THE Stowers REPORT

NEWS AND INSIGHT FROM THE STOWERS INSTITUTE FOR MEDICAL RESEARCH

Stowers Institute for Medical Research principal investigators who have received recent noteworthy awards and honors gather at the west end of the Stowers Institute® campus. Front row, from left: Paul Trainor, Robb Krumlauf, Chunying Du. Second row, from left: Olivier Pourquié, Peter Baumann, Jennifer Gerton, Ting Xie.

FALL 2003

VOLUME 6

Ultimate solutions take time. That's particularly true with complex human diseases and birth defects since there is still much we don't understand about the fundamentals of life. At the Stowers Institute for Medical Research, investigators seek to increase the understanding of the basic processes in living cells – a crucial step in the search for new medical treatments.

Inside this issue . . .

SCOTT HAWLEY:

The Bonds of Matrimony in Meiosis

"Organisms are very, very careful about meiosis. The glaring exception is humans. No other organism is as fundamentally sloppy as we are about this most fundamental biological process."

-Scott Hawley, Ph.D.

It has been 120 years since scientists first described meiosis, the process of forming reproductive cells such as the egg and sperm. But how the process works at the molecular level is still shrouded in mystery. Solving that mystery has been Stowers Institute for Medical Research Investigator Scott Hawley's holy grail for 20 years.

Meiosis is at the heart of how Mendelian genetics works in sexually reproducing organisms, he explained. It is also at the heart of human joy – and misery.

"You mess meiosis up; you lose offspring," Dr. Hawley said. "We humans are lousy at meiosis. We lose 25 to 50 percent of our conceptions because we make mistakes in the process of sorting our chromosomes. It is a testament to other drives (best discussed by psychologists) that our population continues to increase."

As described in the October 2003 issue of *Genetics*, Dr. Hawley's lab at the Stowers Institute has discovered a key protein involved in meiosis, and its name is Matrimony. "Matrimony holds paired things together for a while," Dr. Hawley said.

Match, Lock, and Move

In meiosis, the chromosomes in diploid cells (containing two copies of each chromosome) segregate and form haploid reproductive cells (the sperm and the egg, which carry just one copy of each chromosome). Dr. Hawley nicknames the three fundamental steps in meiosis "match them; lock them; move them." In a review article in the August 8, 2003 issue of *Science*, he and his Stowers colleague Dr. Scott Page described these steps in more detail as a pas de deux ballet.

Scott Hawley, Investigator, joined the Stowers Institute in 2001 from the University of California-Davis and continues to research the molecular mechanisms of meiosis.

During the matching step, the homologous (similar) chromosomes somehow recognize each other and form pairs. The chromosome 21 you received from dad picks the chromosome 21 you received from mom out of the crowded tangle of DNA in your cell's nucleus. Biologists still don't understand how this pairing occurs, so according to Dr. Hawley they use textile analogies like button, zipper, or Velcro to describe the combination.

Then, the chromosomes segregate and move to opposite poles of the cell, which divides and forms two daughter cells. The chromosomes are pulled apart by thread-like spindles that attach them to the poles.

Drifting Apart

The locking step is where things can really go wrong. For humans and many other organisms, the main locking system is the exchange of DNA (also called recombination, crossover, or chiasma formation), in which chromosomes interlock long portions of their arms. If the exchange fails, the homologous chromosomes may drift apart and lose track of each other, inviting disaster. For example, one daughter cell may have two copies of chromosome 21 and the other may have no copies at all. If a normal sperm fertilizes these eggs, the resulting embryo will have either three copies of chromosome 21 (trisomy), which results in Down Syndrome, or just one copy (aneuploidy), which is usually not viable. For humans, a locking failure is most relevant to chromosome 21. It is one of the few cases in which errors in chromosome segregation can produce viable embryos, probably because it has the fewest genes.

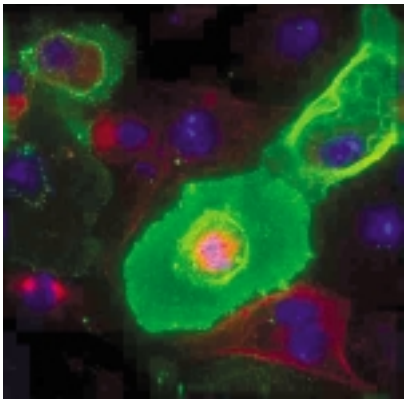


Photo of membrane around spindles. A homolog (close relative) of the meiotic Axs protein defines a membrane that encases the spindles during mitosis. In this photo of a Drosophila cell undergoing mitosis, the chromosomes (blue) are attached to microtubular spindles (red). They are encased in a membrane (green) produced by an Axs homolog, a close relative in the family of Axs proteins. (Deconvolution microscopy photo by Dr. Cathy Lake, Research Specialist I at the Stowers Institute)

Backup Matrimony

Because locking is so important, most organisms have a backup system, known as homologous achiasmate segregation or the distributive system. Using this backup, the chromosomes are linked together not by exchange but by the persistent pairing of a specific region of DNA, known as heterochromatin. Heterochromatin is made of highly repetitive DNA sequences, also called satellite DNA, and it is normally found around the centromere, near the middle of the chromosome.

Humans, who are unusually "sloppy" at meiosis, appear to have a backup system that works well while women are young, but fails as they approach menopause. Thus, a 20-year-old woman's chromosomes can segregate properly even when the main exchange program fails during meiosis, but that is frequently not the case for a woman in her forties. That failure may account for the increasing difficulty of pregnancy and risk of birth defects as a woman ages.

To learn more about the backup system, Dr. Hawley studies a very simple meiotic system: the backup mechanism used by female fruit flies of the species *Drosophila melanogaster*. These studies uncovered the locking protein his lab termed Matrimony, which binds to the heterochromatin and holds the chromosome pairs together. Mutations in Matrimony appear to destroy the heterochromatin's bonds.

Dr. Hawley continues to investigate exactly where Matrimony binds on the chromosomes, whether it is part of a larger protein complex, and if so, how that complex is assembled and then disassembled when it is time for the chromosomes to separate. He is exploring what dose of Matrimony is sufficient for meiosis, and how the backup system stands in relation to the exchange mechanism. However, that is proving to be quite challenging.

"We are just now creating the genetic tools we need to do it," Dr. Hawley said. "Eventually, though, this research will tell us exactly how this conjunction in meiosis works. We will be able to describe at a molecular level how homologous chromosomes hang on to one another and then separate."

A Surprising Spindle Membrane

Earlier this year, Dr. Hawley's lab reported another important finding in the February/March 2003 journal *Nature Cell Biology*. On Christmas Eve in 1983, Dr. Hawley had discovered a mutant known as Axs (for Aberrant X chromosome Segregation) that causes defective segregation of chromosomes during meiosis. A few years ago, much to everyone's surprise, his lab realized that the product of this gene, the Axs protein, is a transmembrane protein.

"That was weird," Dr. Hawley said. "What was a membrane protein doing inside the cell? It sounded messy."

Then postdoctoral student Joseph Kramer, now a Lab Manager II at the Stowers Institute, showed Dr. Hawley stunning photographs of membranes encasing the meiotic spindles. They determined that Axs helps build those spindle membranes. Without them, the chromosomes cannot stay in position, resulting in faulty meiosis.

The discovery of this whole new biological structure and the importance of the Matrimony protein may help explain how meiosis functions – or, as is too often the case in humans – malfunctions.

Discovering Matrimony was not a planned event. Two researchers in Hawley's lab made a chance observation about the failure of meiosis in a control for an unrelated experiment. Later, David Harris, a research technician, who is now in graduate school at the Massachusetts Institute of Technology, investigated the problem on his own. He identified a DNA binding protein (and the gene that produced it). Then he demonstrated that mutations in that gene, which he named Matrimony, disrupt the locking step in *Drosophila's* meiosis.

Recent Papers from the Hawley Lab

Harris, D., Orme, C., Kramer, J., Namba, R., Champion, M.D., Palladino, M.J., Natzle, J.E., & Hawley, R.S. (2003) A deficiency screen of the major autosomes identifies a single gene (matrimony) that is haplo-insufficient for achiasmate segregation in Drosophila oocytes. *Genetics* (in press).

Page, S.L. & Hawley, R. S. (2003) Chromosome Choreography: The meiotic ballet. *Science*, 301(5634), 785-789.

Hawley, R.S. (2003) The human Y chromosome: Rumors of its death have been greatly exaggerated. *Cell*, 113(7), 825-828.

Kramer, J. & Hawley, R.S. (2003) The spindle-associated transmembrane protein, Axs, identifies a membranous structure ensheathing the meiotic spindle. *Nature Cell Biology*, 5(3), 261-263.

OLIVIER POURQUIÉ:

A Time and a Place for Every Segment

As a physical characteristic, segmented bodies abound among animals. From insects and worms on up the animal kingdom, bodies are subdivided into very similar units, formed by the reiteration of the same developmental sequence in the embryo. In humans and other vertebrates, these segments are called somites, and they become vertebrae and their associated muscles. Defects in the cyclical developmental pattern of somites can produce spinal deformities.

"I'm trying to understand how our vertebral column is built and what molecular mechanisms control the periodic production of the vertebral precursors in the embryo," Associate Investigator Olivier Pourquié said.

His group has discovered two interrelated systems that govern this periodic growth, and he was recently awarded a $1.145 million grant from the National Institutes of Health to investigate further the process of segmentation.

Associate Investigator Olivier Pourquié works with a chick embryo in his laboratory at the Stowers Institute, which he joined in 2002 from his position as Director of Research at the Developmental Biology Institute of Marseille, France.

The first system is a timing mechanism that he named the segmentation clock, run by oscillating waves of gene expression that determine when each successive segment will form. The second system is a signaling pathway that specifies where those segments will form. These processes are described in a review authored by Dr. Pourquié in the July 18 issue of *Science*.

"The embryonic cells read the temporal pattern of gene expression," Dr. Pourquié said, "and translate that information into a spatial progression of growth."

The Segmentation Clock

In embryonic development, the formation of the body begins with the head and progresses towards the posterior end or tail. "This progressive event is fascinatingly rhythmic," Dr. Pourquié said. "In chickens, a new somite is formed every 90 minutes; in mice, every two hours." The number of somites is fixed for each species. Chickens and humans have around 50, mice have 65, and snakes can have 400.

Several years ago, Dr. Pourquié's team described regular "flashes" of gene expression in the notch pathway, which is involved in many developmental processes. Those flashes indicate a molecular oscillator or "clock" that regulates the segmentation process. The period of one oscillation precisely corresponds to the timing required to produce one segment.

"We and other labs have now found oscillating genes in multiple species, which suggests the clock has been conserved throughout vertebrate evolution," Dr. Pourquié explained. "It's very exciting, because it turns out that invertebrates such as spiders use similar machinery. If this observation is confirmed in other invertebrates, it may resolve a 200-year-old debate about the conservation of an ancestral patterning mechanism in the animal kingdom."

A Spatial Gradient

More recently, Dr. Pourquié realized that the temporal clock tells only part of

the segmentation story. "The embryo is a dynamic system and changes shape with time," he explained. "In addition to the clock, it needs a second system that specifies space. The clock tells when to form, not where."

His group discovered what he calls a "traveling gradient" that defines the position where the segments form. The posterior end of the embryo secretes the growth factor FGF (fibroblast growth factor), which maintains cells in an immature state, preventing them from differentiating. When the next segment forms, the earlier segment is pushed away from the tail. As a segment gains distance from the tail's FGF, it becomes increasingly differentiated and eventually develops into specialized tissues and organs. This progression explains why an early embryo looks more developed in the head region than at the tail.

"We've identified FGF signaling in chickens and mice, and I'm prepared to bet that this is conserved in humans, too," Dr. Pourquié said.

"Our work on segmentation patterns can explain a number of syndromes involving malformed vertebral columns, such as scoliosis," he said. "It doesn't help patients yet, but it's a start."

Dr. Pourquié researches the progressive process of embryonic vertebrate development in the chicken and mouse. Recently, he has become interested in snakes. "They make a huge number of segments," he said. "The process gets crazy!"

The Chicken Genome Project

First, scientists sequenced the worm's genome. Then we had sequencing projects for mice and men, as well as dogs and fish. Why not the chicken? The genome – the entire sequence of DNA – of an organism contains valuable information about its development, evolution, and diseases. Genome sequences allow scientists to identify and study the genes that orchestrate those processes. However, while the chicken is a valuable organism, both as a source of food and as a model organism for biologists, it has been slow to attract a genome project of its own.

"The chicken community has not been united," Dr. Pourquié explained. "One half was interested in agriculture and the other in basic biology, and they had nothing in common."

Since having the sequenced genome would help both camps, Dr. Pourquié and a small group of colleagues proposed a coordinated effort. He and Dr. Dave Burt of the Roslin Institute now co-chair the newly formed International Chicken Genome Consortium, as discussed in the June 13 issue of *Science*.

As a model organism for embryology research, the chicken has much to offer. "It's a warm-blooded vertebrate and amniote with an accessible egg," Dr. Pourquié said. It's also very close developmentally to that other important model, the mouse, which is so genetically close to humans.

"The mouse is great for genetic experiments, but we don't have good embryological data about it compared to chicken," he said. "We get an idea and try it in the chick embryo, which can take only weeks. Then we refine it with genetic experiments in mice, which can take years. They are very complementary systems. Having access to the chicken genome will change our lives."

Recent Papers from the Pourquié Lab

Dale J.K., Maroto, M., Dequeant, M.L., Malapert, P., McGrew, M., & Pourquié, O. (2003) Periodic Notch inhibition by Lunatic Fringe underlies the chick segmentation clock. *Nature*, 421(6920), 275-278.

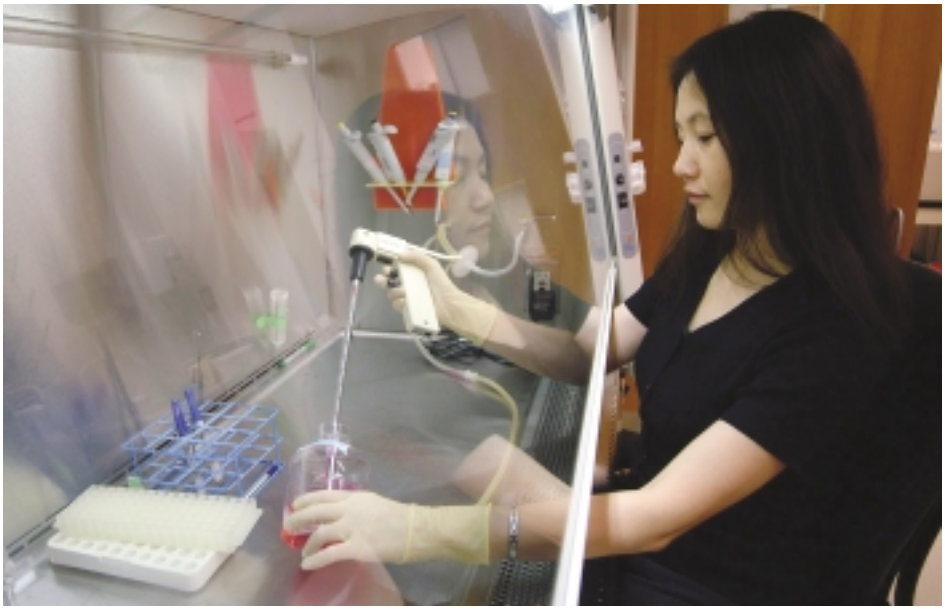
Pourquié, O. (2003) The Segmentation Clock: Converting embryonic time into spatial pattern. *Science*, 301(5631), 328-330.

Burt, D. & Pourquié, O. (2003) Chicken Genome: Science nuggets to come soon. *Science*, 300(5626), 1669.

CHUNYING DU:

Using Smac to Sensitize Cancer Cells to Therapy

Our cells have a program that tells them when it is time to die – and that also forces them to do so when they misbehave. This cell death program, known as apoptosis, provides a vital pruning of unnecessary cells during development and prevents cells that have become too old or too damaged from lingering on and causing harm. Cancer cells, however, evade apoptosis, so they continue living and dividing long after they have become dangerous. Thus, restoring the cell death program is a crucial goal for cancer researchers. Assistant Investigator Chunying Du's research suggests an elegant way to revive apoptosis and sensitize tumors to anti-cancer therapies. The U.S. Department of Defense has awarded her a $358,000 grant to apply this research to radiation-resistant prostate cancer.



Assistant Investigator Chunying Du continues the research on apoptosis that she began as a Howard Hughes Medical Institute postdoctoral fellow at the University of Texas Southwestern Medical Center in Dallas.

Promoting the Cell Death Program

Dr. Du discovered a protein called Smac (Second mitochondrial-derived activator of caspase), which functions to promote apoptosis's programmed cell death. She and her colleagues also discovered that a small portion of Smac protein, a tetrapeptide fragment, can do the same job of the complete Smac protein.

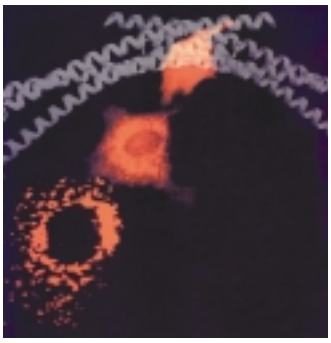
When a living cell receives a stimulus like UV radiation or a chemical that damages its DNA, it activates enzymes called caspases that cut up other proteins. Caspases are normally quiescent (inactive), but upon receiving the danger signal from some damaging event, they become activated. They are then able to cleave, or chop up, other proteins as a way of putting the cell to death.

But first, the cell's death sentence must pass a type of fail-safe test to ensure that the cell really is beyond repair. This hurdle is known as IAP (Inhibitor of Apoptosis Protein). IAP binds to caspase and puts its activation on hold while the cell appeals the death sentence and DNA maintenance crews check to see if the damage can be repaired. If the cell is indeed damaged beyond repair and thus too dangerous to the surrounding tissues, the death verdict is upheld. Smac then binds to the IAPs and releases the caspases. In a kind of double negative action, Smac inhibits the inhibitor, thereby enabling apoptosis to go forward.

"In cancer cells, IAPs are expressed at a higher level than in normal tissues," Dr. Du said, "especially in some prostate and ovarian cancers." That's a problem, since chemotherapy and radiation work by activating apoptosis, causing the cancer cells to die. Introducing extra doses of Smac to the tumor could conceivably sensitize it to anti-cancer treatments.

A Promising Drug Candidate

Smac, which is easily synthesized, seems virtually designed for use as a drug agent. "It's almost perfect, because it can get into the cell by itself," Dr. Du explained. "It's hydrophobic, meaning it doesn't like to dissolve in water. It dissolves in lipids (fats), and our cell membranes are made of lipids. That's lucky, because it means that Smac can be delivered into the cell. Any drug must be delivered into the cell. If a drug candidate can't be delivered, then it can't be a drug!"



This composite image shows the structure and biological role of the Smac protein. The crystallized protein appears as the gray structure at the top. Below are three human cervical cancer (HeLa) cells that were exposed to ultraviolet radiation to induce the release of Smac (stained red). In the bottom cell, the uneven dots show that Smac is still inside the mitochondria. The partial to complete smearing of red in the middle and top cells indicates Smac's release into the cytoplasm where it inhibits the inhibitor of apopotosis. (This image appeared on the cover of Nature, August 24, 2000, Volume 406.)

TING XIE:

For Stem Cells, Location is Everything

In real estate, it's all about location, location, location. Stem cells occupy the "Park Place" of living tissues, and they cannot function properly outside their exclusive niche or "microenvironment," according to Assistant Investigator Ting Xie.

Stem cells are immature, undifferentiated, self-renewing cells with the potential to generate the many different cells a tissue requires. Scientists and non-scientists alike have high hopes for using stem cells in regenerative medicine and treatments for diabetes, Parkinson's, and other diseases. A major hurdle is the difficulty of growing stem cells in large quantities. Dr. Xie believes that researchers must understand a stem cell's niche and its associated signals before they can grow and maintain stem cells for therapeutic uses. "The niche tells stem cells how to reproduce and generate cell types," he said. Dr. Xie has received the inaugural 2003 Hudson Prize from the Texas-based M.R. and Evelyn Hudson Foundation to pursue this line of inquiry.

The Right Place

"In some tissues, such as the skin, stem cells are active and divide continuously. In others, like the brain, they don't reproduce often. How do the stem cells know when to divide?" Dr. Xie asked.

To find out, he located a stem cell in the *Drosophila* fruit fly ovary, tagged it with a visible dye, and watched it divide into two cells. One daughter cell occupied the same position or niche as the original cell. The other daughter cell occupied the next position, one cell away from that site. That second daughter cell became differentiated, while the one occupying the niche remained a stem cell.

Dr. Xie decided to test a theory dating back to 1978 that the microenvironment contains cues that control a stem cell. He removed one stem cell from a niche that normally accommodates two or three stem cells and created an empty space. A nearby cell that would normally differentiate moved into that vacated space. It became a stem cell, thus demonstrating that the critical information lies in the niche, not in the cell itself.

The Right Signal

Dr. Xie then asked, "What signals does the microenvironment provide to the stem cell?" He discovered that the niche cells produce BMPs (bone morphogenetic proteins), a growth factor family that regulates many developmental processes. "Reducing those growth factors greatly reduces stem cell stability and growth, so BMPs must give important instructions to stem cells, including how to proliferate," Dr. Xie concluded.

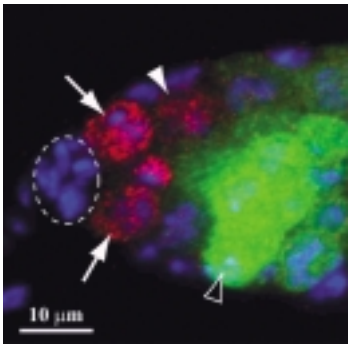
Next he asked, "What keeps the stem cell in the right niche?" He identified cadherin, an adhesive produced by the niche cells that binds the stem cell to the site.

Restoring the Niche

In many diseases, the microenvironment is destroyed as a tissue degenerates. "Everybody hopes to transplant stem cells into diseased tissue to treat such diseases. But if the niche is destroyed, stem cells can't do their work," Dr. Xie explained. "The niche needs to direct them to repair the damage." He speculates that recreating the niche signals and adhesives may stimulate stem cell growth.

"If we can figure out how tissues form niches in the first place, maybe we could make new niches containing functional stem cells in the laboratory and transplant them together into diseased tissues, such as in the brain to treat Parkinson's," he said. "But we still know so little about how tissues actually assemble those niches."

Assistant Investigator Ting Xie (middle) first explored stem cell niches as a Howard Hughes Medical Institute postdoctoral fellow at the Carnegie Institution of Washington. The recipient of the 2003 Hudson award from the M.R. and Evelyn Hudson Foundation, he is shown here (from left to right) with Wally Hooser, M.D., and M.K. Larson of the Hudson Foundation and Virginia and James Stowers Jr. of the Stowers Institute for Medical Research.



This image shows a stem cell niche (microenvironment) in an adult female fruit fly's ovary. Two red stem cells (indicated by arrows) are in direct contact with the bright blue niche cells (highlighted by dashed lines). The red cell indicated by the arrowhead is the daughter of a stem cell. Just one cell removed from the niche cells, it has just begun to differentiate as indicated by the faint Green Fluorescent Protein (GFP), which indicates the expression of genes involved in differentiation. The bright green cells are earlier progeny of the stem cell that have moved further away from the niche. They express strong GFP because they are more fully differentiated. (Confocal microscopy image by Stowers Institute Research Assistant II Xiaoqing Song)

PETER BAUMANN:

Pew Scholar Searches for Telomere Components

Assistant Investigator Peter Baumann is the first Stowers Institute researcher to receive a Pew Scholars award. A native of Germany, he studied at the University of Cambridge and University of London, joining the Stowers Institute in 2002 after completing a Howard Hughes Medical Institute postdoctoral fellowship at the University of Colorado, Boulder.

When invited to apply for the Pew Scholars Program in the Biomedical Sciences, Assistant Investigator Peter Baumann knew which project to propose. He had already discovered the identity of a protein in fission yeast that binds to telomeres, the structures at the ends of chromosomes. That protein, named Pot1 for Protection of Telomeres, protects chromosomes from degradation or improperly fusing with other chromosomes. Pot1 was not previously believed to exist in higher organisms, but Dr. Baumann found homologs (relatives) of it in plants and animals, including humans. When starting his laboratory at the Stowers Institute in 2002, he suspected that several other proteins help Pot1 protect telomeres, but searching for them might be an open-ended "fishing expedition" not likely to be supported by most funding organizations.

The Pew Program specifically aims to give young investigators with a track record of discovery the freedom to pursue innovative independent research. Dr. Baumann proposed an ingenious genetic screen to find new factors involved in maintaining telomeres and ensuring DNA integrity and genomic stability. He uses fission yeast for his research because it divides in a similar manner to mammalian cells, yet as a single-celled organism it is easy to grow in the lab and it reproduces rapidly.

The Trouble with Chromosome Ends

When cells divide, they cannot completely replicate the very ends of their chromosomes. As a result, the telomeres shorten with each cell division. "This shortening acts as a molecular clock, limiting a cell's lifespan," Dr. Baumann said. "When telomeres get too short, cells stop dividing."

Telomere length plays a part in both aging and cancer. Many age-related conditions may result from the shortening of telomeres. On the other hand, cancer cells can rebuild telomeres by activating the repair enzyme telomerase. Those restored telomeres enable the abnormal and dangerous cancer cells to evade death and become essentially immortal.

"Inhibiting the ability of telomerase to replenish telomeres could be a major victory in the fight against cancer," Dr. Baumann explained. "Instead of taking drugs that harm many other cells, we could take a telomerase inhibitor that would predominantly hit cancer cells since healthy cells usually don't require or contain telomerase."

The first step, though, is to fully understand how healthy cells maintain telomeres and how cancer cells are different.

"Going Fishing"

"The ideal screen for finding novel genes that maintain chromosomal stability would involve deleting each individual gene and noting the effect on telomeres," Dr. Baumann said, "but that is very tedious and labor intensive."

Instead, he created a strain of fission yeast in which only cells that cannot maintain telomeres can grow on a specific culture medium. In contrast, yeast cells with normal telomeres die. As such, the strain "reports" on which cells do and do not have telomeres. He combines that reporter strain with a technique called insertional mutagenesis which randomly inactivates a gene in each yeast cell and marks the location of the inactivated gene. Any cell that survives on his culture medium probably has an inactivated gene that normally helps maintain the telomeres.

Recent Awards and Honors

"We select the cells without telomeres and look for the insertional markers to locate the inactivated genes," he explained. "We want to know the identities of those genes and their precise functions in protecting telomeres."

Dr. Baumann is one of 20 honorees selected from a group of candidates nominated by more than 120 invited research institutions and universities to receive the $240,000 Pew Scholar award.

"Our National Advisory Committee felt that Dr. Baumann has an impressive track record in the area of DNA recombination, repair, and chromosome replication," said Silvia Montano de Jiménez, Director of the Pew Programs in the Biomedical Sciences. "His description of a genetic screen to define factors necessary for the maintenance of telomere ends is lucid, and likely very productive. We look forward to the next four years to witness his scientific progress in the area."

The Pew Scholars program is administered by the Pew Charitable Trusts in Philadelphia. Four children of Sun Oil founder Joseph N. Pew and his wife, Mary Anderson Pew, founded the Trusts in 1948 and 1979 to support programs in culture, education, the environment, human services, public policy and religion.

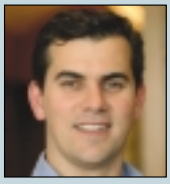
Robb Krumlauf

The **American Academy of Arts and Sciences** elected Scientific Director **Robb Krumlauf** as a Fellow of the Academy, acknowledging his contributions to understanding how genetic and regulatory pathways control patterning of the nervous system, formation of the body, and development of the head and brain in vertebrates. His research on the Hox gene family helped elucidate how fundamental patterning processes are conserved in evolution. Dr. Krumlauf came to the Stowers Institute in 2002 from England's National Institute for Medical Research. He is the third Stowers Institute scientist to be honored by the AAAS and one of only three Kansas City residents to be elected to the Academy.

The **March of Dimes Birth Defects Foundation** awarded Basil O'Connor Starter Scholar Research Awards, each for $150,000, to Assistant Investigators **Jennifer Gerton** and **Paul Trainor**.

Jennifer Gerton

Dr. Gerton's grant funds her research into chromosome cohesion, a process required for the appropriate distribution of chromosomes during cell division. Defects in chromosome cohesion can lead to birth defects, spontaneous abortion, cancer, and cell death. She joined the Stowers Institute in 2002 following postdoctoral studies at the University of California, San Francisco.



Paul Trainor

Dr. Trainor's grant funds his research into the role the cranial mesoderm plays in normal and abnormal craniofacial development. Mistakes in this process are responsible for one-third of congenital defects in newborn children. He came to the Stowers Institute in 2001 from the National Institute for Medical Research in England.

Peter Baumann

Assistant Investigator **Peter Baumann** has been named one of "America's most promising biomedical researchers" by the **Pew Charitable Trusts**. The award included $240,000 for his research on telomeres. (See page 8.)

Chunying Du

Assistant Investigator **Chunying Du** received a grant of $358,000 from the **Department of Defense** to expand her research on genetically programmed cell death and the protein she discovered that releases the normal inhibition of this process. (See page 6.)

Olivier Pourquié

Associate Investigator **Olivier Pourquié** received a $1.145 million grant from the **National Institutes of Health** for studying the molecular processes involved in the formation of somites. (See page 4.)

Ting Xie

The **M.R. and Evelyn Hudson Foundation** awarded Assistant Investigator **Ting Xie** the $50,000 Hudson Prize to fund his continuing research on the genetic and molecular analysis of stem cells in the fruit fly. (See page 7.)

Stowers by-the-Sea: The MBL at Woods Hole

When summer arrives in Massachusetts, so do scientists, including several Stowers Institute investigators. They convene at the Marine Biological Laboratory (MBL) in Woods Hole on Cape Cod, often with family members – and lab equipment – in tow. This past summer, Stowers Institute Scientific Director Robb Krumlauf, Associate Investigator Olivier Pourquié, and Assistant Investigator Paul Trainor taught embryology at MBL to an energetic mix of graduate students and postdoctoral fellows.

Woods Hole's MBL has a 100-year-plus history as a scientific meeting ground of international repute. "Investigators went to collect sea urchins or other marine animals, which were important model organisms for comparative embryology. They frequently brought their families along while they conducted research and taught courses," explained Dr. Krumlauf, who has taught at Woods Hole for six summers and who recently became a member of the American Academy of Arts and Sciences.

In addition, leading scientists from Boston and elsewhere dropped by while vacationing on Cape Cod for the exchange of ideas. That tradition has evolved into a unique research and learning opportunity in a relaxed yet stimulating intellectual atmosphere. "The students appreciate the opportunity to speak to famous scientists," Dr. Krumlauf said. "What makes the MBL special, for instructors as well as students, is the opportunity to learn what scientists are thinking about doing, not just what they have accomplished."

The embryology course remains a prominent feature of the MBL program. It lasts for six weeks, with approximately 20 students participating in the course. The day begins at 9 a.m. with lectures followed by extensive lab work and then discussions that can extend into the wee morning hours.

Among visiting scientists at the MBL in 2003 was Doug Melton, Ph.D., from Harvard University, the chair of the Stowers Institute's Scientific Advisory Board. Another Scientific Advisory Board member, Mike Levine, Ph.D., of the University of California-Berkeley, was also an instructor and is a former director of the embryology course.

Dr. Melton said, "The Stowers Institute was a major presence in the MBL embryology course this year. With Robb, Olivier, and Paul playing such a visible and important role, Stowers is becoming better known to the developmental biology and embryology community. The students I spoke to were also very interested to learn about the research opportunities and facilities at Stowers."

Photo by Elizabeth Armstrong/Marine Biological Laboratory

The Summer of 2003

In 2003, the three Stowers investigators provided complementary insights into the embryonic development of vertebrates. Drs. Krumlauf and Trainor focused on craniofacial development, explaining the role of the nervous system in head and facial development and demonstrating the genetic control over that process. Dr. Trainor taught students laboratory methods he has perfected for studying embryonic development in mice. Using whole embryo culture techniques, he fashioned experiments for observing how cells make decisions about what they will become, and he showed how to set up mouse experimental models to investigate the role of genes in development.

Dr. Pourquié's sessions explored the timing of development of the vertebrae, trunk, and associated muscle, which follows a different pattern and uses a different mechanism from the head. (See article on page 4.)

"We stressed that to understand and develop strategies for correcting craniofacial, spinal, and other embryonic abnormalities, we need to understand not the end point (deformity), but when and how things go wrong," Dr. Krumlauf said.

The Planned Experiment

Teachers go to the MBL with prepared experiments, knowing they may have to develop impromptu experiments to address the students' inevitably clever questions. Before leaving the Stowers Institute for Woods Hole, Drs. Krumlauf and Trainor designed an experiment to label cells with a fluorescent tag so students could observe them as they migrate away from the neural tube and form the bone and connective tissues in the face of a mouse embryo.

"We wanted students to understand that the cells that form structures in one place may actually arise and be patterned in another place," Dr. Krumlauf said. "We need to study their history and fate to see how cells receive their instructions to migrate and specialize."

Impromptu Experiments

From Dr. Pourquié's lectures, the students knew that cells from the somites (vertebral segments) normally make the bones in the trunk, while the head bones are made from cells that migrate from the neural tube. Following the planned experiment, students asked, "What if we put somite cells in the place of head neural crest? Would those cells carry with them the instructions from the somite and migrate back to the vertebral column, or would they follow instructions from their new home?"

Students designed a new experiment transposing tissue from the somites to the neural crest. The result? The cells made bone and connective tissue, but it was neither facial nor trunk tissue. It was as if the cells were confused by conflicting instructions. The conclusion? The cells carried some information from the somite, but they needed the right environment and signals to properly specialize.

Harbor at Woods Hole

"These experiments demonstrated that development is not hard wired," said Dr. Trainor. "It depends upon a carefully orchestrated series of signals and events that generate intricate structures and organs."

That result suggested a follow-up question: "Do head neural crest cells know their position? What if we rotated them by 180°? Will they go to their normal location or migrate to a new direction, and will they make normal or abnormal structures?" Again, students devised an experiment, and they were surprised by the result. The face in the experimental embryos developed normally, indicating some cells that find themselves in new locations can respond to local signals and generate the proper structure. That suggested that the cell's environment plays an important role in telling the cells what to become.

Stimulating the Teachers

For many students, Woods Hole is a life-altering experience. One student said, "Woods Hole is to scientists what Paris is to artists." It's also a formative experience for the teachers. "Normally, when you go to a conference or give a seminar, you meet with scientists during the break or at lunch, but it's a short-term interaction," Dr. Krumlauf said. "At the MBL, you listen to someone talk about the fundamental principles over a long period of time. You can delve deeper and get insight into their thought processes. The experience is as stimulating for the teachers as it is for the students."

Related Papers from the Stowers Institute

Trainor, P.A. (2003) Development: The bills of qucks and duails. *Science*, 299(5606), 523-524.

Trainor, P.A, Ariza-McNaughton, L., & Krumlauf, R. (2002) Role of the isthmus and FGFs in resolving the paradox of neural crest plasticity and prepatterning. *Science*, 295(5558), 1288-1291. (Comments about this paper may be found in *Nature Reviews Neuroscience* 3, 254 and *Nature* 416(6880), 493-494.

See page 5 for papers from the Pourquié Lab.

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

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