.

Parp1 uses NAD to build a polymeric molecule, poly(ADP-ribose), that is coupled to Parp1 itself or to other proteins. The binding of a specific Alc1 region to poly(ADP-ribose) coupled to Parp1 helps recruit Alc1 to bind to and move nucleosomes along DNA.

"This finding is particularly interesting because Parp1 and poly(ADP-ribose) are known to play important roles in transcriptional regulation, DNA repair, and DNA replication, but how they do so is really not at all clear," said Ron Conaway, Ph.D., Investigator and co-senior author on the publication. "Finding that Parp1 and poly(ADP-ribose) recruit the chromatin remodeling enzyme Alc1 to chromatin and activate Alc1 activity suggests a mechanism by which they might function."

Medical researchers at universities and pharmaceutical companies are investigating Parp inhibitors for treatment of cancer and other diseases. The Conaway team has shown that Parp inhibitors block Alc1 activities in the test tube and live cells. The team's observation suggests that the therapeutic activities of these inhibitors could be due in part to indirect affects on Alc1. If true, drugs that target Alc1 function could also be useful in the treatment of disease.



National Institute on Drug Abuse, National Institutes of Health

Nucleosomes slide apart or become tightly compacted during chromatin remodeling, controlling the activity of a gene by increasing or decreasing its availability to the gene expression machinery, including RNA polymerase. RNA polymerase copies the DNA into mRNA, which acts as a "ticker tape" to direct protein production.

PAPER: Poly(ADP-ribosyl)ation Directs Recruitment and Activation of an ATP-Dependent Chromatin Remodeler

JOURNAL: *Proceedings of the National Academy of Sciences*

ISSUE: August 18, 2009

AUTHORS*: **Aaron Gottschalk**, Predoctoral Researcher; **Guyla Timinszky**, **Ph.D.**, European Molecular Biology Laboratory; **Stephanie Kong**, **Ph.D.**, Senior Research Associate; **Jingji Jin**, **Ph.D.**, Senior Research Associate; **Yong Cai**, Research Specialist I; **Selene Swanson**, Research Specialist II; **Michael Washburn**, **Ph.D.**, Director of Proteomics; **Laurence Florens**, **Ph.D.**, Managing Director of Proteomics; **Andreas Ladurner**, **Ph.D.**, European Molecular Biology Laboratory; **Joan Conaway**, **Ph.D.**, Investigator; and **Ron Conaway**, **Ph.D.**, Investigator

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

Joan Conaway, Ph.D., and Ron Conaway, Ph.D., hold faculty appointments as Professors in the Department of Biochemistry & Molecular Biology at The University of Kansas School of Medicine. Learn more about their research program at www.stowers.org/labs/ConawayLab.asp.

Michael Washburn, Ph.D., Director of Proteomics, holds a faculty appointment as an Associate Professor in the Department of Pathology & Laboratory Medicine at The University of Kansas School of Medicine. Learn more about his work at www.stowers.org/labs/WashburnLab.asp.

SHILATIFARD LAB POSTDOCS NAMED TO PRESTIGIOUS FELLOWSHIPS

The work of postdoctoral research associates in the Shilatifard Lab has been recognized recently with prestigious fellowships from the Leukemia & Lymphoma Society (LLS) and the Jane Coffin Childs Memorial Fund for Medical Research (JCC Fund).

Since 2003, the LLS has selected eight Stowers Institute postdocs for their highly competitive fellowships. In July, Shima Nakanishi, Ph.D., Postdoctoral Research Associate, became the ninth.

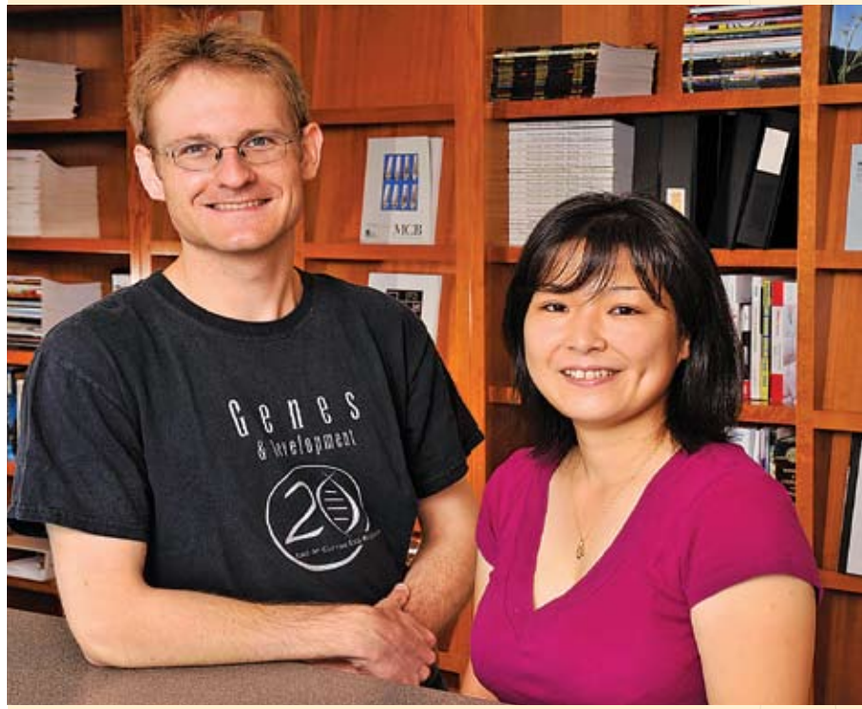
Dr. Nakanishi's appointment provides $165,000 over three years. The funding will support her study of the molecular role of histone modifications in polyploidy (cells containing more than two homologous sets of chromosomes) and her work in defining the molecular role(s) of post-translational modifications of chromatin in polyploidy and genomic instability – a subject that is currently poorly understood and that may shed light on cancer pathogenesis.

The LLS seeks promising investigators with less than two years of postdoctoral research training for their fellowships. Grantees are encouraged to embark on an academic career involving clinical or fundamental research in, or related to, leukemia, lymphoma, or myeloma under the direction of a research sponsor.

Hans-Martin Herz, Ph.D., Postdoctoral Research Associate, was selected for a fellowship from the JCC Fund.

The JCC Fund was established in 1937 to support research into the causes and treatment of cancer. It has taken a broad approach by encouraging the study of cell growth and development, emphasizing the basic biology and chemistry of the underlying processes. The JCC Fund supports fewer than two dozen new three-year fellowships each year with stipends averaging $44,000 a year.

As a Jane Coffin Childs Fellow, Dr. Herz will investigate how the fusion of the gene mixed-lineage leukemia (MLL) with other genes – a process called chromosomal translocation – causes leukemia. He will focus on the biochemical characterization of Dot1, a factor that is required for leukemogenesis.



Hans-Martin Herz (left) and Shima Nakanishi

A large proportion of leukemias in infants result from chromosomal translocations in MLL.

Additionally, Dr. Herz will participate in an annual JCC Fund Symposium where Fellows study a timely topic in cancer research and report on the status of their JCC Fund projects.

Ali Shilatifard, Ph.D., Investigator and mentor to Drs. Nakanishi and Herz, was awarded a Jane Coffin Childs Fellowship in 1995 while completing a postdoctoral fellowship in the lab of Drs. Joan and Ron Conaway, now Stowers Institute Investigators, at the Oklahoma Medical Research Foundation.

SWEET REWARDS

Visiting Scientist Awarded Grant from Alex's Lemonade Stand Foundation for Childhood Cancer

Erin Guest

ERIN GUEST, M.D., SPENDS MOST OF HER TIME TREATING CHILDHOOD CANCERS AS A PHYSICIAN IN THE DIVISION OF PEDIATRIC HEMATOLOGY/ONCOLOGY AT CHILDREN'S MERCY HOSPITALS AND CLINICS, BUT AS A VISITING SCIENTIST IN THE STOWERS INSTITUTE'S SHILATIFARD LAB, SHE IS ALSO EXPLORING THE ROOTS OF THE DISEASE. AND HER WORK IS GETTING NOTICED.

In April, Dr. Guest was awarded a Young Investigator Grant from Alex's Lemonade Stand Foundation for Childhood Cancer. The award provides $80,000 over two years and will support her efforts to uncover the molecular basis of chromosome translocations in the mixed-lineage leukemia (MLL) gene, which is found in a significant portion of infant leukemias and offers a particularly poor prognosis. Translocations are caused by the rearrangement of parts between non-homologous chromosomes (those that are not members of the same pair).

"When I learned of an opportunity to join Dr. Shilatifard's laboratory to investigate MLL gene rearrangements in the pathogenesis of human leukemia, I felt it would be a great opportunity to enter into basic research in a world-class facility, performing relevant and important work," said Dr. Guest.

A more robust understanding of the molecular properties of MLL in blood cells is critical to understanding its role in the onset of leukemia. That understanding will open the door to the development of therapies targeted to the MLL gene – therapies that promise to improve the disease's cure rates.

Dr. Guest's work piqued the interest of Alex's Lemonade Stand Foundation for Childhood Cancer, a foundation dedicated to carrying out the vision of Alexandra "Alex" Scott, who was diagnosed with neuroblastoma before her first birthday. In 2000, at the age of 4, Alex announced a seemingly simple idea – she would hold a lemonade stand to raise money to help find a cure for kids with cancer. The idea grew, and with the help of thousands of lemonade stands around the country, Alex raised $1 million for childhood cancer research before passing away in 2004.

Today, Alex's Lemonade Stand Foundation has raised over $25 million for childhood cancer research and has given millions of dollars for childhood cancer research across the country. The Young Investigator Grant given to Dr. Guest is designed to fill the critical need for start-up funds for early career physicians to pursue promising research ideas. These grants encourage and cultivate the researchers of the future and lead to long-term commitments to research projects.

Alex's Lemonade Stand Foundation works directly with physicians and researchers to identify the specific challenges faced in bringing new treatments to children with cancer. Grants distributed from the Foundation are designed to fill critical gaps in funding identified by doctors and researchers. This careful distribution of grants has allowed doctors to bring the latest and most promising lifesaving treatments to seriously ill children.

"As I build close connections with my patients and their families, I have a sense of responsibility to contribute to the overall knowledge of their disease," explained Dr. Guest. "I feel privileged to participate in research that will help clinicians and scientists to better understand the driving forces of leukemia and to ultimately improve the cure rates of this disease."

Dr. Guest earned her M.D. at the University of Oklahoma College of Medicine and her B.S. at the University of Oklahoma. She completed a Pediatric Residency at Children's Mercy Hospitals and Clinics in 2007 before beginning her Pediatric Hematology/Oncology Fellowship there.

KAUSIK SI NAMED MCKNIGHT SCHOLAR

Kausik Si

The Stowers Institute's Si Lab is dedicated to investigating the brain's ability to store information as memories and exploring how learning occurs via experience-dependent changes in the electrical properties of ensembles of neurons. A better understanding of the process of memory acquisition promises to shed light on memory-related disorders such as dementia and Alzheimer's disease.

Based on this work, Kausik Si, Ph.D., Assistant Investigator, was selected in May for a McKnight Scholar Award by the McKnight Endowment Fund for Neuroscience, which works to bring science closer to the day when diseases of the brain and behavior can be accurately diagnosed, prevented, and treated. To that end, the Endowment Fund supports innovative research through three competitive annual awards.

The award provides $225,000 over three years and is designed to encourage neuroscientists in the early stages of their careers to focus on disorders of learning and memory. Dr. Si will use the funding to pursue the role of a specific molecule in the persistence of memory by exploring the possibility that long-term memory may recruit a molecule, called CPEB, at the activated synapse, which maintains memory through the consistent production of a specific set of synaptic proteins.

"We are interested in understanding how long-term memories are formed," said Dr. Si. "The support from the McKnight Foundation will allow us to try new approaches to solve this important but yet unresolved problem. We hope that knowledge of the basic biology of the memory processes will help us to understand how various diseases or aging causes memory loss."

Dr. Si joined the Institute in June 2005 from the Columbia University Center for Neurobiology and Behavior where he conducted postdoctoral research since 1999 with Dr. Eric Kandel, winner of the 2000 Nobel Prize in Physiology or Medicine.

Dr. Si was named a Klingenstein Fellow in the Neurosciences in 2008, a Searle Scholar and a Basil O' Connor Fellow in 2006, a Francis Goelet Fellow in Neuroscience in 2002, and a Jane Coffin Childs Fellow in 2000. He earned a Ph.D. in molecular biology from the Albert Einstein College of Medicine and holds undergraduate and master's degrees in science from the University of Calcutta. He holds a faculty appointment as an Assistant Professor in the Department of Physiology at The University of Kansas School of Medicine.

SUE JASPERSEN AWARDED 2009 HUDSON PRIZE

Sue Jaspersen

Each spring, the Stowers Institute's leadership team and principal investigators gather at a ceremony to award the Hudson Prize, a $75,000 grant designed to accelerate the pace of laboratory experimentation of an Assistant Investigator at the Institute. The prize was created by the Texas-based Hudson Foundation to recognize and encourage excellence in basic biomedical research at the Stowers Institute.

The 2009 Hudson Prize winner is Sue Jaspersen, Ph.D., Assistant Investigator.

"Winning the Hudson Prize was a huge surprise and is a wonderful affirmation from the Hudson Foundation, Scientific Advisory Board, Bill, Robb, and Dave that ongoing and future research in my lab has and will impact the field of chromosome biology," said Dr. Jaspersen.

The additional resources provided by the Hudson Foundation will provide support for an undergraduate researcher in the Jaspersen Lab to extend his research through his senior year of college and beyond as a Research Technician in the lab the following year.

Peter Jabbour is working to determine the function of the SUN-like protein Slp1 in budding yeast. SUN-like proteins are a conserved family of proteins whose function is unknown in any organism. They contain a domain related to the SUN domain and are essential for growth of cells lacking SUN proteins, another evolutionarily conserved protein family that localizes to the inner nuclear membrane and functions as linker proteins between the nucleus and cell's "scaffolding," known as the cytoskeleton.

Mps3 is the budding yeast equivalent of the SUN protein. In a genome-wide synthetic lethal screen conducted in collaboration with the Stowers Institute's Molecular Biology Facility, the Jaspersen Lab discovered that Slp1 is essential for growth of certain Mps3 mutants. Given the genetic interaction and the similar SUN-like sequence, the team is working to understand if Slp1 performs a partially redundant function with Mps3, is in a parallel pathway, regulates Mps3, shares common binding partners, or has other traits in common.

To that end, Mr. Jabbour is using genetic and biochemical approaches to study Slp1 function and analyze its binding partners.

"I am excited that I can use the Hudson Prize to support the career of a new scientist, who is very enthusiastic and eager to learn new things," said Dr. Jaspersen. "Eventually, I expect Peter to go on to graduate school and do many more great projects, so by training him, I not only advance the work of my lab, but I also make a long-term investment in the future of the field."

Dr. Jaspersen holds a Ph.D. in Biochemistry from the University of California, San Francisco and a B.S. in Chemistry from Georgetown University. Since joining the Stowers Institute, she received the March of Dimes Basil O'Connor Starter Scholar Award because of the relevance of her research to the cause and prevention of birth defects. She holds a faculty appointment as an Assistant Professor in the Department of Molecular and Integrative Physiology at The University of Kansas School of Medicine.

AN ACADEMIC EXPEDITION

Science Teachers Hunt Phages at the Stowers Institute

High school teachers Melanie Brink (left) and Melanie Heath sift through dirt for phages

High school science teachers Eric Kessler (left) and Azadeh Taghizadeh

Deborah Jacobs-Sera, Co-Coordinator of the HHMI Professorship Phagehunting Program

Twice per year, the Science Teachers Access to Research at Stowers (STARS) program brings area science teachers on campus to deliver information and tools designed to bolster the high school and community college scientific curriculum. The Spring 2009 STARS program was offered in collaboration with a Howard Hughes Medical Institute-funded program at the University of Pittsburgh, and it was a bit unusual.

The price of admission: a small bag of dirt — specifically, dirt from warm, moist environments, where bacteria thrive. The program's 22 participating teachers were going phagehunting.

A phage is a type of virus whose host organism is a bacteria. Phagehunting is an endeavor to isolate, identify, and characterize novel bacteriophages from a variety of habitats. Over the three-day workshop, teachers used soil samples to isolate bacteriophage and then applied techniques of bioinformatics (the union of biology and computer science for the analysis of large sets of data) to annotate and analyze microphage genomes.

Phagehunting is an interactive lesson that is ideal for the classroom. Because phages play important roles in bacterial gene transfer and evolution, their study has illuminated basic genetic rules that pertain to all organisms, including humans. Only a miniscule proportion of the world's phages have been identified, and only a fraction of these have been studied, so students are introduced to a nearly boundless area of research.

"The workshop was intended to provide teachers with the knowledge and tools to adopt and implement a similar project for their students," said Arcady Mushegian, Ph.D., Director of Bioinformatics and organizer of the Stowers' phagehunting symposium. "Phagehunting is an exciting opportunity for a teacher to engage his or her students in a research project that helps to survey the diversity of organisms in the soil using the most up-to-date molecular and computational approaches."

Two of the symposium participants were successful in their hunts. Brenda Bott, a teacher at Shawnee Mission West in Shawnee Mission, Kansas, and Jeff Witters, a teacher at Olathe South in Olathe, Kansas, succeeded in isolating phages. Ongoing work at the Stowers Institute and the University of Pittsburgh is evaluating whether these phages have been previously characterized, or if they are new to science.

To receive information about future STARS symposia, send an e-mail with your full contact information, including school, subject, and grade level, to STARS@stowers.org.

Summer Scholars

Undergraduate Students Dedicate their Summer Vacations to Basic Science

Each year, as colleges and universities around the world let out for summer break, small groups of talented students find their way to the Stowers Institute to pursue summer research opportunities. This summer, those groups included 11 Stowers Scholars from undergraduate institutions around the United States; six students from Peking University in Peking, China; and six students from France, Italy, and Germany.

"The thrill of swimming is in the water and the thrill of skiing is on the slope. The same is true for research," said Ron Yu, Ph.D., Assistant Investigator, who has mentored several summer researchers. "When students apply what they have learned from textbook to real experiments and, in turn, gain insights into how the knowledge is acquired, it becomes addictive. Over the years I have given summer researchers increasingly challenging projects, and they thrive on the challenges. The Scholars program is invaluable to me, and I believe it is invaluable to the students, too."

Each student is placed with a mentor in a lab or support facility and is given an opportunity to conduct significant basic biomedical research utilizing cutting-edge technology and the most advanced research techniques. In the fall, they return to their home institutions with valuable experience and, sometimes, a new perspective on their future career path.

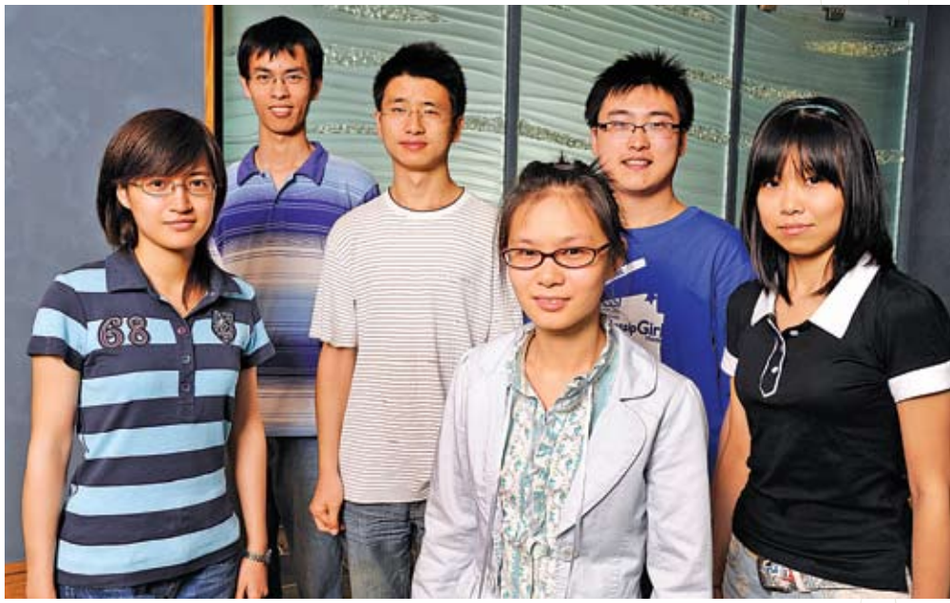
"I enjoyed the learning atmosphere at the Institute," said Jonathan Scoville, a third-year student majoring in Biochemistry at Brigham Young University who spent his summer conducting research in the Cytometry Facility. "There is always someone willing to help you understand difficult things, but they allow you to work and learn on your own. I always wanted to be involved in research, I just

2009 Stowers Scholars (back row from left) Jonathan Scoville, Stephanie Rawlings, John McGinnis, Spencer Karr, Jessica Samuelson, Kinjal Majumder (front row from left) Priyanka Surana, Steven Tan, Brian McCandless, Andrew Satterlee, and Megan Fracol

didn't know what kind. Now I know that I would like to study developmental cancer biology."

"After three years of courses, I had hardly gained any research experience, but I was interested in solving biological problems in a computational way," said Lingxue Zhang, a fourth-year student in Biology, French, and Mathematics at Peking University, who spent her summer providing bioinformatics support in the Yu Lab. "This experience allowed me to combine my knowledge in different subjects, including programming and statistics. I learned new skills and applied them in my research. It is also really amazing to compare my methods with a published paper, and to discover something new to be done in the field."

To learn more about the Stowers Scholars program and other summer research opportunities at the Stowers Institute, visit www.stowers.org/ScientistsSought/TrainingPrograms.asp.



International Scholars from the University of Peking (from left) Zhangli Su, Chuankai Zhou, Ye Qiu, Yu Jiang, Su Wang, Lingxue Zhang

Stowers Scholars Research Projects

Student Scholar	Lab	School	Project
Megan Fracol	Yu Lab	University of Kansas	A Genetic Approach to a Self-Propagating Neuronal Tracer
Spencer Karr	Media Prep	Tulane University	Preparation of Reagents and Growth Media
Kinjal Majumder	Baumann Lab	Drury University	Identification of Novel Protein at the Mature 3′ End of TER1 in *S. Pombe*
Brian McCandless	Rong Li Lab	Kansas State University	Molecular Mechanisms of Symmetry Breaking in Mouse Oocytes
John McGinnis	Linheng Li Lab	Luther College	Purification and Functional Verification of R-Spondin 1
Stephanie Rawlings	Abmayr Lab	University of Oregon	The Effect of SNS Immunoglobulin Domain Deletions on Cell Aggregation
Jessica Samuelson	Si Lab	University of Kansas	Persistence of Memory in *Drosophila*
Andrew Satterlee	Yu Lab	Kansas State University	Identification of an Estrus-Dependent Pheromone
Jonathan Scoville	Cytometry Facility	Brigham Young University	Assay Development for Analysis of Bone Marrow
Priyanka Surana	Zeitlinger Lab	Purdue University	Extracting High Resolution Information from ChIP-Seq Data
Steven Tan	Gerton Lab	University of California - Davis	Characterizing Psh1 in Budding Yeast

2009 Young Investigator Research Day

Each year, Stowers Institute students, postdoctoral researchers, research technicians, and research associates have an opportunity to highlight their research and hone their presentation skills at Young Investigator Research Day. Posters and oral presentations are scored by the Institute's principal investigators, and prizes are awarded for the highest scores. This year's event included plenary speakers Marc Kirschner, Ph.D., Department of Systems Biology, Harvard Medical School, and Martin Cohn, Ph.D., University of Florida Genetics Institute, plus 16 talks and 64 posters from Institute members.

Young Investigator Research Day Winners (back row from left) Liang Liang, Amber Mosley, Erin Katzfey, Erica White-Grindley, Laura Schaefer, Yan Hao (front row from left) Samantha Pattenden, Aaron Gottschalk, Karen Smith, and (not pictured) Matthew Goering

Best Poster Presentation by Scientific Staff		
Winner: Erin Katzfey	Abmayr Lab	Migration of Fusion Competent Myoblasts and Founder Cells During Myogenesis
Honorable Mention: Laura Schaefer & Yan Hao	Mak Lab	Identification of EGL-4 Downstream Effectors
Best Poster Presentation by a Graduate Student		
Winner: Aaron Gottschalk	Conaway Lab	Poly(ADP-ribosyl)ation Directs Recruitment and Activation of an ATP-Dependent Chromatin Remodeler
Honorable Mention: Liang Liang	Gibson Lab	Cell Cycle-Dependent Transcriptional Programs in the Developing *Drosophila* Wing
Best Poster Presentation by a Postdoctoral Researcher		
Winner: Karen Smith	Workman Lab	Subunit Composition of the Sin3 Histone Deacetylase Complex is Altered by Histone Deacetylase Inhibitors
Honorable Mention: Amber Mosley	Proteomics	Quantitative Proteomic Analysis of RNA Polymerase II Uncovers Changes in Subunit Composition During Interaction with the CTD Phosphatase Rtr1
Honorable Mention: Erica White-Grindley	Si Lab	Tob and Lim Kinase Act Consecutively to Increase Orb2 Stability and Multimerization
Best Oral Presentation by a Graduate Student		
Winner: Matthew Goering	Gerton Lab	Homologous Recombination in the Context of Rec8 or Mcd1 Cohesin in *Saccharomyces cerevisiae*
Best Oral Presentation by a Postdoctoral Researcher		
Winner: Samantha Pattenden	Workman Lab	Differential Recruitment of RSC1 and RSC2 Complexes to Highly Transcribed Genes in *S. cerevisiae*

The Hope Share Endowment

An Extraordinary Value of Long-Term Investment to Support Basic Scientific Research

BY JAMES E. STOWERS JR., CO-FOUNDER

When you make contributions to the Stowers Institute, the experience is radically different from giving to other worthwhile causes. Why is it different? Your money is not immediately spent, and you are not forgotten. All proceeds are added directly into the "Hope Share Endowment" of the Institute.

Each year, at least 3.5% of that dynamic long-term Endowment will be spent for scientific research. It is invested for long-term appreciation, and, over time, should earn more than the 3.5% that is paid out for scientific research each year.

Our scientific effort is made possible by the proceeds we receive from our Hope Share Endowment. We believe in endowment-based research, rather than a costly, unpredictable, yearly fund-raising effort.

The Institute issues you "Hope Shares®" to indicate your degree of participation in the Endowment for uninterrupted scientific research.

You will learn that the Hope Share Endowment is truly the lifeblood of the Institute.

The minimum initial Hope Share investment is $1,000.

The Hope Shares are registered in your name, while the value of the shares remains with the Endowment of the Institute.

Understanding "Hope Shares"

As a Hope Share owner, you have invested in our "Hope for Life" effort. The Stowers Institute issued you Hope Shares to indicate your degree of participation. The value of the shares fluctuates along with the value of the Endowment.

As an owner of Hope Shares, you will:

- Become personally involved in the long-term effort to provide Hope for Life — a better life for everyone
- Be remembered forever for your contribution to research because your gift keeps on giving
- Be informed of how your Hope Shares are contributing to the scientific effort each year
- Receive regular statements from the Stowers Institute for Medical Research so that you can follow our progress
- Receive an annual "Hope Share Statement," informing you of:
  - -The amount invested during the year
  - -Your total investment
  - -The present value of your Hope Shares
  - -The amount you are contributing to scientific research this year

You express your "Hope for Life" when you invest in "Hope Shares."

To establish a Hope Shares account, visit www.stowers.org or call (816) 926-4000.

Hope Shares®

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

Lifetime Contributions

The information listed below represents contributions from, in memory of, or in honor of the following, as of September 1, 2009.

$1 Million or More

American Century Foundation
From Pamela Stowers in Memory of Laura Stowers

$500,000 or More

Dunn Family Foundation
Barnett and Shirley Helzberg
Margaret Lichtenaur Estate

$100,000 or More

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

$50,000 or More

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

$25,000 or More

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

$10,000 or More

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

$5,000 or More

Clay Blair Family Foundation
Mary Breed Brink
Cancer Golf Association
Enrique Chang and Catherine Farley
Michael and Jenny Cormack
David and Nancy Dilley
In Memory of James and Eleanor Drake
David and Susan Keefer
Thomas Kmak Family
From Bo Kreiling in Memory of Helen Jayne Kreiling
Dawn Lind
Lucent Technologies (in kind)
Amy Noelker
From John and Susan McMeel in Memory of John O'Day
In Memory of Albert Otten and William Ellis
Austin and Laura Wilson

$1,000 or More

Don and Christine Alexander
From Rob Aneweer in Memory of Dave Aneweer and Jim Aneweer
Elmer and Verna Armbruster
Malcolm M. and Kathy B. Aslin Fund
Donald and Margaret Austin
From Michael and Dana Schaadt in Memory of Carol Barry and Herbert Schaadt
Paul Jr. and Joan Bartlett
From Bert and Joan Berkley in Memory of Kitty Berkowitz and Janice McInrath
John and Sheryl Block

From Jim and Virginia Stowers in Memory of Arthur Brand
Gregory Broome
In Memory of Carol Ann Brown
Mary Jo Browne
In Memory of Evelyn Louise "Lovey" Bryer
Michael and Gretchen Carter
Shirley Christian
In Memory of Alice "Penny" Cohn
Gilbert and Lois Cole
From Lauren and Ryan Contillo and Kathleen Stowers-Potter in Memory of Lawrence Joseph Contillo
From Cathryn and Jay Linney in Memory of William Cordes
From Frederick Coulson III in Memory of Frederick Coulson Jr.
Michael and Joyce Cunningham
Phillip Davidson
From Jim and Virginia Stowers in Memory of Walter Day
In Memory of Walter Day
Marshall and Jill Dean
In Memory of Carol Denicole
In Memory of Mark Dover
Terrence and Peggy Dunn
In Memory of Dana Eckles
In Memory of William Edwards
Ron and June Estabrook
Jill Farrell
Banning Flynn
Jody Anne Frederickson
Abby Freeman
William and Laura Frick Foundation Fund
The William George Family Charitable Trust
Jules and Marsha Goldman
Samuel and Melody Goller
Laura Greenbaum
Mary Louise Greene
Edward Jr. and Jodie Griffin
From Drs. James Griffin III and Margo Denke in Memory of James Griffin Jr.
Andrea Lynn Hazle
From Jim and Virginia Stowers in Memory of Paul Henson
Henson Trust Fund
Irv and Ellen Hockaday
In Memory of Estelline Huey
Robert and Lynette Jackson
Harrison Jedel
Jeffrey Johnson
Mr. and Mrs. Leroy Larsh Johnson
Otto and Margarete Katke Charitable Foundation
In Memory of Gary Kostuke
Bob and Myrna Krohn
In Memory of Jane Lundgaard
Linsley and Jane Lundgaard
Mary Kay McPhee
From Thomas and Janet Ink in Memory of Hazel Meany
Robert and Shirley Meneilly
Jeannette Nichols
Stephen Novak
From Herbert and Estelle Adler in Memory of Caryn Lisnek O'Connell
Robert Pearson
Robert and Jan Peterson
From Jim and Alex Potter, Lauren and Ryan Contillo, and Kathleen Stowers-Potter in Memory of James William Potter
Don and George-Ann Pratt
Michael J. Rainen Family Foundation
Isabell Berry Reed Revocable Living Trust
Craig and Maryanne Roepke
Felix Sr. and Carmen Sabates
From Jack Searcy in Memory of Barbara Searcy
In Memory of Elanor Smith
Darrell and Marjorie Spaedy
In Memory of Paul Stoffel and Aimee Stoffel
From Sierra Aviation in Honor of Jim and Virginia Stowers
Michele Stowers
Pamela Stowers
Mark A. Susz Revocable Trust
Ten Ten Foundation
In Memory of the Honorable Elwood Thomas
Harold and Ruthie Tivol
Robert and Roselle Tomsovic
Charles and Carol Diane Tritschler
David Tucker
John and Ollie Urie
Howard and Frances Vaughan Charitable Foundation
Dennis and Sally Von Waaden

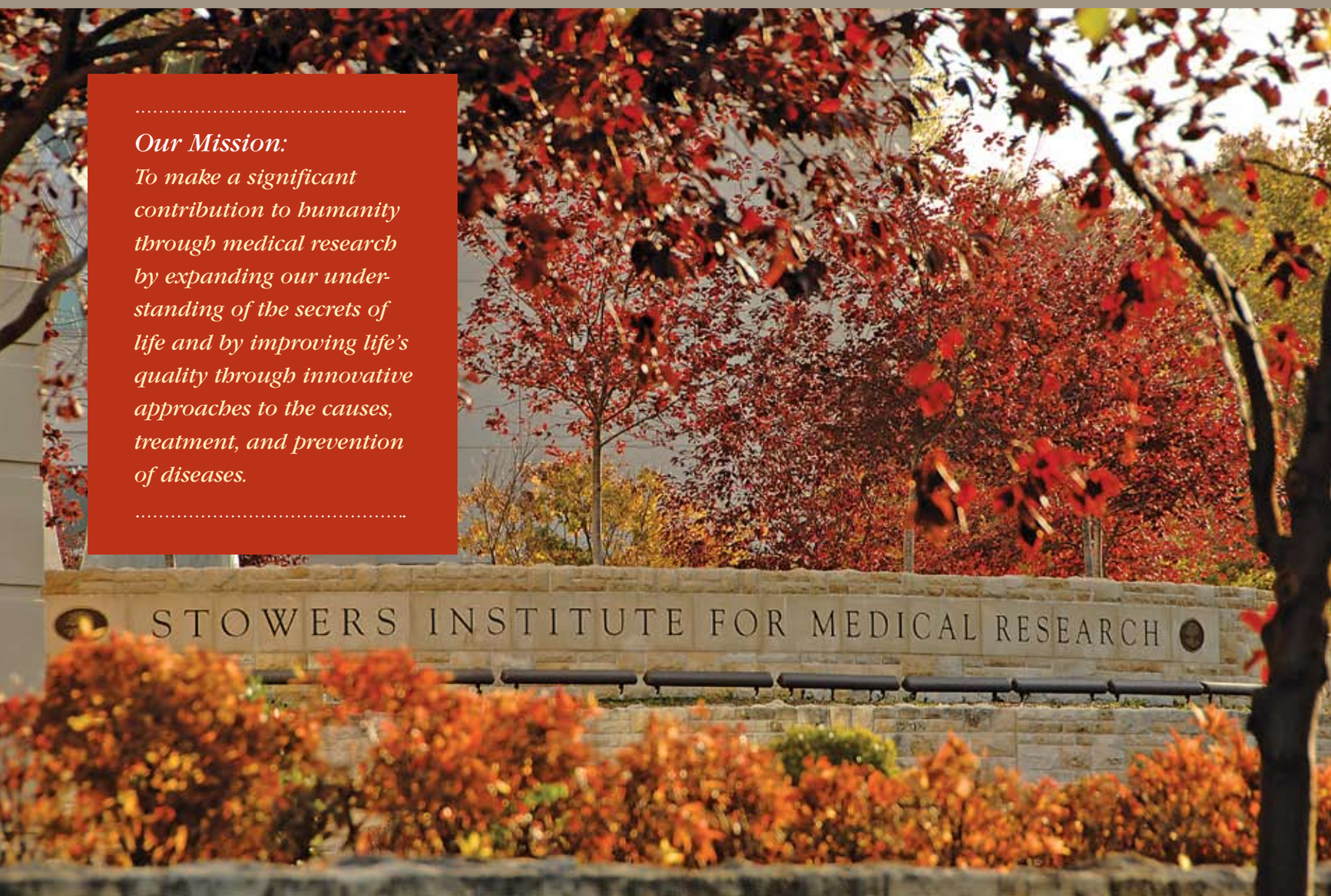
For information about establishing a Hope Shares account, visit www.stowers.org or call (816) 926-4000.

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.

STOWERS INSTITUTE®
FOR MEDICAL RESEARCH

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

Address Service Requested



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.