THE Stowers REPORT

NEWS AND INSIGHT FROM THE STOWERS INSTITUTE FOR MEDICAL RESEARCH

Stowers Institute Aims High in Fly Research

***Kent Golic**, a leading fly geneticist who moved to the Stowers Institute from the University of Utah, in his new lab on the top floor of the Stowers research facility.* *Photo by Don Ipock*

With three highly regarded fly researchers already on board and others likely to join, the Stowers Institute is poised to occupy a significant place in *Drosophila* research at a time when the tiny fly is yielding up remarkable secrets about the development of life. Drs. Kent Golic, Scott Hawley and Ting Xie, all credited with breakthrough research on fruit flies, have settled into adjacent laboratories on the top floor of the Institute's main research facility to improve collaboration and communication among them. Their field of research is looked to with great hope now because fruit flies and human beings have so many counterpart genes that cause disease in both.

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ALSO...

Reaching across the Atlantic and to California, the Stowers Institute adds two laboratory leaders. Drs. Olivier Pourquie and Jennifer Gerton will join 10 other scientists already directing independent research programs at the Institute. Both will arrive in June.
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Two-day Stowers Institute symposium, October 30-31, emphasizes narrowing gap between research focuses of biologists and medical needs of people who suffer and die from diseases with genetic bases.
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FRUIT FLIES –

Nuisance in the Kitchen but a Biologist's Tea and Cake

Fruit flies are a nuisance when they invade your kitchen after you've left a banana or a peach out on the counter until it is too ripe. Appearing seemingly from nowhere, the tiny insects linger far too long after the forlorn fruit is banished from the scene.

Among many biologists, however, fruit flies enjoy a respect and a following usually described as cult-like. Worldwide, about 5,000 brainy people, all of them Ph.D.s, dedicate their careers to studying what happens to fruit flies when their genes are scrambled. These scientists delight in producing fruit flies with pink or purple eyes, extra sets of wings, no wings at all, two abdomens and other exotic characteristics.

After nearly a century of doing this, fly geneticists think their research has put science on the threshold of breakthroughs toward understanding and maybe curing a number of human diseases. Research on fruit flies and various other lower organisms has established that the fundamental genetic mechanisms of development appear to be the same in all living things. But scientists are especially confident of future payoffs from fruit-fly research because fruit flies and human beings have so many counterpart genes – what scientists call "homologues" – that cause disease in both flies and people.

In fact, there are so many overlapping genes that – as Nicholas Wade, a science writer for *The New York Times*, noted last year – "Fly people . . . are easily provoked into confessing that they think of people as large flies that lack wings."

Fly Standouts for Stowers

Though it is new to the research scene, the Stowers Institute is poised to stake out a significant role for itself in this area because it has already attracted three highly regarded fly experts to its research team – Kent Golic, Scott Hawley and Ting Xie – and expects to add two or three others. Drs. Golic, Hawley and Xie have settled into adjacent laboratories on the top floor of the main research building. Being neighbors allows them to collaborate easily.

Officially, the fruit fly is called *Drosophila melanogaster* or *D.melanogaster*. It is only one of an estimated 900 species of flies worldwide, but the eighth of an inch-long *melanogaster* was launched on the path to scientific stardom in 1910 when Dr. Thomas H. Morgan, a Columbia University professor, succeeded in producing the first mutant, a white-eyed fruit fly. Doing controlled crosses with fruit-fly mutants over the next five years, he and three principal students formulated a revolutionary chromosome theory of heredity, for which Dr. Morgan won the Nobel Prize in 1933.

Not the least of the fruit flies' attractiveness to Dr. Morgan lay in the fact that they were cheap to feed and house and reproduced like – well, like flies. They provided genetic knowledge economically. The story is that his students stole empty half-pint milk

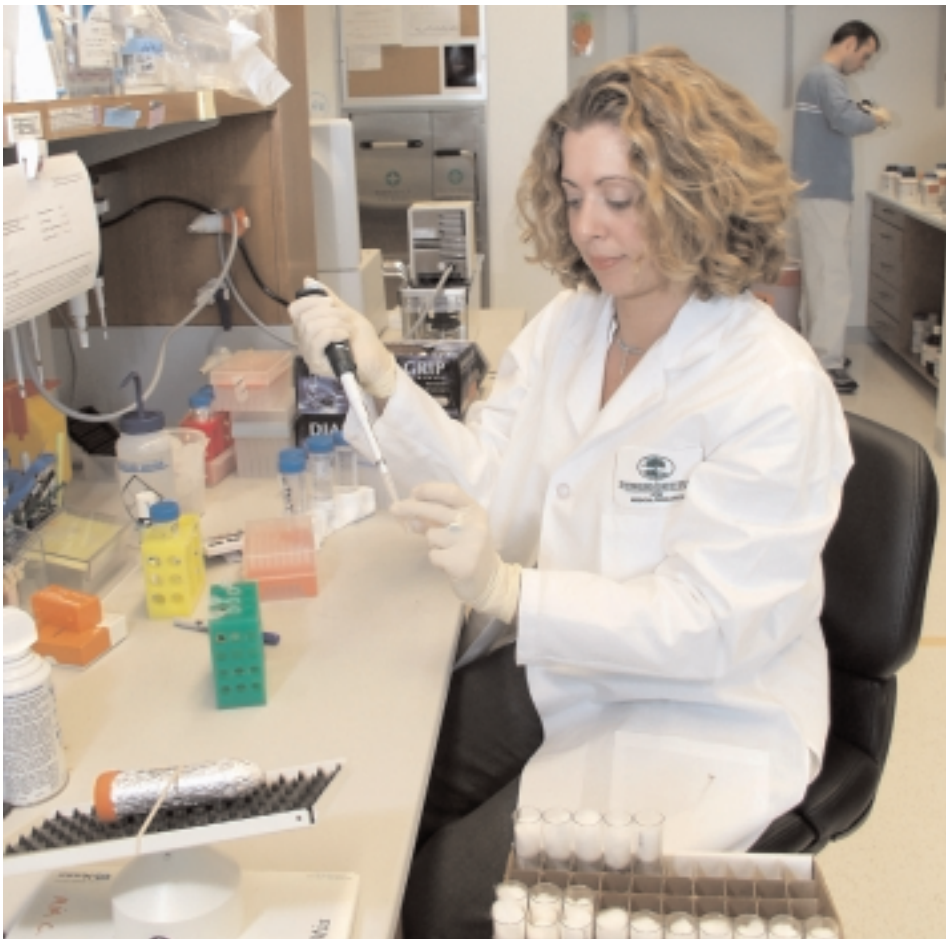

Photo by Don Ipock

Mia Champion, *who is completing her Ph.D. from the University of California-Davis, came to the Stowers Institute as part of the research team of Scott Hawley when he moved from the California campus to Stowers.*

bottles from Manhattan doorsteps and turned them into cozy homes for fly families.

At the Stowers Institute, flies live in lots of small tubes scattered around laboratories. By contrast, mice get their own house, the state-of-the-art animal care facility in the sub-basement built at a cost of several hundred dollars a square foot, including a $1.5 million-dollar robotic cage washing system. Stowers flies do have their own chef, however. Cliff Sonnenbrot, with the skill of someone with a master's degree in chemistry, cooks up a fly-food recipe made of yeast, cornmeal, agar and molasses.

Important Development Clues

Even since Dr. Morgan's ground-breaking work, flies have provided the knowledge for other important steps in understanding how a many-celled complex animal – or person – develops from a single egg cell. Study of the fly revealed the basic system of genes and signaling molecules that set up the patterns in the developing embryo and lead to development of organs in their proper places.

Further, the much-heralded sequencing of the human genome only begins to make sense if a scientist already knows the functions of the individual genes, and that is possible only because people have already done a lot of research on so-called "model organisms," particularly fruit flies.

The way scientists find out what a gene does is by generating a mutation – such as mixing the genes of flies to produce flies with extra wings, wings in the wrong places and other anomalies – and looking at the consequences. Obviously, these are things that cannot be done on humans. Fly scientists say that the wealth of mutants they have generated over a century's time has taught biologists more about flies than they have learned about any other single complex organism, although biologists who concentrate their research on the worm known as *C. elegans* also make a claim in that regard.

***Ting Xie**, a Stowers Assistant Scientist and the first fly geneticist to join the Stowers Institute, in his laboratory on the top floor of the research building.*

Photo by Don Ipock

Fly Genome Decoding Timely

In early 2000, nearly a year ahead of the completion of the human genome project, the fly genome was decoded. As William B. Neaves, Ph.D., President and CEO of the Stowers Institute, explained, this event had great significance to medical research and for the recruitment underway at the Institute:

"When the *Drosophila* genome was sequenced and published, one of the notable revelations of that event was the sudden realization that there were nearly 200 human-disease-causing gene homologues in the fly genome. That is, nearly 200 fly genes are essentially identical to genes in humans known to be associated with major disease susceptibility.

"Two months later, in June of 2000, Kent Golic published his paper in *Science* solving the problem of doing targeted gene knockouts in flies. And suddenly it seemed that his exciting new ability to study fly genes would be very much at home in the Stowers Institute."

Gene knockouts – removing certain genes to see what reaction that produces in the developing organism – had been done in mice for more than a decade, but Dr. Golic was the first to discover how it could be done in fruit flies. The accomplishment is especially significant because of the large number of overlapping genes causing disease in both fruit flies and people.

Dr. Golic was then Professor of Biology at the University of Utah, but the Stowers Institute and Kansas City were holding a high card when it came to attracting him. He had grown up in the suburbs of Kansas City, where he still has close family, and he received his

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Photo by Don Ipock

No, that's not a fruit fly in the wall art behind these members of the laboratory team of Scott Hawley, but Dr. Hawley, who came across it in an art gallery, thought it looked close enough like the real thing to be appropriate for the break room on the fly floor of the Stowers research building. From left: Ed Van Veen, Heather Peters, Kathy Wierman, David Harris, Charisse Orme, Mia Champion and Scott Page.

bachelor's degree from Kansas State University in 1980.

This past spring, he accepted a position as Senior Scientist at the Institute, where he intends to systematically knock out each of the human-disease-associated genes in fruit flies and study the results.

Asking the Right Question

Even before Dr. Golic came, the Stowers Institute had a leg up in building a fly research capability with the recruitment of Ting Xie as an Assistant Scientist in 1999, when the first group of four independent scientists was selected. Dr. Xie, previously a Postdoctoral Fellow at Carnegie Institution of Washington, was already having remarkable success with his *Drosophila* work. It is aimed at understanding whether what becomes of stem cells, which are capable of morphing into the many different cells of which the body is composed, is intrinsic to the genetics of those cells or whether it is the result of their immediate environment.

"Ting was asking a really important question," Dr. Neaves said. "That was, 'What causes a stem cell to grow up to become a specialized cell type?' His work is already revealing that it is really the micro-environment that determines the fate of a stem cell, not a genetic program intrinsic to that stem cell.

"That's a very hopeful finding for anyone interested in using stem cells to replace diseased or damaged cell populations and tissues in humans. It suggests that you might be able to take any kind of stem cell, and if you put that stem cell in the micro-environment of the heart, for example, it could grow up to be a functioning heart muscle cell. Or, if you put it in the micro-environment of the brain, it could grow up to be a functioning neuron."

Appeal Broadens

With both Kent and Ting at the Stowers Institute, Dr. Neaves said, "We began to create an intellectual environment for fly research that attracts other outstanding fly geneticists. That's why Scott Hawley was delighted to come here and why we have the attention of others."

Three internationally known fly geneticists have presented their research before seminar gatherings at the Stowers Institute in recent months, further improving the environment for fly research. They were Perniell Rorth and Stephen Cohen of the European

Molecular Biology Laboratory and Nancy Bonini, a Howard Hughes Medical Institute investigator at the University of Pennsylvania.

Dr. Hawley, who joined the Institute over the summer from the University of California-Davis where he was Professor of Genetics, does research that has particular relevance for finding the biological cause of babies being born with Down Syndrome. Using the very advanced optical deconvolution microscope, Dr. Hawley is able to observe in living eggs the process of meiosis, or the sorting of chromosomes. He is looking for errors in this process.

"We now believe, as do others, that a failure to properly control meiosis by hormonal changes may underlie many of the meiotic errors that produce children with Down Syndrome," he said.

"We can study this process of hormonal regulation in the fly," he said, "and we are avidly doing so. It is, perhaps, not unreasonable to suggest that our studies may soon lead to tests that may help determine which would-be mothers are at the greatest risk for meiotic failures. We may even be able to help develop techniques to reduce that risk."

"Nonetheless, as lofty as our aspirations are, and as human-focused as our research is," he said, "not a day goes by when I am not reminded that it begins and ends with a fly."

POURQUIE, GERTON –

New Lab Heads from East and West

Thanks to successful recruitment of scientists from prestigious institutions in France and California, two additional laboratories will open at the Stowers Institute in the coming months, joining the ten laboratories now functioning. Olivier Pourquie, Ph.D., will join the Institute from the Developmental Biology Institute of Marseille, France, and Jennifer Gerton, Ph.D., will come from the University of California-San Francisco.

Dr. Pourquie will be an Associate Scientist, and Dr. Gerton will be an Assistant Scientist, positions equivalent to associate and assistant investigators of the Howard Hughes Medical Institute.

Attracting Dr. Pourquie to the Stowers Institute involved a trans-Atlantic effort that grew out of contacts between Dr. Pourquie and Robb Krumlauf, Ph.D., Scientific Director of the Stowers Institute, in the years when Dr. Krumlauf was working in London and regularly attended scientific meetings on the Continent. Since 1996, Dr. Pourquie has been an independent research group leader and has held various administrative responsibilities at the Developmental Biology Institute of Marseille. Dr. Krumlauf was formerly head of the Division of Developmental Neurobiology at Britain's National Institute for Medical Research at Mill Hill.

Year-long, Trans-Atlantic Effort

Soon after joining the Stowers Institute in mid-2000, Dr. Krumlauf invited Dr. Pourquie to come to Kansas City and deliver a presentation on his research at the Institute's Wednesday Seminar Series. Further contacts followed, including a second visit by Dr. Pourquie.

William B. Neaves, Ph.D., President and CEO of the Stowers Institute, said that, at first, he was not optimistic about recruiting Dr. Pourquie because it was felt that he would eventually cap his career by going to the Pasteur Institute in Paris, the pinnacle of French biological science.

But on his second visit to Kansas City, Dr. Pourquie told Drs. Neaves and Krumlauf that he had no interest in

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Photo by Don Ipock

***Jennifer Gerton and Olivier Pourquie**, the newest appointees to positions as laboratory leaders at the Stowers Institute, got together with new colleagues during the October 30-31 symposium, "From Genes and Genetics to Molecular Medicine." Stowers Institute lab leaders and other key scientists gathered in the library, front row from left: Scott Hawley, William B. Neaves, Paul Trainor, James A. Coffman, Arcady Mushegian, Linheng Li, Dr. Pourquie. Second row from left: Ron Conaway, Joan Conaway, Brian Sauer, Robb Krumlauf, Kent Golic, Ting Xie, Dr. Gerton, Chunying Du.*

Hope Shares®

New contributions of at least $1,000, the minimum for establishing a Hope Shares® account in the endowment of the Stowers Institute, were received from, or in memory or honor of, the following individuals and foundations between July and November of 2001:

$100,000 or more
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[1] Additional gift brought cumulative total to $100,000 or more.
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living in Paris and, furthermore, advancement beyond his current level at Marseille could only be achieved by taking on more administrative responsibility and devoting less attention to research.

"He's at a very productive period of his exciting work on the genes that influence how muscle and bone are formed from the masses of tissue along the axis of the body behind the head, the so-called somites," Dr. Neaves said, "and he wants to work intensively on this research." Dr. Pourquie is recognized as the pioneer in revealing the mechanisms governing temporal control of patterning in somatic mesoderm, a field of research with significant relevance to developmental disorders and human birth defects.

So, the offer was made, and he accepted. In November, he brought six associates from his French lab to look over the Stowers Institute and Kansas City in hopes that some or all of them might decide to join him in making the move.

"It's a substantial coup getting Dr. Pourquie," Dr. Neaves said. "It would be a triumph for any organization to recruit him. Organizations elsewhere in the United States and in Europe have tried very hard to recruit him. But to recruit him to Kansas City from Marseille – his having never lived outside of France – is quite remarkable."

First Lab of her Own

For Dr. Gerton, the Stowers Institute will provide the first opportunity to head her own laboratory and lead her own research team. Since 1997, she has been a Postdoctoral Fellow at the University of California-San Francisco, most recently in the lab of Joseph DeRisi, Ph.D., pursuing genomic and biochemical approaches aimed at understanding chromosome segregation, initiation of double-strand DNA breaks, and chromosome dynamics in yeast.

"Dr. Gerton's research focuses on the mechanisms that ensure fidelity of chromosome distribution to the daughters of dividing cells," said Dr. Neaves. "The survival of all living organisms depends on the pair of cells produced from the division of a single cell having the proper number of chromosomes. The dividing cell ensures that chromosomes are copied exactly once and then distributed correctly to daughter cells.

"If this process fails, the resulting daughter cells contain either too few or too many chromosomes, and severe abnormality or death ensues. The research Dr. Gerton will conduct at the Stowers Institute is fundamental to understanding how genes and proteins govern normal multiplication of cells."

Olivier Pourquie, Ph.D., Associate Scientist. Since 1996, research group leader, Developmental Biology Institute of Marseille, France. Previously at the Cellular and Molecular Embryology Institute of the National Center of Scientific Research (CNRS) at Nogent-sur-Marne, France. Graduate and undergraduate studies at the Cellular and Molecular Embryology Institute, Nogent-sur-Marne. Ph.D. thesis at the National Agronomy Institute, Paris-Grignon.

Jennifer Gerton, Ph.D., Assistant Scientist. Since 1997, Postdoctoral Fellow University of California-San Francisco. In 2001, instructor of course, "Making and Using DNA Microarrays," Cold Spring Harbor. In 1989-1990, Howard Hughes Undergraduate Researcher. Ph.D. in Microbiology and Immunology, Stanford University, 1997; B.A. in Human Biology, Stanford, 1990.

Basic Research Edges Closer to Disease Answers

The gap is narrowing between the research that biologists do on flies, mice, worms and other model systems and some of the major diseases that afflict humanity, including Parkinson's disease, diabetes, cancer, congestive heart failure and maybe even malaria. This message came through clearly from those who talked about their research before an overflow crowd of area scientists gathered at the Stowers Institute on October 30-31 for the symposium, "From Genes and Genetics to Molecular Medicine."

The three keynote speakers – Robert Horvitz of MIT, Gerry Rubin of the Howard Hughes Medical Institute, and Bob Waterston of Washington University in St. Louis – plus the 12 who spoke on the second day gave example after example of the medically relevant research now occurring as extensions of basic research.

Dr. Horvitz, a leader in research on genetics of the worm *C. elegans*, said his laboratory was working on the discovery and characterization of genes that act in programmed cell death. Even though his research is based on the worm, cell death is a phenomenon that plays a role in causing or preventing any number of human diseases, including cancer, congestive heart failure, acute liver failure, stroke and AIDS. At times, he said, the disease may be caused by too much cell death; at other times, particularly in cancer, by too little cell death.

Therefore, Dr. Horvitz said, identifying genes and proteins that function in programmed cell death provides potential new targets for drug or treatment intervention in many diseases.

Doug Melton of Harvard, who is also chairman of the Scientific Advisory Board of the Stowers Institute, laid out his case for trying to reconstruct the insulin-secreting part of the pancreas known as the islet by reminding his listeners that diabetes affects 16 million Americans.

"So there's a strong medical need to try to understand what we might do to replace cells that are lost in this very specific cellular deficiency, namely, the absence of the insulin-producing cells in Type I diabetics," Dr. Melton said. "Ours is an embryological approach to try to understand how the organ and tissue is normally made, then use that information to see if we can reconstruct things *ex vivo*. The idea is that if we learned enough about the cells and the gene products that were involved in the normal development of the islet, we might be able to reproduce that."

Ron McKay of the National Institutes of Health put forth a similar case for Parkinson's disease. "It is a devastating disease," he said. "A million Americans have it. There's not much you can do about it. In the early stages, you can give people L-dopa, which is the precursor for dopamine, the neurotransmitter that they lack."

But eventually that ceases to work because the cells on which it works are gradually dying.

After tracing several paths of research, including grafting fetal human tissue into the brain and growing stem cells, Dr. McKay said he was convinced that the most promising line of inquiry lay in the use of embryonic stem cells, which he said are able to differentiate into the different cell types of the brain.

Probably the most daunting task was the one that Joe DeRisi of the University of California-San Francisco has created for himself and his research associates: to take some of the lessons learned from genomics research on yeast and apply them to malaria, the seemingly intractable Third World health problem.

Malaria, caused by the parasite *Plasmodium falciparum*, is responsible for an estimated 2.7 million deaths a year, mostly in Sub-Sahara Africa, Southeast Asia and South America.

Dr. DeRisi said mosquito abatement works in countries that can afford to spend the money, with the result that most developed countries are virtually free of malaria. That doesn't work in the poorest countries, where the disease is often endemic. Drugs help, he said, but malaria quickly develops resistance to each new drug, and new drugs are not developed quickly enough to be ready to replace those that lose their potency.

"Why?" he observed. "It's pretty obvious. People who get sick with malaria don't carry credit cards."

Photo by Don Ipock

***Speakers at the Stowers symposium**, "From Genes and Genetics to Molecular Medicine," gathered in the Institute library with Drs. Krumlauf and Neaves. From left, front row: Irv Weissman, Mike Levine, Bob Waterston, Dr. Krumlauf, Catherine Dulac, Phil Beachy, Joe DeRisi, Dr. Neaves. Back row: Ron McKay, Matt Scott, Gerry Rubin, Ron Evans, Doug Melton, Bob Horvitz, Mark Fishman, Scott Fraser, Andrew Murray.*

Stowers Advisory Board Member Named to Head Whitehead Institute

Susan L. Lindquist, Ph.D., a member of the Scientific Advisory Board of the Stowers Institute, has become director of the Whitehead Institute for Biomedical Research in Cambridge, Mass., one of the most highly regarded independent research institutions in the country. Dr. Lindquist, an acclaimed molecular biologist, plans to continue as a member of the Stowers advisory body, which approves the appointments of all scientists named to positions as lab leaders at the Stowers Institute.

In her new position, Dr. Lindquist was also named a professor of biology at the Massachusetts Institute of Technology, which is adjacent to the Whitehead Institute. All Whitehead faculty members hold joint appointments in MIT's biology department.

Dr. Lindquist came to her new position from the University of Chicago, where she was Albert D. Lasker Professor of Medical Sciences, Department of Molecular Genetics and Cell Biology, and a Howard Hughes Medical Institute investigator. At Whitehead, she replaced Dr. Gerald Fink, a genetics pioneer who had served the maximum 10 years allowed as director of the institute.

Dr. Lindquist's research thrust her into the scientific limelight when it provided the definitive evidence for a new form of genetics based upon the inheritance of proteins with new, self-perpetuating shapes. This provided a biochemical framework for understanding other mysteries in biology, including mad cow disease. But her research has also led her into other areas, and she is known as an advocate of the interdisciplinary approach to research, particularly incorporating physics and chemistry.

"When worlds collide, sparks fly," she has said. "This is allowing us to take old problems and attack them in new ways."

A Chicago native, she earned a B.A. in microbiology at the University of Illinois and a Ph.D. in biology at Harvard.

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1000 E. 50th Street
Kansas City, Missouri 64110
Tel: (816) 926-4000
Fax: (816) 444-8644
www.stowers-institute.org

Editor:
Shirley Christian
Tel: (816) 926-4024
email: shc@stowers-institute.org

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1000 E. 50th Street
Kansas City, Missouri 64110
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