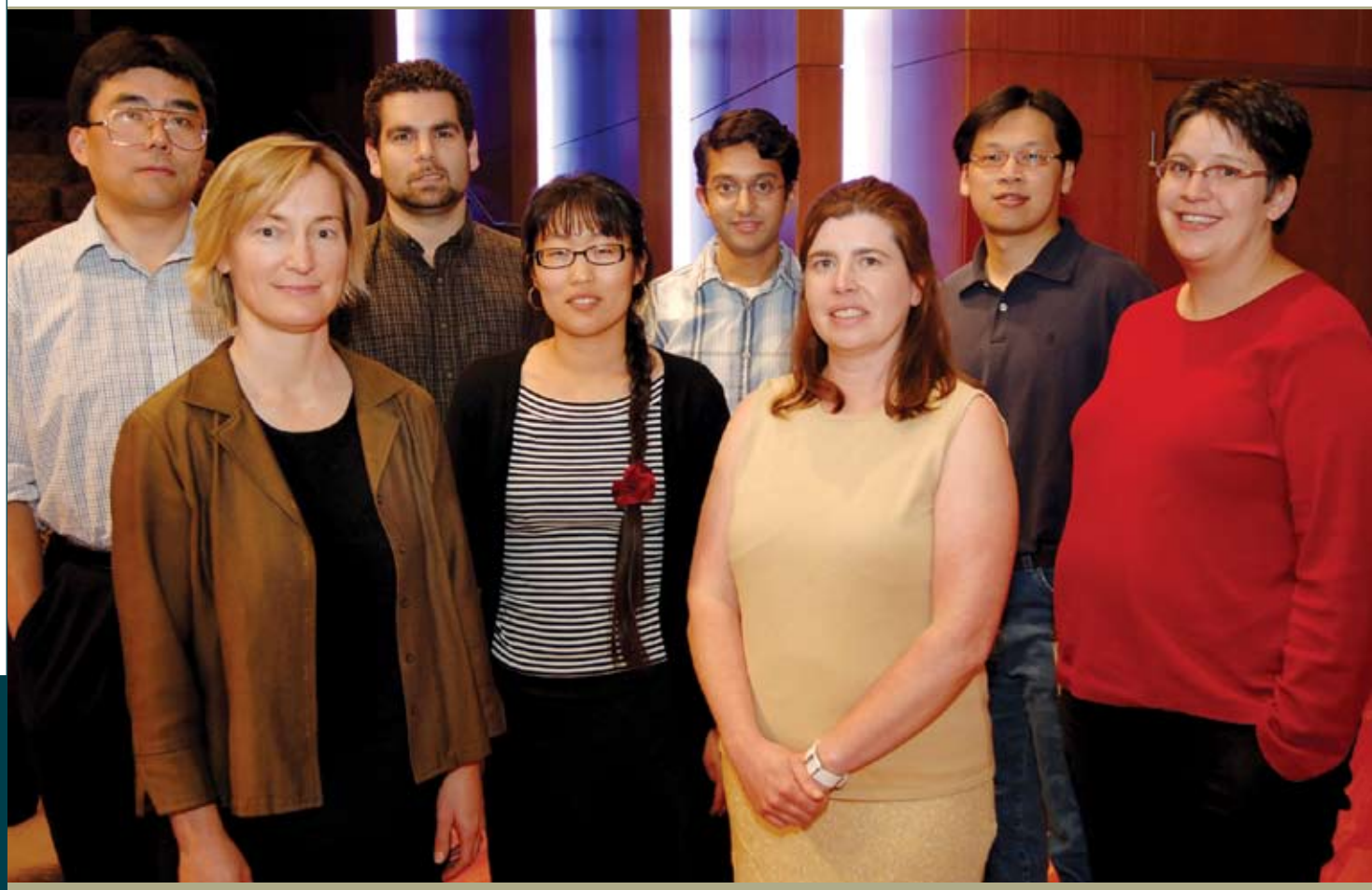
THE Stowers REPORT

NEWS AND INSIGHT FROM THE STOWERS INSTITUTE FOR MEDICAL RESEARCH



Participants in the Institute's first Young Investigators Research Day oral presentation competition gained valuable experience presenting their work to colleagues. Back row from left: Xiaogang Li, Ray Camahort, Mark Chandy, Wei-Jong Shia, Amber Mosley. Front row from left: Lisa Sandell, Mary-Lee Dequeant, Erica Grindley-White. See page 14 for more information about the event.

FALL 2006

VOLUME 9

Jim and Virginia Stowers believe basic research of the highest quality will lead to practical solutions for human disease. This important research is a long-term process. It may seem slow for those awaiting breakthrough treatments for presently incurable illnesses, but it will, ultimately, point the way to better means of preserving health and preventing disease. Stowers Institute scientists pursue the dream of Jim and Virginia Stowers by dedicating their professional lives to basic research. The results of their innovative research appear regularly in the world's leading scientific journals.

Inside this issue . . .

Why the Stowers Institute Supports Stem Cell Research

By William B. Neaves, Ph.D., President and CEO

People often ask why research with stem cells is so important to the Stowers Institute.

Appreciating the emphasis placed on stem cell research requires an explanation of the Institute's mission and strategies. Jim and Virginia Stowers articulated the mission when they announced the founding of the Institute. They said the Institute would conduct basic research that could give their grandchildren better options than they had if diagnosed with a serious illness decades from now. The strategy chosen by the Institute focuses on basic research to reveal how genes and their protein products control the most fundamental events in living cells — how cells multiply, differentiate, migrate, and die — all in the context of how a single cell becomes an entire organism.

Stem cell biology is central to the research strategy of the Stowers Institute, and several labs at the Institute concentrate on understanding the role of stem cells in health and disease. At our campus in Kansas City, where researchers study animal models, far more work has been done with adult and germ-line stem cells than with early, or so-called embryonic, stem cells (ES cells). The Institute takes great pride in the results of its scientists' research with adult and germ-line stem cells. Outstanding examples include the discovery of the bone marrow stem cell niche by a team led by Linheng Li, Ph.D., Associate Investigator, and the demonstration by the lab team of Ting Xie, Ph.D., Associate Investigator, of how stem cells must be physically anchored in their niche to develop properly.

The Institute aspires to conduct more ES cell research, but the persistent threat of state legislation to criminalize research with ES cells made by somatic cell nuclear transfer (SCNT) has dissuaded scientists working in this field from accepting appointments in Missouri. Consequently, Jim and Virginia Stowers personally support SCNT research at the Harvard Stem Cell Institute while co-chairing the Missouri campaign to protect stem cell research allowed under federal law. Missouri citizens will vote in November 2006 on a constitutional amendment to eliminate the threat of criminal sanctions against scientists who conduct research with ES cells made by SCNT. The future growth of the Stowers Institute in Missouri hinges on passage of the amendment.

Why is SCNT worth the effort to protect it as a research tool? No procedure other than SCNT has yet been shown to unlock the built-in capacity of the genome to regenerate functional cell types lost from disease or injury. Every one of the 50 trillion cells in a person's body has the entire human genome in its nucleus. No genes are discarded during development. Just because a cell ends up in your liver does not mean it lacks the genes for making a brain, heart, or pancreas. All the genes responsible for making the more than 220 functional cell types in the body still reside in every ordinary body cell.

Our challenge is learning how to induce expression of otherwise silent genes that could, for example, transform neuroglial cells into dopamine-secreting neurons to alleviate the symptoms of Parkinson's disease; or transform scar-tissue cells in a heart-attack victim's heart into myocardial cells; or to transform fibroblasts in the pancreas of a diabetic child into insulin-secreting islet cells.

Today, we know of only one way to unlock the regenerative potential inside the nucleus of every ordinary body cell — the procedure known as SCNT. By placing the nucleus of an ordinary body cell inside a donated egg lacking its own nucleus, the special biochemical factors in the egg cytoplasm reprogram the genome of the body cell nucleus and cause it to become a tiny cluster of undifferentiated cells in a lab dish, any one of which can be coaxed to develop into any of the more than 220 cell types of the body.

We believe that SCNT is an essential but temporary investigative tool, and that by studying how the egg cytoplasm reprograms the genome of body cells, we may eventually learn how to induce ordinary cells in an organ or tissue to transform into functional cell types destroyed by disease or injury without needing a donated egg.

By holding the key to unlocking the body's built-in capacity for self-repair, the SCNT procedure has remarkable potential to advance regenerative medicine. It is supported by dozens of patient advocacy groups, such as the American Diabetes Association, the Leukemia and Lymphoma Foundation, the Parkinson's Action Network, the Christopher Reeve Foundation, The Lance Armstrong Foundation, and the Michael J. Fox Foundation, and it is endorsed by leading medical and scientific organizations, including the National Academy of Sciences, the American Association for the Advancement of Science, the Association of American Medical Schools, and the American Medical Association.

Some people oppose research with ES cells made by SCNT because they believe those undifferentiated cells in a lab dish are a human being no different than a child with diabetes, a teenager with spinal cord injury, or an adult with Parkinson's disease. Most people, including most people of faith, reject this view. The majority of Americans support the search for cures through research with ES cells made by SCNT. By a two-to-one margin, Missourians also support this research.

Together, adult and ES cell research represent tremendous promise for understanding, treating, and curing many of the diseases that afflict humankind. The Stowers Institute, with its $2 billion endowment, state-of-the-art facilities, and world-class scientists, is poised to make groundbreaking stem cell discoveries in fulfillment of our mission — to provide Hope for Life®.

About the Stem Cell Ballot Initiative

The Missouri Stem Cell Research and Cures Ballot Initiative will appear on the November 7, 2006 ballot as Question 2. If passed, the Initiative will:

- Ensure that any stem cell research permitted under federal law may be conducted in Missouri, and any stem cell therapies and cures allowed under federal law may be provided to patients in Missouri.
- Ban and criminalize any attempt to clone a human being (appropriately defined as placing or attempting to place cells made by Somatic Cell Nuclear Transfer (SCNT) in a uterus to initiate pregnancy).
- Prohibit making human blastocysts by fertilization solely for research (thus ensuring that early, or so-called embryonic, stem cell research will use either leftover *in vitro* fertilization (IVF) clinic blastocysts that would otherwise be discarded or blastocysts made with the SCNT process), and prohibit taking stem cells from a blastocyst more than 14 days after cell division begins (an internationally-accepted ethical standard).
- Prohibit the purchase or sale of human blastocysts or eggs for stem cell research or stem cell therapies and cures.
- Allow human ES cell research to be conducted only after (i) approval by an Embryonic Stem Cell Research Oversight committee whose membership includes representatives of the public and medical and scientific experts (as recommended by the National Academy of Sciences), (ii) adoption of ethical standards that comply with the requirements of this amendment, and (iii) determination by an Institutional Review Board that the research complies with all applicable federal statues and regulations.

Contrary to claims by opponents, the ballot initiative:

- Will not create or increase any taxes.
- Will not require the state or taxpayers to fund any stem cell research.

You can read the full text of the ballot initiative on the Web site of the Missouri Coalition for Lifesaving Cures, www.MissouriCures.com.

Institute Appoints Three New Scientists

The Stowers Institute has welcomed three new Assistant Investigators to Kansas City — Marco Blanchette, Ph.D., Matt Gibson, Ph.D., and Ho Yi Mak, Ph.D. These appointments bring the Stowers Institute to a total of 20 independent research programs in cellular and molecular biology plus three technology centers in Bioinformatics, Imaging, and Proteomics.

"All of us at the Stowers Institute are delighted with the group of principal investigators who joined the Institute this year," said William B. Neaves, Ph.D., President and CEO. "The intellect, enthusiasm, and excellence of these three young scientists represent precisely what Jim and Virginia Stowers dreamed of bringing to Kansas City when they planned the Stowers Institute more than a decade ago."

"I'm very excited about the arrival of Drs. Blanchette, Gibson, and Mak," said Robb Krumlauf, Ph.D., Scientific Director, "not only for the things they will surely achieve independently, but also for the opportunities for collaborative research that each brings with his respective area of expertise."

Marco Blanchette

Dr. Blanchette joined the Institute from a postdoctoral fellowship in the lab of Donald C. Rio, Ph.D., at the University of California, Berkeley.

Dr. Blanchette's research focuses on three areas relating to pre-mRNA splicing: understanding alternative pre-mRNA splicing; identifying factors involved in regulating specific splice junction use; and using biochemical methods to examine detailed molecular mechanisms controlling specific alternative splicing events.

"I strongly believe that by joining the Institute I will be able to do research I would not have been able to do in a traditional academic environment," said Dr. Blanchette. "The infrastructure, the shared core facilities, and the resources provided by the Institute will allow me to design and perform experiments I simply would have been unable to do as a junior faculty member anywhere else."

Marco Blanchette

RNA splicing holds the key to understanding how the hundreds of thousands of complicated processes of cellular life in human beings are conducted and regulated

Institute Appoints Three New Scientists (cont.)

by only 23,000 genes. By alternative splicing of the RNA transcripts from a single gene into many different mRNA molecules, a single gene can have many different protein products that perform many different roles in living cells.

A better comprehension of RNA splicing is fundamental to understanding how genes control the multiplication, differentiation, migration, and death of cells. When things go wrong with these fundamental processes in living cells, a broad spectrum of human diseases can result.

Dr. Blanchette holds a Ph.D. in Microbiology from the Université de Sherbrooke in Québec, Canada, where he also completed his undergraduate degree. He received the Human Frontier Scientific Organization Long Term Postdoctoral Fellowship, the Governor General of Canada Academic Gold Medal, and the Hoffman-La Roche Award for Graduate Achievement.

Matt Gibson

Dr. Gibson joined the Institute this summer from a postdoctoral fellowship in the lab of Norbert Perrimon, Ph.D., a Howard Hughes Medical Institute Investigator at Harvard Medical School.

"I was attracted by the Institute's focus on high-quality basic science and the spirit of collegiality amongst scientists at all levels," said Dr. Gibson. "People really seem to have positive interactions with their colleagues working in different areas, which is a key to good science. I also felt this was an environment where I could keep doing experiments myself, rather than splitting my time between the many obligations of a traditional faculty appointment."

Dr. Gibson's research focuses on fundamental aspects of epithelial cell biology. He uses the fruit fly, *Drosophila melanogaster*, to understand the cellular and molecular mechanisms that sculpt epithelial tissues to precise parameters of size and shape. From the most primitive animals to humans, the organization of cells into epithelial sheets is essential for the development of normally functioning tissues and organs.

Dr. Gibson brings to the Institute a Burroughs-Wellcome Career Award in the Biomedical Sciences, an honor carrying $500,000 over five years to bridge advanced postdoctoral training and the early years of faculty service (see page 12 for more information).

The Gibson lab will pursue new ideas about how cells organize into epithelia and how epithelial integrity is maintained during cell division. His work provides insight into normal development while clarifying abnormal processes that lead to diseases such as cancer.

Dr. Gibson earned a Ph.D. in Zoology from the University of Washington, and a B.S. in Biology from Yale University. He held a fellowship awarded by the Jane Coffin Childs Foundation for Medical Research while completing postdoctoral research in the Department of Genetics at Harvard Medical School.

Ho Yi Mak

Dr. Mak comes to the Institute following a postdoctoral fellowship in the lab of Gary Ruvkun, Ph.D., at Harvard Medical School.

His research focuses on genetic factors that regulate how cells metabolize and store fat, a subject with implications for obesity-related disorders such as type-2 diabetes, cardiovascular disease, and other chronic illnesses. His previous research, using the nematode *C. elegans*, demonstrated that an ancient signaling axis linking food sensation and lipid metabolism may be conserved from nematodes to humans.

"I was drawn to the Stowers Institute because of its open scientific environment and welcoming atmosphere, which were evident from my very first visit. The commitment of everyone to do great science is obvious," said Dr. Mak. "Collaboration with the core facilities will allow me to pursue new lines of research and expand my work on the genetics of fat storage from invertebrates to vertebrates."

Dr. Mak earned a B.A. in Biochemistry from the University of Cambridge and a Ph.D. in Molecular Pathology from the Imperial Cancer Research Fund and the University College London. He was awarded a postdoctoral fellowship from the Massachusetts General Hospital Fund for Medical Discovery and a postdoctoral fellowship from the Human Frontier Science Program.

Matt Gibson

Ho Yi Mak

Laurence Florens and Michael Washburn Awarded 2006 Hudson Prize

Laurence Florens, Ph.D., Managing Director of Proteomics, and Michael Washburn, Ph.D., Director of Proteomics at the Stowers Institute for Medical Research, were named the winners of the 2006 Hudson Prize at a ceremony at the Stowers Institute on June 10.

The Hudson Prize, which carries a grant of $50,000, was created by the Texas-based H.R. and Evelyn Hudson Foundation to recognize and encourage excellence in basic biomedical research at the Stowers Institute.

"Laurence and I are deeply honored to receive the 2006 Hudson Prize because it recognizes the team effort in the Stowers Institute Proteomics Center and the highly collaborative nature of our work," said Dr. Washburn. "The beauty of the Hudson Prize is that it enables us to think outside of our proverbial proteomics box and move into a new area of applied research where we hope we can have an impact."

Laurence Florens

Dr. Florens' work at the Institute includes collaboration with investigators across multiple disciplines to apply the techniques of molecular biology, biochemistry, and genetics to analyze the structure, function, and interactions of proteins. She was listed as a co-author on 15 Institute publications in peer-reviewed journals in 2005.

Dr. Florens joined the Stowers Institute for Medical Research in 2003 from the Scripps Research Institute in La Jolla, California. She holds a Ph.D. in Structural Biology and Microbiology from the University of Aix-Marseilles in Marseilles, France.

From left: Hudson Prize winners Mike Washburn and Laurence Florens are joined by Virginia and Jim Stowers at the Hudson Prize Dinner.

Michael Washburn

Dr. Washburn's research focuses on quantitative proteomics as well as mRNA and protein expression. He leads a team of scientists who provide comprehensive proteomics to the Institute's independent research programs while advancing the field of protein identification by mass spectroscopy. The team's work has contributed significantly to the scientific progress of the Institute in its early years.

Dr. Washburn joined the Stowers Institute from the Torrey Mesa Research Institute in San Diego in 2003. He earned a Ph.D. in biochemistry and environmental toxicology from Michigan State University before completing a postdoctoral fellowship with Professor John Yates, III, in the Department of Molecular Biotechnology at the University of Washington.

The Proteomics Center

Since its creation in 2003, the Proteomics Center has consistently contributed to the quality of science conducted at the Institute. Under the dedicated supervision of Drs. Washburn and Florens, the Proteomics Center's team of nine scientists has collaborated on significant discoveries by Institute researchers published in leading peer-reviewed journals including *Science* and *Cell*.

PTEN and the Delicate Balance of Hematopoietic Stem Cells

Hematopoietic stem cells serve many functions in the human body, but perhaps the most important is maintaining the balance of cell expansion and lineage commitment in the bone marrow. Improper expansion creates an excess of cells that may lead to leukemia.

Linheng Li, Ph.D., Associate Investigator, and his colleagues at the Stowers Institute have long studied the role of hematopoietic stem cells, and recently they may have discovered the "tipping point" of the delicate balance described above. It resides in an understanding of a signaling molecule known as phosphatase and tensin homologue, or PTEN.

Dr. Li and his colleagues published on the *Nature* Web site on April 23 and in the May 25 print edition findings that show that this molecule, which normally keeps in check the phosphatidylinositol-3-OH kinase (PI(3)K) proliferation pathway, is crucial in maintaining the balance of hematopoietic stem cells.

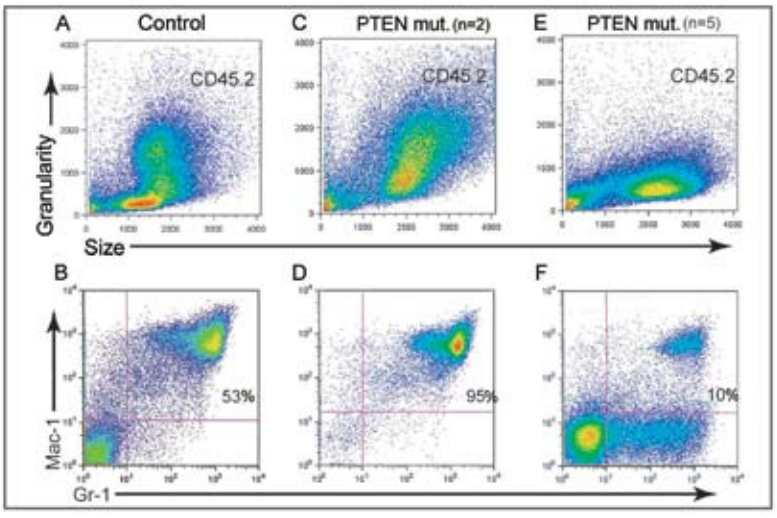
The team placed bone marrow stem cells containing an inactive form of PTEN into recipient mice and found that the PTEN-deficient hematopoietic stem cells could regenerate multi-hematopoietic lineages initially, but this ability declined later due to depletion in stem cells resulting from their over-proliferation and exhaustion. In contrast, the PTEN mutant cells generated myeloid and lymphoid leukemia with unlimited expansion of leukemia cells. Thus, PTEN functions to distinguish between normal versus cancer stem cells.

The similar self-renewal property shared by normal and cancer stem cells poses a problem for therapies designed to target cancer stem cells. The finding that PTEN is able to distinguish them makes it possible to target leukemia cells without adversely affecting normal stem cells.

"Stem cells hold great promise for the treatment of many human diseases," said Robb Krumlauf, Ph.D., Scientific Director. "But the body's limited supply of adult stem cells and our current inability to expand stem cells outside of the body have created major bottlenecks in developing practical therapies. These findings, paired with Dr. Li's earlier work, are bringing us closer to translating this research into long-awaited therapies."

"This publication was a true cooperative effort, which would not have been possible without the contributions of Drs. Grindley, He, and Yin, and the members of the Cytometry core facility," said Dr. Li. "No single person can take credit for these findings, so we're very fortunate to have such a dedicated team of collaborators here at the Stowers Institute."

Jiwang Zhang, Ph.D., formerly a Senior Research Associate at the Stowers Institute for Medical Research, and Dr. Li are credited as the first and last authors, respectively. Additional contributing authors from the Stowers Institute include Justin Grindley, Ph.D., Senior Research Associate; Tong Yin, Ph.D., Postdoctoral Research Associate; Sachintha Jayasinghe, formerly a Cytometry Laboratory Manager I; Cici He, Research Specialist II; Jason Ross, Predoctoral Researcher; Jeffrey Haug, Managing Director - Cytometry Facility; Dawn Rupp, Research Technician II; Kimberly Porter-Westpfahl, Research Technician I; and Leanne Wiedemann, Ph.D., Staff Scientist. Hong Wu, Ph.D., at University of California, Los Angeles also contributed to the article.

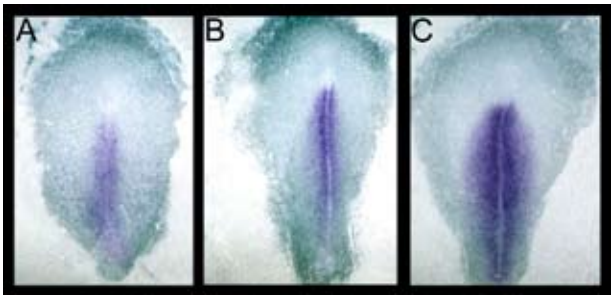


Flow cytometry images show in the left column a healthy ratio of bone marrow blood cell size to granularity (A) and a normal distribution of myeloid to lymphoid cells (B), indicating a healthy PTEN balance, and an absence of leukemia. Conversely, the middle and right columns show the result of PTEN removal. The middle column shows a skewed ratio of cells with increased size and granularity (C) and an abnormally high ratio of myeloid to lymphoid cells (D), suggesting Acute Myeloid Leukemia. The right column shows another example of a skewed ratio of cells with altered size and granularity (E) and an abnormally low ratio of myeloid to lymphoid cells (F) indicating possible Acute Lymphoblastic Leukemia.

Understanding the Role of Transcription Factors in Spinal Development

Olivier Pourquié, Ph.D., Investigator, and Howard Hughes Medical Institute Investigator, together with colleagues at the Stowers Institute published two important papers this year that shed light on the role of two families of transcription factors in the formation of the spine. Transcription factors are the proteins that bind to DNA and play a role in the regulation of gene expression by promoting transcription.

Transcription factors localize to regions of promoter and enhancer sequence elements either through direct binding to DNA or through binding other DNA-bound proteins. They act by promoting the formation of the preinitiation complex (PIC) that recruits and activates RNA polymerase.



In the early stages of the developing chicken embryo, spine precursors activate HoxB gene expression. The blue staining here demonstrates the increase in HoxB gene expression as the embryo develops.

Clarifying the Role of *HoxB*

In June, Dr. Pourquié, and Tadahiro Iimura, Ph.D., a Senior Research Associate, published "Collinear activation of *HoxB* genes during gastrulation is linked to mesoderm cell ingression," on the *Nature* Web site (it later appeared in the August 3 print edition of *Nature*). The paper provided insight into the role of *Hox* genes in spine formation.

The vertebral column is a highly regionalized structure, with each vertebra bearing a specific identity established in embryonic development. Vertebral identity is known to be under the control of a group of transcription factors called *Hox* genes. These genes are found in four clusters in the genome and their arrangement along the chromosome reflects their distribution in nested domains along the length of the future spine. This surprising property is termed "spatial co-linearity."

Previously, it was believed that the spatial co-linearity of *Hox* genes along the body axis was established during posterior growth of the vertebrate embryo. Dr. Pourquié's lab demonstrated that, in fact, *Hox* genes control the moment when cells leave the superficial layer of the embryo to join the precursors of the vertebrae in the mesoderm, demonstrating that the establishment of spatial co-linearity in the embryo is directly controlled by the *Hox* genes themselves.

"These findings have changed our perception of the regionalization of the vertebral column and opened the way to a new area of research," said Dr. Pourquié. "Very little is known about the targets and the functions of *Hox* genes. These experiments provide us with a convenient assay to understand how *Hox* genes control the ingression behavior of epiblast cells, and they might clarify the function of this fundamental class of transcription factors."

"We believe these findings will help to understand the progressive regionalization of the spine and the problems that arise when regionalization is ineffective or incomplete, as in severe cases of congenital scoliosis," said Dr. Iimura.

The findings challenge the conventional scientific understanding of spinal development, and move this field of research to a more productive track — opening the door for additional important findings in the future.

Understanding *Snail*

Jacqueline Kim Dale, Ph.D., formerly a Senior Research Associate at the Institute, and Dr. Pourquié demonstrated that the long-studied family of transcription factors called *Snail* is expressed in a cyclic fashion during the formation of the vertebral precursors in the mouse and chick embryo.

The findings, which were published in the March 7 issue of *Developmental Cell*, indicate that the genes governing many cellular properties are downstream of the segmentation clock, the mechanism that controls the formation of the vertebral column.

"We are trying to understand how the periodic formation of the vertebral precursors in the embryo is controlled at the molecular level and how this process is integrated with the overall growth of the embryo," said Dr. Pourquié.

The findings implicate a novel family of transcription factors — the *Snail* proteins — in the process of embryonic segmentation, thus providing a link between the morphogenesis of the tissue that generates the vertebrae and the periodic production of their precursors.

The *Snail* factors are known to control the transition of the epithelium to a mesenchyme state and have been actively studied in cancer, where they are thought to play a role in controlling tumor invasion. Understanding their function in embryonic development may provide insight into their dysfunction in cancer.

Additional contributing authors to this paper from the Stowers Institute include Pascale Malapert, formerly Lab Manager II; Jérome Chal, Predoctoral Research Associate; Gonçalo Vilhais-Neto, Predoctoral Research Fellow; Miguel Maroto, Ph.D., formerly a Senior Research Associate; Teri Johnson, Managing Director of the Histology Facility; Sachintha Jayasinghe, formerly a Cytometry Laboratory Manager I; and Paul Trainor, Ph.D., Assistant Investigator.

Solving a 90-Year Genetics Mystery

The first article in the 1916 premier issue of the scientific journal *Genetics* was Calvin Bridges' "Nondisjunction as proof of the chromosome theory in heredity." In addition to proving that genes map on chromosomes, and that mistakes in the segregation of chromosomes results in the aberrant transmission of genes, the paper presented a mystery.

When one crosses appropriately marked XY males to XX females, one in every 2,000 occurrences results in an XXY female, a disorder known as primary nondisjunction. If you take those XXY daughters and cross them back to XY males, the frequency of nondisjunction rises nearly one hundred-fold to one in 20, and the phenomenon is known as secondary nondisjunction.

What caused this dramatic rise in non-disjunction? Bridges offered an explanation that was quickly disproved, and it wasn't until 1948 that researcher Kenneth Cooper offered an alternative, albeit speculative, explanation that those X chromosomes that failed to pair and recombine with each other would then couple with the Y in mid-prophase to form a trivalent (the Y is metacentric and the Xs are acrocentric). The Y would then direct the Xs to the opposite pole of the developing spindle resulting in XX<->Y segregation.

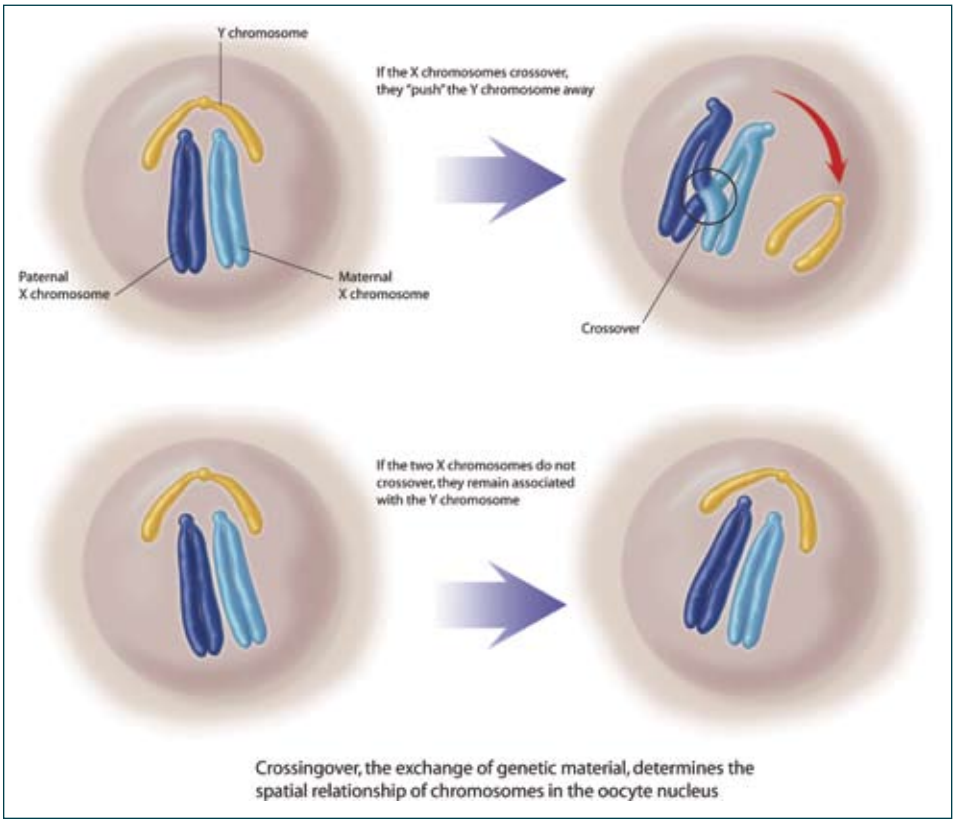
Cooper went on to a distinguished career in genetics that included teaching chromosome biology at the University of California, Riverside. His theory of secondary nondisjunction remained the dominant one for nearly six decades, even though it had never been tested.

This year, just in time for the 90th anniversary issue of *Genetics*, one of Cooper's former UC Riverside students, Scott Hawley, Ph.D., Stowers Institute Investigator, and Youbin Xiang, Ph.D., a Research Specialist in Hawley's lab, put Cooper's theory to the test.

"What we found was that although Cooper was right about the trivalent, he was wrong about how it was formed, and he was wrong in a very important way," said Dr. Hawley. "It turns out that the XXY trivalent is there from the very beginning of prophase. If the Xs fail to crossover, the trivalent is maintained. But if the two Xs do crossover, they dissociate themselves from the Y chromosome and form a monogamous bivalent."

"The good news is, we've resolved the fascinating nondisjunction problem posed by Bridges 90 years ago," said Dr. Hawley, "and the better news is that in doing so, we've opened a whole new venue of research and uncovered so many new questions to answer."

"It is a great honor for Dr. Hawley and for the Institute that his findings resolving the question of secondary nondisjunction will appear in the 90th-anniversary edition of *Genetics*," said Robb Krumlauf, Ph.D., Scientific Director. "He has contributed so much to the field of genetics both as a researcher and a teacher. I can think of no one better to revisit Dr. Bridges' 1916 findings."



Crossingover, the exchange of genetic material, determines the spatial relationship of chromosomes in the oocyte nucleus

Tracing the Cellular Origin of Treacher Collins Syndrome

Paul Trainor, Ph.D., Assistant Investigator, and his team at the Stowers Institute have collaborated with colleagues from the University of Manchester Dental School in the UK on a paper that identifies the cellular origins for craniofacial abnormalities that occur in Treacher Collins syndrome.

Treacher Collins syndrome is a rare disorder of craniofacial development affecting about 1 in 50,000 individuals. It is characterized by ear, nose, upper, and lower jaw anomalies that include cleft palate.

The findings, published in the September 5 issue of the *Proceedings of the National Academy of Sciences* (PNAS), establish that the craniofacial anomalies associated with a mouse model of Treacher Collins syndrome arise due to a high degree of cell death, which leads to a failure to produce sufficient neural crest cells. Moreover, the team found, the few neural crest cells that are produced have compromised proliferation capacites.

"Since neural crest cells ultimately form most of the bone, cartilage, and connective tissue in the head and the face, it is not surprising that a deficiency in the number of neural crest cells leads to craniofacial malformations," said Natalie Jones, Ph.D., former Postdoctoral Research Associate in the Trainor lab and co-first author on the paper.

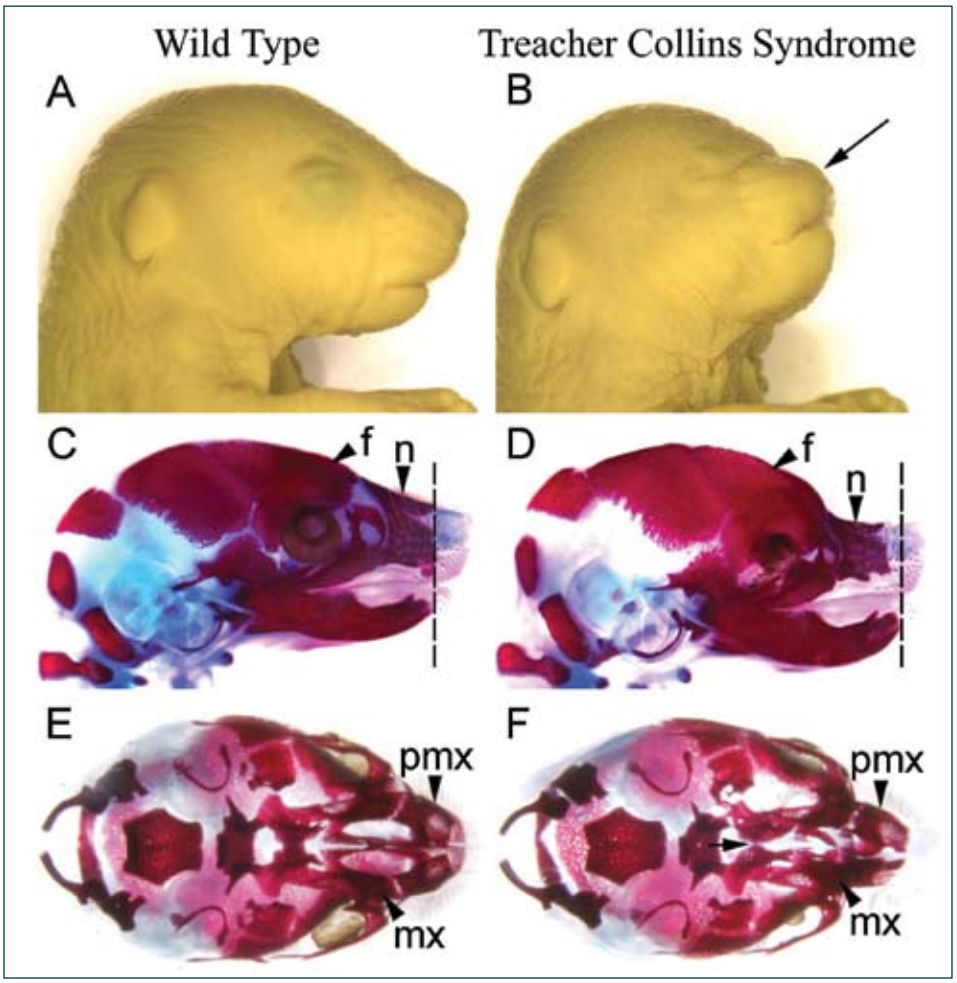
The team believes that when translated to human development, these findings indicate that within the first 3-8 weeks of pregnancy, a similar period of extensive cell death results in a failure to produce enough neural crest cells and causes the facial characteristics observed in individuals with Treacher Collins syndrome.

"These findings are an exciting step in our investigation of genetic birth abnormalities," said Dr. Trainor. "In ongoing studies in the lab, we are testing a number of methods for chemically and genetically inhibiting the early period of cell death, known as apoptosis, in an effort to stimulate the production of neural crest cells which could help to prevent the development of craniofacial anomalies."

"These results represent a major breakthrough in our understanding of Treacher Collins syndrome," said Robb Krumlauf, Ph.D., Scientific Director. "But the door that these findings open — to the possibility of intervening *in utero* to prevent the disease — is truly groundbreaking."

Jill Dixon, Lecturer, University of Manchester School of Dentistry, is an equal first author on this paper. Michael Dixon, Professor, University of Manchester School of Dentistry, is a corresponding author. Additional Stowers Institute contributing authors are Lisa Sandell, Ph.D., Senior Research Associate; Sachintha Jayasinghe, formerly a Cytometry Laboratory Manager I; Jennifer Crane, Predoctoral Researcher; and Jean Philippe Rey, Histology Specialist II.

Comparison of wild-type (normal) (A) and Treacher Collins (B) newborn mice. Treacher Collins mice exhibit shortened and domed-shaped heads with frontonasal dysplasia (arrow). Skeletal staining of E17.5 wild-type (C,E) and Treacher Collins (D,F) embryos reveals hypoplasia of numerous craniofacial bones including the nasal (n), frontal (f), premaxillary (pmx), maxillary (mx), together with cleft palate (arrow) in mutant embryos.



Scott Hawley Elected to American Academy of Arts and Sciences

The American Academy of Arts and Sciences (AAAS) elected Scott Hawley, Ph.D., Investigator, to its 227th class. He was among 175 new American Fellows announced in April.

Dr. Hawley is the Institute's fourth member to be elected to the Academy, joining Robb Krumlauf, Ph.D., for his contribution in understanding how *Hox* genes and regulatory pathways control brain development in vertebrates (elected in 2003); and Investigators Joan Conaway, Ph.D., and Ron Conaway, Ph.D., for their work in understanding the molecular mechanisms of gene transcription (elected in 2002). The Conaways were the first residents of Kansas City ever elected to the AAAS.

Founded in 1780 by John Adams, James Bowdoin, John Hancock, and other scholar-patriots, the Academy has elected as Fellows and Foreign Honorary Members the finest minds and most influential leaders from each generation, including George Washington and Ben Franklin in the eighteenth century, Daniel Webster and Ralph Waldo Emerson in the nineteenth, and Albert Einstein and Winston Churchill in the twentieth.

Current AAAS membership includes 4,000 American Fellows and 600 Foreign Honorary Members, consisting of more than 170 Nobel Laureates and 50 Pulitzer Prize winners. Functioning as an independent policy research center, the Academy undertakes studies of complex and emerging problems facing society. Current research at the Academy focuses on science and global security; social policy; the humanities and culture; and education.

"I can't overstate the significance of this announcement for Kansas City, the Stowers Institute, and, especially, Dr. Hawley," said William B. Neaves, Ph.D., President and CEO.

"Jim and Virginia Stowers have created an environment at the Stowers Institute that attracts scientists who can be counted among the brightest intellects in America's history. Dr. Hawley is certainly worthy of this recognition, and we are proud of his many achievements."

Dr. Hawley leads a team of 19 scientists who study the mechanisms by which cells transmit genetic information during routine cell division (mitosis) and during the process of creating gametes (meiosis). Many cancer cells gain or lose chromosomes during abnormal cell divisions that accompany malignant transformation. A clearer view of how chromosomes are properly transmitted during cell division has direct implications for understanding cancer.

Dr. Hawley came to the Institute in 2001 from the University of California, Davis where he was a professor of genetics in the department of Molecular and Cellular Biology. As an internationally renowned expert in the genetics of meiosis, Dr. Hawley has conducted research with the fruit fly, *Drosophila*, to make discoveries about reproductive genes that have important implications for understanding particular birth defects in humans, such as Down syndrome.

In addition to his appointment at the Stowers Institute, Dr. Hawley holds the prestigious designation of American Cancer Society Research Professor. He is also Professor of Physiology at the University of Kansas School of Medicine and Adjunct Professor at the University of Missouri, Kansas City. He holds a B.S. in Biology from the University of California, Riverside and a Ph.D. in Genetics from the University of Washington, Seattle.

Connecting with the Past in the Book of Members

By R. Scott Hawley, Ph.D., Investigator

Because genetics is such an incredibly "young" science, I've been able to meet most of my heroes in the field. It's been my honor and privilege to know many of those who have won Nobel Prizes for their work in genetics, as well as many more individuals who should have won them. What I find most intriguing about these people is that they are so much more than just geneticists, cell biologists, or biochemists — they are scholars in the truest sense of the word.

This respect for such true scholars obviously extends beyond the boundaries of genetics and cell biology to include people such as John Adams, Thomas Jefferson, and Benjamin Franklin. Unfortunately, as much as I admire their scholarship, creativity, and writings, I was born far too late to meet them.

Thus, it was a tremendous honor when, on October 2 of this year, I was inducted into the American Academy of Arts and Sciences, a learned society founded by these incredible intellects. Signing my name in the Book of Members, as those individuals did years before, created for me a historical connection not only to our founding fathers, but to those subsequent members of the society, such as Alexander Graham Bell and Albert Einstein, whose scholarship has built the world in which we live.

I'm privileged to join in this year's class not only the ranks of an incredibly distinguished cadre of biologists and scientists, but also people such as former Presidents Bill Clinton and George Bush, Chief Justice John Roberts, and the actor and director Alan Alda, who have contributed so much to our culture by their creativity and accomplishments.

The fact that the American Academy of Arts and Sciences has chosen to recognize four of the senior members of the Stowers Institute says something very special about this place. The "house that Jim and Virginia built" has, indeed, become a centerpiece for scientific inquiry; and the world is beginning to recognize that. I'm indebted to the people who made my selection possible — most especially the people in my lab who've done the hard work that made our scientific achievements possible. I am deeply honored to become a part of the Academy's storied history. I can't imagine being in better company.

The fact that the American Academy of Arts and Sciences has chosen to recognize four of the senior members of the Stowers Institute says something very special about this place.

Institute's Early Career Scientists Receive Major Awards

Recent recruiting efforts by the Stowers Institute have yielded a group of early-career scientists who come from postdoctoral appointments in prominent laboratories, and who are quickly establishing reputations for excellence in their own research programs. These young principal investigators are joined by a talented team of postdoctoral researchers who make significant contributions to the Institute's research.

The Institute expects its early-career scientists to accomplish great things, but the pace of accomplishments by the current group is more than anyone could have expected. This year, three principal investigators and three postdoctoral researchers have received significant competitive research grants.

"We always recruit scientists whom we believe represent the best of the very best," said William B. Neaves, Ph.D., President and CEO, "but even we are surprised by the number of prestigious appointments bestowed upon the Institute's young scientists this year. The recognition of their work by these competitive grant awards gives us increased confidence that significant scientific accomplishments will follow."

American Cancer Society Postdoctoral Fellowship

Justin Blumenstiel, Ph.D., a Postdoctoral Research Fellow in the Hawley Lab, has been awarded an American Cancer Society (ACS) Postdoctoral Fellowship.

The ACS Postdoctoral Fellowship supports research training for those who have just received their doctorate and enables recipients to qualify for an independent career in cancer research. Dr. Blumenstiel's award of $138,000 will be distributed over three years.

Dr. Blumenstiel is developing a genetic screen to identify novel genes that facilitate somatic pairing of chromosomes. In turn, he will examine meiotic pairing in these mutants to determine if somatic and meiotic pairing are mechanistically related. Additionally, he is testing whether heterochromatin, nucleated by the RNA interference machinery, facilitates pairing between chromosomes.

Burroughs-Wellcome Fund Career Award

Matt Gibson, Ph.D., Assistant Investigator, joined the Institute from a Postdoctoral Research Fellowship at Harvard University, where he was selected as Harvard's nominee for the highly competitive Burroughs-Wellcome Fund Career Award. After accepting his appointment at the Stowers Institute, Dr. Gibson learned he had been selected for the award which carries a stipend of $500,000 over five years.

The Burroughs-Wellcome Fund fosters the development of the next generation of academic medical scientists. By providing funding to help bridge the gap between the postdoctoral and early faculty years, the Fund hopes to bolster the careers of the most promising up-and-coming scientists. Additionally, winners attend biennial meetings and mentoring networks, designed to give scientists early in their careers the information they need to be successful.

Dr. Gibson will dedicate the award to pursuing new ideas about how cells organize into epithelia and how epithelial integrity is maintained during cell division. His work provides insight into normal development while clarifying abnormal processes that lead to diseases such as cancer.

Leukemia and Lymphoma Society Special Fellow

Philippe Prochasson, Ph.D., a Postdoctoral Research Fellow in the Workman Lab, was named a Leukemia and Lymphoma Society Special Fellow in January. The three-year appointment provides $60,000 of funding annually. Dr. Prochasson previously held a regular postdoctoral fellowship from the Leukemia and Lymphoma Society.

Dr. Prochasson's work focuses on studying the function and selectivity of bromodomain, a protein domain found in a variety of mammals and invertebrates. Currently the function of bromodomains remains largely unknown, but its importance has been linked to understanding DNA and gene regulation. Additionally, Dr. Prochasson is working on defining the role of the HIR complex during cell cycle. Understanding the role of the HIR complex and the basic functions involved in transcriptional regulation may help to develop new ways to cure cancer.

Leukemia and Lymphoma Society Special Fellows must have completed a minimum of two years of postdoctoral research training and continue to conduct their research under the direction of a research sponsor. The Special Fellowship is designed to permit the fellow to begin transitioning to an independent research program.

National Institutes of Health Postdoctoral Fellowship

Gretchen Dollar, Ph.D., a Postdoctoral Research Associate in the Pourquié Lab, transferred a National Institutes of Health Postdoctoral Fellowship when she joined the Stowers Institute this summer. The grant carries $48,796 in funding over one year.

Dr. Dollar will work to analyze the role of *Wnt* signaling in development of the vertebrae. In particular, she focuses on the regulation of proteins required for cell polarity and movements in this process by *Wnt* signalling.

National Institutes of Health Research Grant

Ron Yu, Ph.D., Assistant Investigator at the Stowers Institute, was awarded a National Institutes of Health grant for his work, "Genetic Mapping of Functional Vomeronasal Circuit" in January. The award totaling nearly $2 million will be allocated over a five-year period.

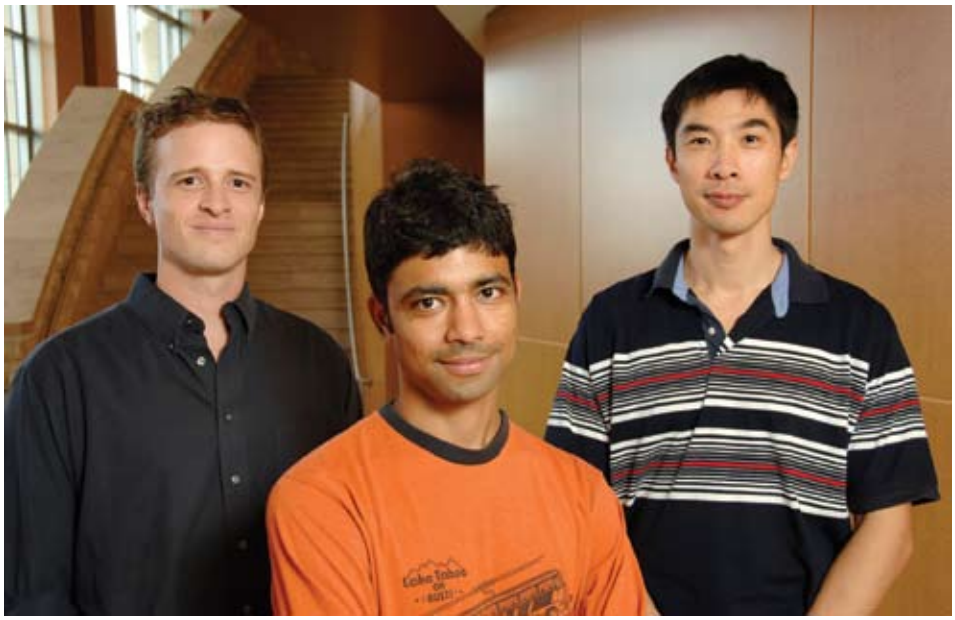
Dr. Yu's work deals with the mechanisms of sensory information processing in the brain, especially as it relates to the sense of smell. He studies the neural circuits and their physiological functions in the mouse olfactory and vomeronasal systems to reveal how the nervous system detects, parses, and integrates sensory information and generates meaningful behaviors.

Searle Scholars Program

Kausik Si, Ph.D., Assistant Investigator at the Stowers Institute, was named a Searle Scholar in April. The distinction carries an award of $240,000 over three years and is bestowed on just 15 early-career scientists each year.

Since its beginning in 1980, the Searle Scholars Program has awarded 393 scholars in academic and research institutions across the world. Dr. Si is the Stowers Institute's first scientist to receive the Searle Scholar Award while working at the Institute.

Dr. Si joined the Institute in 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. Dr. Si's lab team 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.



Top photo: *From left: Matt Gibson, Kausik Si, and Ron Yu.* ***Bottom photo:*** *From left: Justin Blumenstiel, Philippe Prochasson, and Gretchen Dollar.*

Institute Hosts First Young Investigators Research Day

Bodo Stern (left) and Kevin Eggan (right) participate in the Young Investigators Research Day panel discussion, "Communicating Science to the Public."

The Stowers Institute's Crossroads Postdoc and Student Association hosted the Institute's first Young Investigators Research Day on April 17. The event gave Stowers Institute research team members, graduate students, and postdoctoral researchers an opportunity to showcase their research projects and interact with senior scientists.

"Crossroads wanted to provide an opportunity for every lab member to present their work, and to establish a conference setting with the potential to foster new ideas and generate collaborations within the Stowers research community," said Samantha Pattenden, Ph.D., Postdoctoral Research Fellow in the Workman Lab, and one of the event's organizers. "It was exciting to see how many of our members actively participated in all of the events."

Throughout the day, the Institute's young investigators participated in poster sessions and oral presentations summarizing their research results. Posters and presentations were judged by the Institute's principal investigators, and winners in each category were awarded a $400 grant to attend a scientific meeting of their choice. Runners-Up received $200 grants to spend on scientific books, journals, or software for use in their research training.

"Young Investigators Day was a very useful and informative event," said Lisa Sandell, Ph.D., a Senior Research Associate in the Trainor Lab and winner of the Best Oral Presentation by a Postdoctoral Researcher. "Having the opportunity to give a talk was a great benefit to me personally. The preparation and practice were invaluable and the experience has already helped me with subsequent presentations outside the Institute."

The event's keynote address was delivered by Kevin Eggan, Ph.D., Assistant Professor of Molecular and Cellular Biology at Harvard University and an Assistant Investigator with the Stowers Medical Institute, an independent Medical Research Organization funded by Jim and Virginia Stowers. Dr. Eggan discussed his quest to understand the earliest steps in the development of neurodegenerative disease by studying neurons differentiated from early stem cells made by nuclear transfer using skin cells from patients.

Bodo Stern, Ph.D., Senior Editor at *Cell*, delivered a presentation titled "Behind the Scenes at *Cell*," which offered insight into the peer-review publication process.

Stowers Institute Investigator Scott Hawley, Ph.D., and Director of Public Affairs and Media Relations Marie Farrell Jennings joined Drs. Eggan and Stern for the final session, a panel discussion moderated by Robb Krumlauf, Ph.D., Scientific Director, titled "Communicating Science to the Public."

Prize winners included:

Lisa Sandell, Ph.D., *Senior Research Associate* — Winner, Best Oral Presentation by a Postdoctoral Researcher

Erica White-Grindley, Ph.D., *Postdoctoral Research Associate* — Runner-Up, Best Oral Presentation by a Postdoctoral Researcher

Ray Camahort, *Predoctoral Researcher* — Winner, Best Oral Presentation by a Graduate Student

Mary-Lee Dequeant, *Predoctoral Researcher* — Runner-Up, Best Oral Presentation by a Graduate Student

Manqi Deng, Ph.D., *Senior Research Associate* — Winner, Best Poster by a Postdoctoral Researcher or Research Team Member

Jose "Leo" Gutierrez, Ph.D., *Postdoctoral Research Associate* — Runner-Up, Best Poster by a Postdoctoral Researcher or Research Team Member

Alexander Aulehla, Ph.D., *Senior Research Fellow* — Honorable Mention, Best Poster by a Postdoctoral Researcher or Research Team Member

Kelly Trujillo, Ph.D., *Postdoctoral Research Associate* — Honorable Mention, Best Poster by a Postdoctoral Researcher or Research Team Member

Claude Shelton, *Predoctoral Researcher* — Winner, Best Poster by a Graduate Student or Research Team Member

Matthew Goering, *Predoctoral Researcher* — Runner-Up, Best Poster by a Graduate Student or Research Team Member

Stowers Scholars

Each summer, college students from around the country apply to participate in the Stowers Scholars Program. This year, seven Stowers Scholars were selected from among 88 applicants. These students conduct research at the Institute under the supervision of Stowers researchers and cap off 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.

2006 Stowers Scholars: From left: James Bernard, Scarlett Savage, Joanna Spaulding, Shaili Sharma, Stefani Fontana, Eva Stephens, Sutton Ansley.

Stowers Scholars 2006 Projects

Student Scholar	Lab	School	Project
W. Sutton Ansley	*Yu Lab*	Washington and Lee University	*Automating a Behavioral Experiment Using an Olfactometer*
James Bernard	*Krumlauf Lab*	University of Kansas	Hox *Genes and Expression in Chick Embryos*
Stefani Fontana	*Yu Lab*	University of Kansas	*Identification of a Novel Male-Specific Pheromone Receptor in the Vomeronasal Organ*
Scarlett Savage	*Gerton Lab*	William Jewell College	*Mutational Analysis of Yeast Scum3*
Shaili Sharma	*Bioinformatics*	University of Minnesota, Duluth	*Identifying Protein Complexes in High-Throughput Proteomics Data*
Joanna Spaulding	*Molecular Biology*	Valparaiso University	*Super FP*
Eva Stephens	*Microarray*	Rockhurst University	*Exploring the IME1 Promoter*

Hope Shares®

Between January 1 and September 30, 2006, contributions of at least $1,000, the minimum for establishing a Hope Shares® account in the endowment of the Stowers Institute, were received from, in memory of, or in honor of the following:

$100,000 or MORE
Margaret Lichtenauer Estate

$5,000 or MORE
American Century Employees
Country Club Bank
Rick and Betsey Solberg

$1,000 or MORE
Terrence and Peggy Dunn
Bob and Myrna Krohn
Dawn Lind
Amy Noelker
Kathleen Stowers

In Memory Of
Carol Ann Brown

These donors and those they honor will never be forgotten.

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.

Housed in a 600,000 square-foot state-of-the-art facility on a 10-acre campus in the heart of Kansas City, Missouri, the Stowers Institute for Medical Research conducts basic research on fundamental processes of cellular life. Through its commitment to collaborative research and the use of cutting-edge technology, the Institute seeks more effective means of preventing and curing disease. The Institute was founded by Jim and Virginia Stowers, two cancer survivors who have endowed it with more than $2 billion in support of basic research of the highest quality.

The Stowers Report
Vol. IX
Published by the
Stowers Institute for
Medical Research

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

CONTRIBUTORS:

Photos:
Don Ipock

Science Writing:
Marie Farrell Jennings

Design and Layout:
Kuhn & Wittenborn Advertising

STOWERS INSTITUTE®
FOR MEDICAL RESEARCH