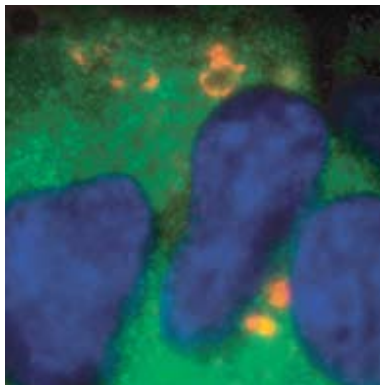
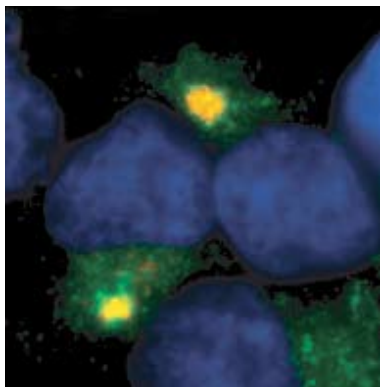
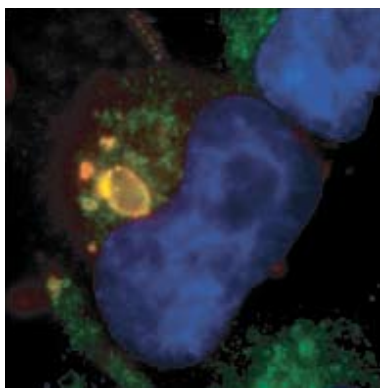
Whitehead Institute

2007 Annual Report







Whitehead Institute for Biomedical Research is a nonprofit research and educational institution. Wholly independent in its governance, finances and research programs, Whitehead shares a teaching affiliation with Massachusetts Institute of Technology (MIT). Whitehead brings together a small group of world-class biomedical researchers in a highly collaborative and supportive environment and empowers them to pursue the questions that engage them most.

ON THE COVER: Studying how cells regulate their growth, David Sabatini's laboratory has shown that Rag family proteins regulate the location of a key protein complex called mTORC1 in the presence of nutrients. Here, mTOR is marked in green, DNA in blue and the Rab7 protein in red. From top to bottom in the sequence here, as the cell is stimulated with amino acids, mTOR moves to be localized in a compartment near the nucleus. Sancak et al., "The Rag GTPases bind raptor and mediate amino acid signaling to mTORC1", Science (2008). Reprinted with permission from AAAS.

Whitehead Institute
2007 Annual Report

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Challenges and celebrations

David C. Page

In 2007, Whitehead Institute for Biomedical Research celebrated its 25th anniversary. That gave us an important opportunity not just to look back, but to pause and look at the Institute today, and to think about the future.

Looking back, we saw once again the unforgettable figure of our founder, Edwin C. "Jack" Whitehead. Jack was passionate, endlessly curious, stubborn, colorful, charming and relentlessly dedicated to creating the world's finest institution for basic biomedical research. Twenty-five years later, he still inspires.

We also recalled the stunning range of major scientific accomplishments that emerged quickly from the Institute.

There was no doubt that Jack Whitehead, Founding Director David Baltimore and many other partners had hit upon a winning formula.

In fact, in 1990, only eight years after Whitehead Institute was formed, *Science Watch* ranked it as the top research institution in the world in genetics and molecular biology.

Today, we continue to rank very highly among our peer institutions, most of which are much larger than Whitehead. The Institute ranked fourth in a *Science Watch* analysis of high-impact genetics and molecular biology papers from 2002 through 2006.

Even more remarkable for such a small institution, two of our Members were the top-ranked authors of those high-impact papers.

I think this is a testament to the soundness of our model and our mission: to recruit and empower the best talent we can find. In addition to retaining the senior faculty whose discoveries have brought such luster to the Institute, we have been successful in attracting superb young researchers. Of our 23 principal investigators, 10 have joined since 2004.

Three of these researchers set up their labs in 2007. Among them, Whitehead Member Iain Cheeseman studies key mechanisms in cell division. His work focuses on the kinetochore, a structure that helps to divide DNA molecules shortly before cells

divide. Because many cancers may be driven by errors in this process, Iain's studies may provide payoffs in cancer research.

New Whitehead Fellow Kate Rubins studies poxviruses, which include smallpox, monkeypox, cowpox and vaccinia (the virus from which the classic smallpox vaccine is developed).

Defne Yarar, a Special Fellow of Whitehead Institute and the MIT Center for Cancer Research, investigates how cells employ a network of proteins called the actin cytoskeleton to engulf large molecules from outside the cell.

We also were very fortunate in bolstering our Board of Directors with several new Members. These include Arthur W. Brill, an attorney with Roberts and Holland, LLP, and the longtime Secretary of the Whitehead Corporation; Peter M. Hecht, co-founder and chief executive officer of Ironwood Pharmaceuticals, Inc. (formerly Microbia); and David H. Koch, executive vice president and co-owner of Koch Industries, Inc. I'd also like to give special thanks to departing Board Member John K. Castle for his major contributions over many years to Whitehead Institute.

This was a banner year for private donations; the total for 2007 exceeded $16 million. Most notably, Whitehead received its largest gift since its founding as Landon and Lavinia Clay gave $10 million to endow the Clay Laboratory Fund. The Clays also donated $1 million to establish the Clay Fellows Program.

A $4 million bequest from the estate of Margaret Sokol allowed Whitehead to establish its first endowed chair, the Margaret and Herman Sokol Chair in Biomedical Research.

Moreover, Liliana and Hillel Bachrach pledged $1 million to fund novel research in the Whitehead Human Embryonic Stem Cell Facility.

With generous support like this, Whitehead research continues to flourish, despite today's challenges in federal research funding.

Throughout the past 25 years, Whitehead has launched new scientific fields of research and careers that have changed the face of biomedical research throughout the world.

This work will have dramatic consequences for our own lives and those of our children and grandchildren.

We don't know what will happen in biology in the next 25 years—except that it will be full of important surprises, that it will bring research findings with enormous implications for human health and that we at Whitehead will succeed by staying faithful to the goals and values and search for excellence that brought us here.

We will stick by our mission, empowering the exceptional individual scientists who can push back the frontiers of biology. We find the right people, and we let them define the future.

Throughout the following pages, you'll see what made 2007 so memorable at the Institute.

I'd like to extend my deepest thanks to the researchers, staff and partners who made this progress possible.

—David C. Page

Research accomplishments

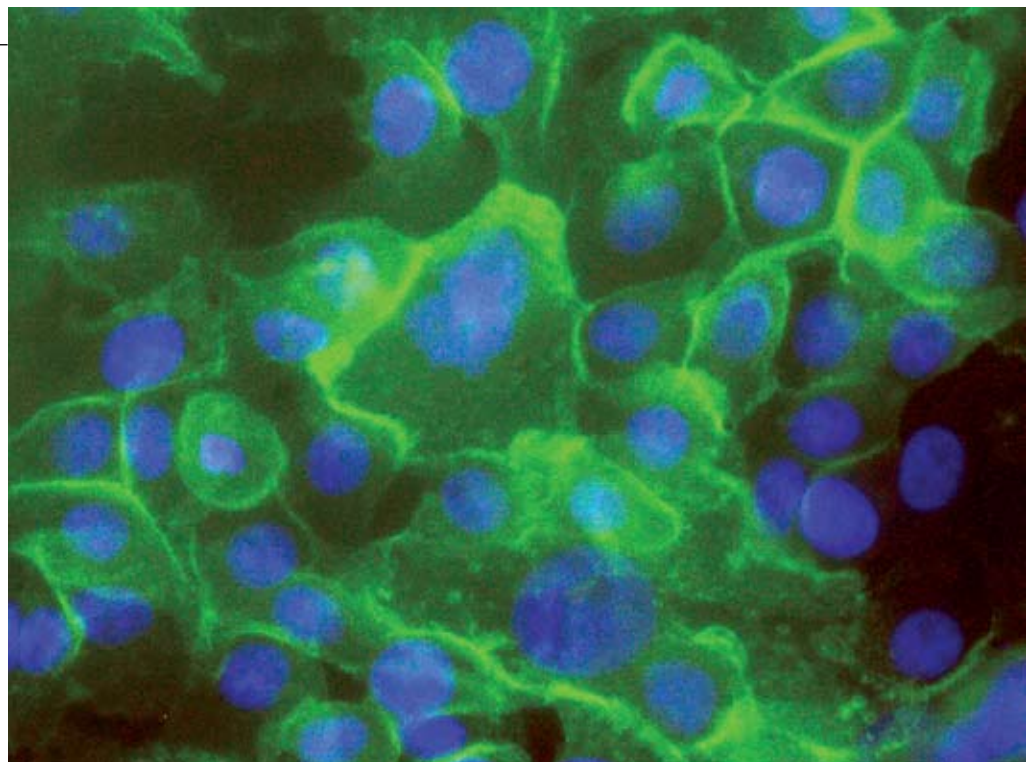
Highlights of Whitehead science reported in 2007

Cancer

- In the past few years, cancer researchers have hotly debated the potential role in solid tumors of cancer stem cells, which may fuel the ability of tumors to renew and spread. In 2007, the lab of Whitehead Member **Robert Weinberg** created a line of human breast cancer stem cells that may help to clarify the role that such cells play. After being injected with just 100 of these cells, mice develop tumors that metastasize.

- Researchers also elucidated the role that microRNAs may play in cancer. Whitehead Member **David Bartel's** lab showed that overabundance of a single microRNA can cause tumors to spread to distant tissues in mice, while the Weinberg lab showed that another microRNA directly regulates a gene implicated in human cancers. (For more on microRNA research at the Institute, see story on page 6.)

- While heat shock proteins play a beneficial role in adapting to stress, they also may be co-opted for cancer pathways, as scientists in the lab of Whitehead Member **Susan Lindquist** demonstrated. Their work suggested that the heat shock master regulator protein HSF1 may offer a uniquely effective target for the discovery of broadly active anticancer agents. (See story, page 8.)



Normal human breast cells were transformed into cancerous cells (with membranes stained green) in a culture medium created by the Weinberg lab. As many as one in ten are cancer stem cells.

Stem cells

- Embryonic stem cells can differentiate into almost any cell of the body, but the need to use embryos in their creation creates ethical and practical issues for possible therapeutic use. The lab of Whitehead Member **Rudolf Jaenisch** was one of three worldwide that in June reported the ability to take cells from mice tails and reprogram them into cells that appear identical to embryonic stem cells—without using an egg. This sparked labs around the world to begin investigating such "induced pluripotent stem" (IPS) cells. In December, the Jaenisch lab followed up with the first proof of principle of therapeutic use of IPS cells, further manipulating such cells to successfully treat sickle-cell anemia in mice. (See story, page 10.)

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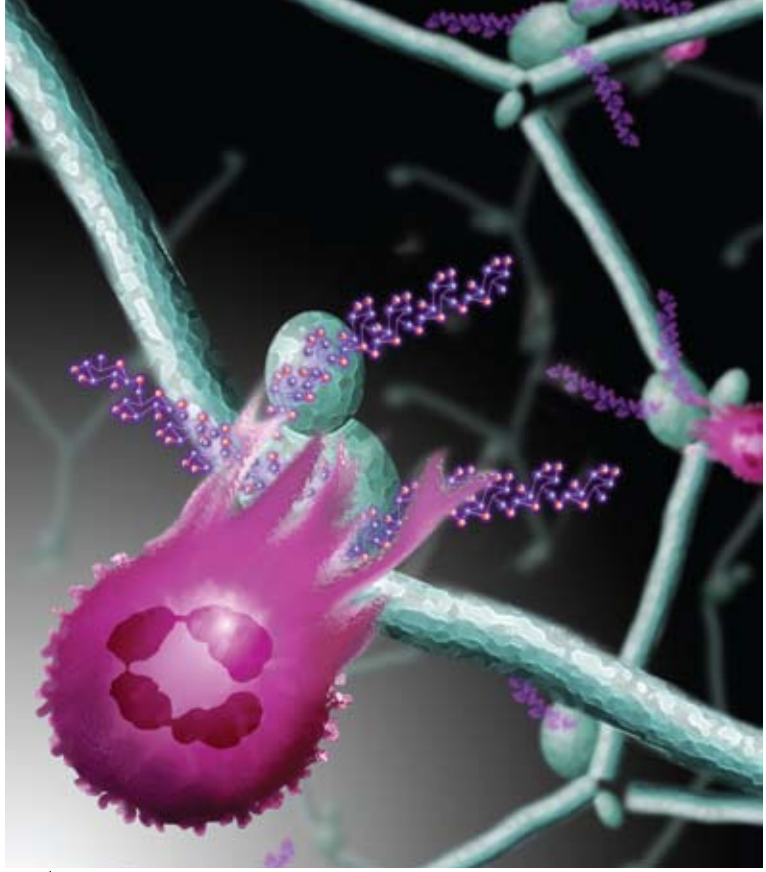
- In other stem cell work, Whitehead Member **Peter Reddien's** lab identified a gene that regulates polarity in regenerating planarian flatworms (a process that is driven by a form of adult stem cells). When a planarian is cut, inhibiting that gene resulted in the animal making a head instead of a tail at the site of the wound.

- Contrary to textbook models, many genes that should be "off" in embryonic stem cells and specialized adult cells remain primed to produce master regulatory proteins, leaving those cells vulnerable to identity changes, as Whitehead Member **Richard Young**'s lab discovered. Understanding this process could bring us a step closer to reprogramming cells in a controlled fashion, which has important applications for regenerative medicine.



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1 Inhibition of the *Smed-beta-catenin-1* gene causes planarian flatworms to regenerate a second head (on right) instead of a tail.

2 Neutrophils, a type of white blood cells shown in pink in this illustration, recognize and respond to a particular form of sugar on the surface of pathogenic fungi.

Infectious disease and drug development

- The lab of Whitehead Member **Gerald Fink** demonstrated that white blood cells can recognize and respond to a particular form of sugar contained on the surface of pathogenic fungi. The work offers hope for combating the growing problem of microbial infections, which can seriously threaten human health, particularly in patients with compromised immune systems.

- Whitehead Member **Harvey Lodish**'s lab worked with collaborators at MIT to develop a cell culture test for assessing a compound's genetic toxicity that may prove dramatically cheaper than existing animal tests of drug candidates.

- The lab of Whitehead Member **Hidde Ploegh** solved the complex structure of a recently discovered protein that is found in a wide range of herpes viruses. The protein may be a good target for drug development.

PLANARIAN: PETER REDDIEN; ILLUSTRATION: TOM DICESARE

Scientific awards and achievements

Some recent recognition for principal investigators

- **Iain Cheeseman** and Whitehead Fellow **Andreas Hochwagen** received Smith Family New Investigator Awards.
- **Rudolf Jaenisch** was given a Vilcek Foundation Prize. These are awarded to foreign-born individuals for extraordinary contributions to society in the U.S.
- **Susan Lindquist** was declared one of Harvard's 100 most influential alumni by *02138* magazine.
- Whitehead Member **Terry Orr-Weaver** was appointed American Cancer Society Research Professor and a trustee for the Genetics Society of America.
- Whitehead Director **David Page** was named a Fellow of the American Association for the Advancement of Science.
- Whitehead Member **Hazel Sive** was appointed associate dean for MIT's School of Science. Sive, the first associate dean in the School's history, is focusing on educational issues and initiatives.
- **Robert Weinberg** received the Otto Warburg Medal from the German Society for Biochemistry and an honorary doctorate from the University of Uppsala in Sweden.

Grant awards

Highlights of first-year funding for selected new federal grants in calendar year 2007

- **Richard Young's** lab received $1,305,134 from the National Human Genome Research Institute to study transcriptional regulatory networks in living cells.
- **Harvey Lodish's** lab received $704,872 from the National Institute of Diabetes & Digestive & Kidney Diseases to study cell signaling in muscle and liver, and $399,750 from the same agency to study the expansion of blood stem cell cultures.
- **Susan Lindquist's** lab was awarded $543,377 by the National Institute of General Medical Sciences to study protein-folding mechanisms.

Also, among the gifts from foundations, **Robert Weinberg's** lab was awarded $325,000 from the Breast Cancer Research Foundation to investigate how epithelial and stromal cells, two primary types of cells found in mammalian tissue, interact in tumors.

RESEARCH STORIES

Here are glimpses of a few research advances—in small RNAs, heat shock proteins and cells that act just like embryonic stem cells.

What one microRNA can do

How scientists connected a single snippet of RNA to a cancer-causing gene

Like many Whitehead researchers, Christine Mayr is an MD. Her clinical work at Ludwig Maximilians University of Munich led to a fascination with the genetics of leukemia and cancer—and then to the role of microRNAs.

These tiny pieces of RNA can repress gene activity by targeting the gene's messenger RNA, which contains the DNA information needed for the process of protein production.

Research in microRNAs has soared in recent years, and the lab of Whitehead Member David Bartel has helped to lead the way.

Two years ago when Mayr joined the Bartel lab, only 250 of these tiny molecules had been discovered in various organisms—about a quarter of the current total.

"MicroRNAs might regulate every physiological process and, intriguingly, they behave the same way in different species," she says. "Investigating this gene mechanism, which was unknown until a few years ago, was exciting. And David's lab was at the center of discovery within this realm."

Researchers were just starting to understand that microRNAs were involved in the regulation of certain cancers, but they hadn't nailed down the specific genes that were regulated by microRNAs. An individual microRNA can target hundreds of genes, making it tricky to confirm target predictions.

Mayr took an unusual approach to studying the microRNA-cancer connections. Rather than modifying the expression of

About two dozen scientists in the lab of David Bartel (foreground) study microRNA activities in organisms ranging from flatworms and fruit flies to mice and humans. "Many microRNAs have been conserved for hundreds of millions of years of evolution," Bartel notes. "We have so much more to learn about the biological consequences of microRNA regulation."

FURNALD/GRAY

microRNAs and seeing how that affected a model organism, she began by examining data on chromosomal translocations—mutations in genes that can be associated with tumor initiation or progression—and then linked them to microRNA regulation.

That led her to single out the gene *Hmga2*, which is defective in a wide range of tumors. She then analyzed whether a mutation in that gene could disrupt a microRNA's ability to regulate it.

As she had predicted, it turned out that a mutation to the non-protein-coding portion of the gene could be critical. She found clear evidence, both in human cell cultures and in mice, that the *let-7* microRNA is involved in regulating *Hmga2*.

In fact, disrupting *let-7*'s ability to repress *Hmga2* leads to tumor creation.

Mayr and her colleagues published their results, the first demonstration that the interaction of one microRNA with one of its target genes can produce a certain trait in mammals, in *Science* in February 2007.

"Because hundreds of human genes appear to be regulated by the *let-7* microRNA, we were concerned that we might not see any difference when we changed only one of these target genes," says Bartel. "Seeing the difference encourages us to explore the biological importance of other examples of microRNA regulation."

"I hope to identify other ways for cancer cells to escape microRNA regulation," says Mayr, "using my unconventional approach of starting with the appearance of a tumor and tracing it back to a particular microRNA."

Chaperoning cancer

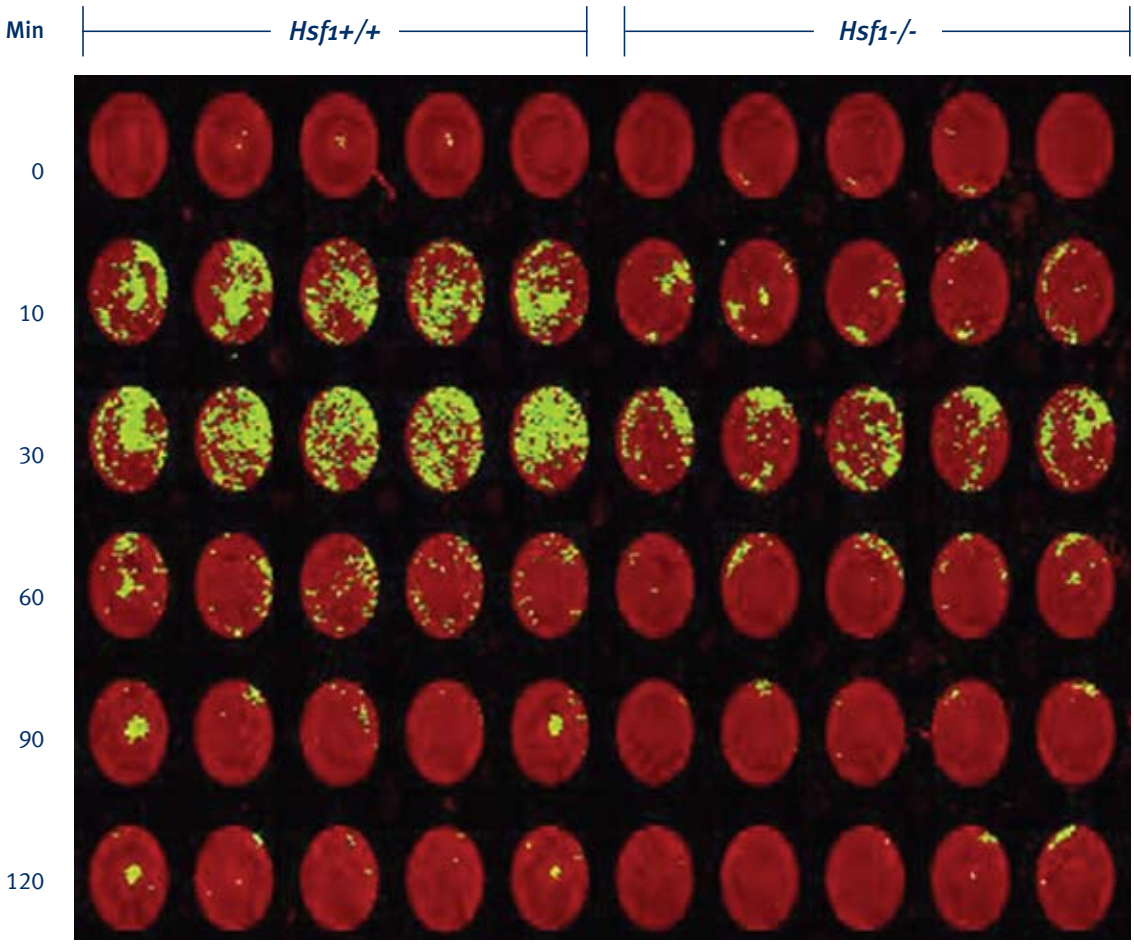
Unveiling the role of heat shock regulators may lead to a new class of cancer drugs

Ten years ago, a young scientist climbed onto a shuttle van from a New York City airport to a conference at Cold Spring Harbor on Long Island. On the 30-mile trip, he chatted with another passenger, Whitehead Member Susan Lindquist.

"I was an assistant professor at the University of Arizona, and she was one of the speakers at the conference, but we were both working on chaperone proteins," recalls Luke Whitesell, now a senior research scientist in Lindquist's group.

Chaperone proteins are specialized molecules that help other proteins in a cell to perform their functions. All proteins need to acquire and maintain the correct three-dimensional shapes to perform properly. If a protein does not have the correct shape, it cannot do its job. The chaperones help proteins fold into the correct shape, prevent proteins from clumping together and escort damaged or malformed proteins to the cellular version of a recycling center. Heat shock proteins are specific chaperone proteins that perform these three vital roles under normal conditions and especially when a cell is stressed by heat, cold, toxins or other hardships that cause proteins to misfold.

At the time, Lindquist was using model organisms such as fruit flies and yeast to study how chaperone proteins work and



After being stimulated with growth factors, mouse cells lacking the heat shock protein HSF1 (on the right) showed less activation of a pathway that often contributes to the abnormal growth of cancers, indicated by much less bright green signal than seen in cells with HSF1.

1

how their function affected cells. As a pediatric oncologist, Whitesell was more interested in a new and intriguing anticancer target, which had been identified as the chaperone protein heat shock protein 90 (HSP90).

Ironically, HSP90 can be too good at its chaperone job. In some cases, mutated versions of proteins trick HSP90 into helping them.

One of these deviants is the cancer-causing protein v-SRC. Without help from HSP90, v-SRC is a long, useless protein string. But instead of shuttling v-SRC off to be recycled, HSP90 mistakenly coddles v-SRC and folds it into its mature, cancerous form.

Several years after their initial conversation on Long Island, Whitesell took a six-month sabbatical from his lab at the University of Arizona in Tucson to work in the Lindquist lab on the master regulator of all heat shock proteins, called heat shock factor 1 (HSF1).

By then, Lindquist and Whitesell knew that organisms need increased heat shock protein levels to survive in all but ideal environments and to fend off protein-accumulating diseases, like Alzheimer's or Parkinson's. But enough of these chaperones could be expressed without HSF1 to allow the organisms to survive. They decided to see how mouse cells that could produce normal amounts of HS90 and other chaperones, but lacked the HSF1 regulator, would deal with the introduction of another cancer-causing gene called *H-RAS*.

Strikingly, cell cultures without HSF1 did not show any evidence of being transformed into cancer cells, while otherwise identical cells with normal HSF1 developed cancer-like clumps of cells.

That encouraged another researcher, postdoctoral fellow Chengkai Dai, to continue the research after Whitesell returned to Arizona.

Dai's work with mice gave dramatic support to the earlier cell culture work. Publishing in *Cell* in September 2007, Dai showed that eliminating HSF1 protected the mice from cancerous tumors.

"HSF1 plays a dual role," Dai says. "It has been shown that HSF1 is involved in protecting against neurodegeneration, in which brain cells die slowly over time. In cancer, the opposite is true: cancer cells don't die. Ironically, cancer cells hijack and exploit this evolutionarily conserved self-protective function of HSF1." In fact, he says, cancer cells appear much more sensitive than normal cells to the loss of HSF1 function.

"It will be interesting to see how the insights gained from studies such as this one can be applied to develop useful therapeutics," says Whitesell, who is now back in the Lindquist lab.

"We propose that HSF1 could provide a uniquely effective target for the discovery of broadly active anticancer agents," adds Lindquist. "It might be possible to target cells with altered signal pathways or metabolism using entirely new therapeutics based on this response."

1 **"HSF1 could provide a uniquely effective target for the discovery of broadly active anticancer agents," says Susan Lindquist.**

Early in 2007, researchers in the Jaenisch lab grew this healthy mouse from an embryo containing induced pluripotent cells (adult cells that had been reprogrammed to an embryonic state).

SAM OGDEN

Reprogrammed for a cure

A new form of stem cells gets its first proof-in-principle for therapeutic use

The race was on.

When Jacob Hanna joined the lab of Whitehead Member Rudolf Jaenisch in March 2007, his co-workers already had learned how to create "induced pluripotent stem" (IPS) cells in mice.

First made by Shinya Yamanaka's lab at Tokyo University the year before, IPS cells are created by taking adult cells and, without using an egg, turning them back into cells that seem to act just like embryonic stem cells, including the ability to generate almost any type of cell.

Researchers in the Jaenisch lab, and their counterparts in the labs of Yamanaka and Harvard's Konrad Hochedlinger (a Jaenisch-lab alum) were working furiously to extend Yamanaka's results with mice. (A few months later in June, all three would report success, creating headlines worldwide.)

Hanna, who had just finished his MD and PhD at the University of Jerusalem, instead raced ahead on a follow-up project. He would combine the powerful new technique with existing methods of reprogramming DNA *in vitro* to show, in principle, that IPS cells could act therapeutically.

The target disease was sickle-cell anemia, a blood disease that afflicts more than 70,000 in the U.S. Researchers have long known the cause of the disease—the mutation of a single nucleotide in a key gene for making the hemoglobin protein—but there is no cure.

There is, however, a mouse model of the disease, developed by the laboratory of Tim Townes of the University of Alabama at Birmingham, that incorporates the defective

human version of that hemoglobin gene.

To create the IPS cells, Hanna started with cells from the skin of the diseased mice. He modified these cells by a standard lab technique employing retroviruses customized to insert genes into the cell's DNA. The inserted genes were *Oct4*, *Sox2*, *Klf4* and *c-Myc*, known to act together as master regulators to keep cells in an embryonic-stem-cell-like state. IPS cells were selected based on their structure and then verified to express genes specific to embryonic stem cells. The potentially cancer-causing *c-Myc* gene then was removed by genetic manipulation from the IPS cells.

Next, with help from Whitehead Fellow Fernando Camargo, Hanna followed a well-established protocol for differentiating embryonic stem cells into precursors of bone marrow adult stem cells, which can be transplanted into mice to generate normal blood cells.

He and his colleagues created such precursor cells from the sickle-cell anemia IPS cells, replaced the defective blood-production gene in the precursor cells with a normal gene and injected the resulting cells back into the diseased mice.

Then Hanna sent off the blood of treated mice for tests on standard hospital analytical equipment.

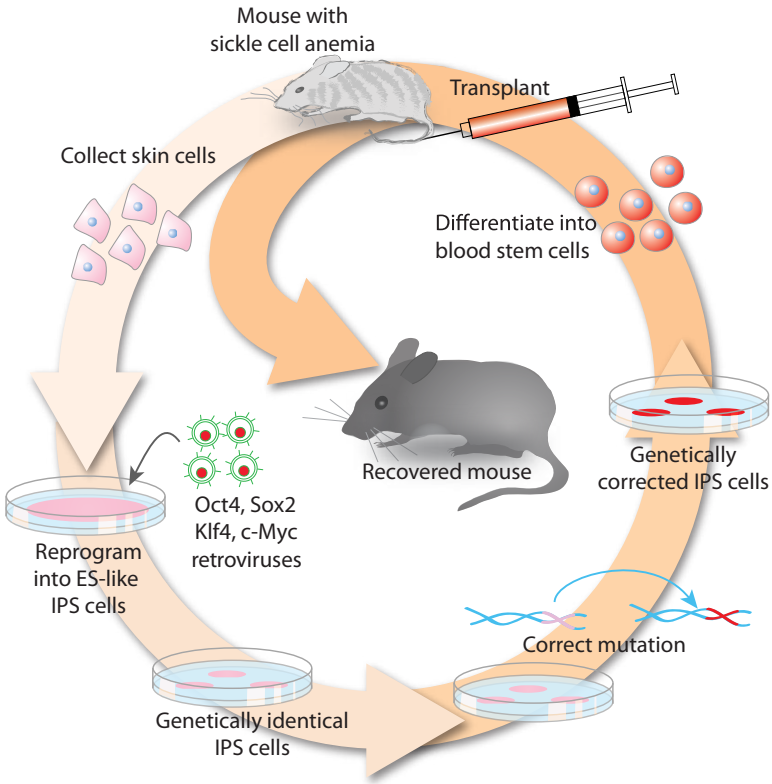
Good news: The results showed that the disease was corrected, with measurements of blood and kidney functions similar to those of normal mice.

When these results appeared in *Science* in December, they sparked great interest in the sickle-cell anemia community.

And Hanna already was moving ahead in another race in IPS research—working 17-hour days this time to reprogram white blood cells.

Fixing sickle-cell anemia

Skin cells from a mouse modeling the blood disease were reprogrammed to an embryonic state, genetically corrected, grown into blood stem cells and then transplanted back into the mouse.



Moving toward medicine

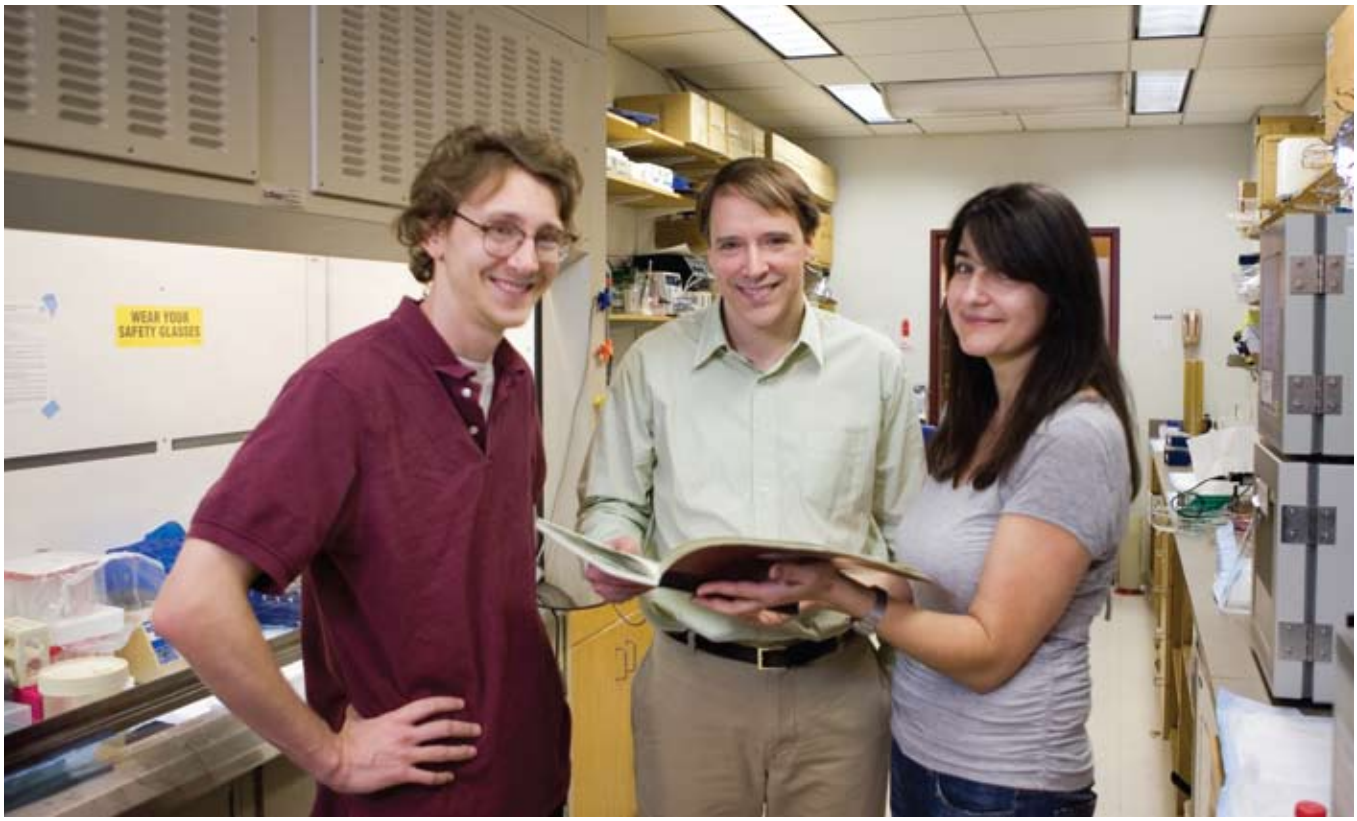
While the work in induced pluripotent stem (IPS) cells has created tremendous excitement, researchers caution that major challenges must be overcome before medical applications for IPS cells can be considered, starting with a better method of gene manipulation for generating the cells. "Retroviruses can disrupt genes that should not be disrupted or activate genes that should not be activated," with dangerous results, Jacob Hanna notes. Also, "we wouldn't have known anything about IPS cells if we hadn't worked with embryonic stem cells," emphasizes Rudolf Jaenisch. "For the foreseeable future, embryonic stem cells will remain the crucial assessment tool for measuring the therapeutic potential of IPS cells."

PRINCIPAL INVESTIGATORS

Whitehead Institute is home to 23 principal investigators (16 Members and 7 Fellows) and more than 300 postdoctoral fellows, graduate and undergraduate students, visiting scientists and technicians from around the world.

Whitehead Members

The Institute is fully independent, but its Members also are faculty members at Massachusetts Institute of Technology.



WHITEHEAD MEMBER

David Bartel

FOCUS OF RESEARCH

The Bartel lab studies the role that tiny snippets of RNA called microRNAs play in gene regulation. Researchers examine microRNA activity in plants, the flatworm *C. elegans*, fruit flies, mice and human cells. In 2005, Bartel's lab showed that microRNAs affect the expression or evolution of the majority of human genes. Scientists want to better understand how microRNAs recognize their target genes, how these protein-coding gene targets are regulated and the biological consequences that ensue when that regulation fails. (See story, page 6.)

RECENT SCIENTIFIC ACCOMPLISHMENTS

In 2007, Bartel's lab showed that a microRNA directly regulates a specific gene implicated in human cancers. In some types of cancer cells the gene is mutated such that the microRNA can no longer recognize and regulate the gene. This is the first demonstration that losing the microRNA regulation of a cancer gene helps a normal cell turn into a cancer cell. "Seeing the effect of changing this single gene so that it no longer responds to the microRNA encourages us to explore the biological importance of other examples of microRNA regulation," says Bartel.

CURRENT TRENDS IN THIS FIELD

Growth in such studies has been explosive. The first microRNA was described in 1993, the second in 2000. Several labs, including the Bartel lab, have found hundreds of genes that produce microRNAs in fruit flies, worms, flowering plants and other species, with more than 400 found in humans.

"Over the last several years we've discovered hundreds of microRNAs in mammalian cells and we've developed ways of accurately predicting which genes the microRNAs are targeting for plants as well as animals."

— DAVID BARTEL
(center)

WHITEHEAD MEMBER

Iain Cheeseman

FOCUS OF RESEARCH

The Cheeseman lab investigates the role of the kinetochore, a group of proteins required for cell division and chromosome segregation. This core network of proteins facilitates the attachment of chromosomes to microtubule polymers—the spindle structures that attach to the ends of cells, pulling and dividing them during cell division. The kinetochore is critical to ensuring duplication without loss or damage to the genetic material. Researchers also are investigating the activities of the individual molecular machines that make up this structure and how these proteins are controlled and regulated.

RECENT SCIENTIFIC ACCOMPLISHMENTS

Cheeseman is noted for discovering multiple new kinetochore proteins within yeast, *C. elegans* and human cells. He has focused particularly on the proteins that are required to generate connections with spindle microtubules. He recently demonstrated a critical and direct role for a protein complex called Ndc80 in directly associating with microtubules.

CURRENT TRENDS IN THIS FIELD

"When I began graduate school, there were 10 total known kinetochore proteins," says Cheeseman. "Now there are about 80. It's estimated that there are about 100 of these proteins in human cells. We are working to identify the remaining kinetochore proteins and their functions."

"It is my hope that within five to ten years, we will have a more detailed understanding of kinetochore proteins during disease progression. There are multiple tantalizing correlations between these proteins and cancer, and this has the potential to provide information about tumor formation and progression which may lead to improved means of diagnosis and treatment for cancer."

— IAIN CHEESEMAN

WHITEHEAD MEMBER

Gerald Fink

FOCUS OF RESEARCH

Fink is best known for building the molecular tools for analyzing simple genomes such as that of yeast. His lab studies infectious disease—both the pathogen and the recognition system for the pathogen. "The immune system recognizes the pathogen by the skin of the pathogen, the cell surface," says Fink. "We're very interested in finding the signature molecules that say, 'I'm a fungus.' And then in studying the receptors on the immune system that recognize those and tell the rest of the immune system that the infection is a fungal infection."

RECENT SCIENTIFIC ACCOMPLISHMENTS

One was to demonstrate that neutrophils (the most prevalent kind of white blood cells) can recognize and respond to a particular form of sugar contained on the surface of pathogenic fungi. Another is ongoing work, in conjunction with the lab of MIT Institute Professor Robert Langer, to develop ways to coat or embed antifungal antibiotics in prostheses or catheters.

CURRENT TRENDS IN THIS FIELD

"We're seeing enormous technical advances in gene sequencing and in gene expression studies, but integrating the results into biological functions is still a major challenge," says Fink. "The theoretical issues have not been fully understood."

"There are moments of clarity that make us think we really understand something, and next moment, a sense of confusion and a recognition that we don't really understand as much as we thought. For experimental science, that's an exciting situation. For problem-solvers, it truly couldn't be better."

— GERALD FINK

WHITEHEAD MEMBER

Rudolf Jaenisch

FOCUS OF RESEARCH

"What makes a given cell a given cell—what makes a liver cell a liver cell versus a brain cell versus an embryonic cell?" asks Jaenisch. "We want to understand this in molecular terms, and we are using this information to convert one cell type to the other. We want to understand that whole process and eventually to directly convert one adult cell to another without going through the detour of embryonic cells."

RECENT SCIENTIFIC ACCOMPLISHMENTS

In June 2007 the Jaenisch lab was one of three worldwide that reported successfully taking cells from mice tails and turning them into "induced pluripotent stem" (IPS) cells that appear identical to embryonic stem cells, without using an egg. In December, the lab followed up by further manipulating IPS cells to successfully treat sickle-cell anemia in mice, the first proof in principle of therapeutic applications of such cells. (See story, page 10.)

CURRENT TRENDS IN THIS FIELD

Discoveries about IPS cells have tremendously accelerated research in embryonic stem cells. "This method has substantial implications for studying human diseases and treating human diseases," says Jaenisch. "It can, in principle, yield us embryonic stem cells from specific patients, so those cells have all the genetic alterations that are probably causing the disease. This would allow you to transfer complex genetic human disease into the Petri dish and study it. That could be the first step to analyze and to define a therapy."

"These are probably the most exciting times in research that I have had, because advances in stem cell research have suddenly opened up so many possibilities for studying really important biological questions that we never could before. That's absolutely fantastic. And clearly this has direct relevance to disease."

— **RUDOLF JAENISCH** (left)

MARIA NEMCHUK/BROAD INSTITUTE

WHITEHEAD MEMBER

Eric Lander

FOCUS OF RESEARCH

Lander and colleagues have pioneered the mapping and sequencing of the human genome; cataloging the vast majority of genetic variation in the human population; and developing the methods to map complex diseases. "We remain stubbornly interested in trying to understand all of the functional information encoded in the human genome—including protein-coding genes, noncoding RNAs, regulatory elements and variants responsible for disease-susceptibility," he says.

RECENT SCIENTIFIC ACCOMPLISHMENTS

Achievements include developing a method for creating whole-genome maps of the state of DNA packaging and applying it to discover new forms of genetic regulation of key developmental genes.

CURRENT TRENDS IN THIS FIELD

"The past year has seen an explosion in understanding the genes underlying complex diseases," Lander notes.

"I could not imagine doing anything in the world that is more satisfying than being involved in human genomic research."

— ERIC LANDER

WHITEHEAD MEMBER

Susan Lindquist

FOCUS OF RESEARCH

The Lindquist lab investigates the mechanisms of protein folding and the consequences of misfolding, in research that moves back and forth between simple and complex organisms (yeast, fruit flies, plants, mice and human cells). Researchers are exploiting the understanding of protein folding to gain insights into neurodegenerative illnesses and other diseases. The lab also has identified potentially important beneficial effects of self-perpetuating alternate protein conformations, including evolutionary change and long-term memory.

RECENT SCIENTIFIC ACCOMPLISHMENTS

Although the infectious proteins called prions have received a great deal of scrutiny, scientists don't understand many of the most fundamental mechanisms of how prions form, replicate and cross from one species to another. Through studying non-toxic yeast prions, scientists in the Lindquist lab discovered small but critical regions within prions that determine much of their behavior. Also in 2007, the lab reported that a certain transcription factor (a protein binds to specific areas of the genome and acts to switch genes on and off) aids in handling stresses but facilitates the survival of cancer cells. (See story, page 8.)

CURRENT TRENDS IN THIS FIELD

"This was once considered an abstruse and arcane subject but it is now clear that protein folding and problems in protein folding are of central interest in virtually all areas of biology, from evolution to inheritance to human disease," says Lindquist.

"There is, somehow or other, tremendous satisfaction in getting something to work that everyone else thought was crazy."

— SUSAN LINDQUIST

WHITEHEAD MEMBER

Harvey Lodish

FOCUS OF RESEARCH

The Lodish lab investigates hematopoietic stem cells—cells in the bone marrow that give rise to all red and white blood cells—focusing on identifying the hormones that cause these cells to divide and make more stem cells. Researchers also are studying the function of individual microRNAs in the development and function of fat cells, muscle cells and hematopoietic cells, in collaboration with Whitehead Member David Bartel and other colleagues. Additionally, other scientists are analyzing red blood cell formation and studying adiponectin, a hormone made by fat cells that controls fatty acid and glucose metabolism.

RECENT SCIENTIFIC ACCOMPLISHMENT

Over a number of years, the lab has discovered a way to multiply mouse and human blood stem cells 30-fold, an expansion that offers tremendous promise for treatments such as bone marrow transplants and perhaps even gene therapy. "The ability to extend human cord blood stem cells in culture could lead to many clinical applications, increasing the efficiency of bone marrow transplantation for a number of diseases," says Lodish.

CURRENT TRENDS IN THIS FIELD

"If we open the most recent edition of our *Molecular Cell Biology* textbook, of which I am an author, we can see that 90 percent of it was unknown 30 years ago," remarks Lodish. "Every four years we completely change 30 or 40 percent of the content of the book."

"Gerald Fink, Rudolf Jaenisch, Robert Weinberg and I have been working together at Whitehead for 25 years. It's very rare among institutions that the Founding Members are actually still collaborating and enjoying each other's company. Now that's an achievement!"

— **HARVEY LODISH**
(second from left)

WHITEHEAD MEMBER

Paul Matsudaira

FOCUS OF RESEARCH

The Matsudaira lab studies the more complex aspects of how cells move: how cells move in three dimensions and how ensembles of cells move together.

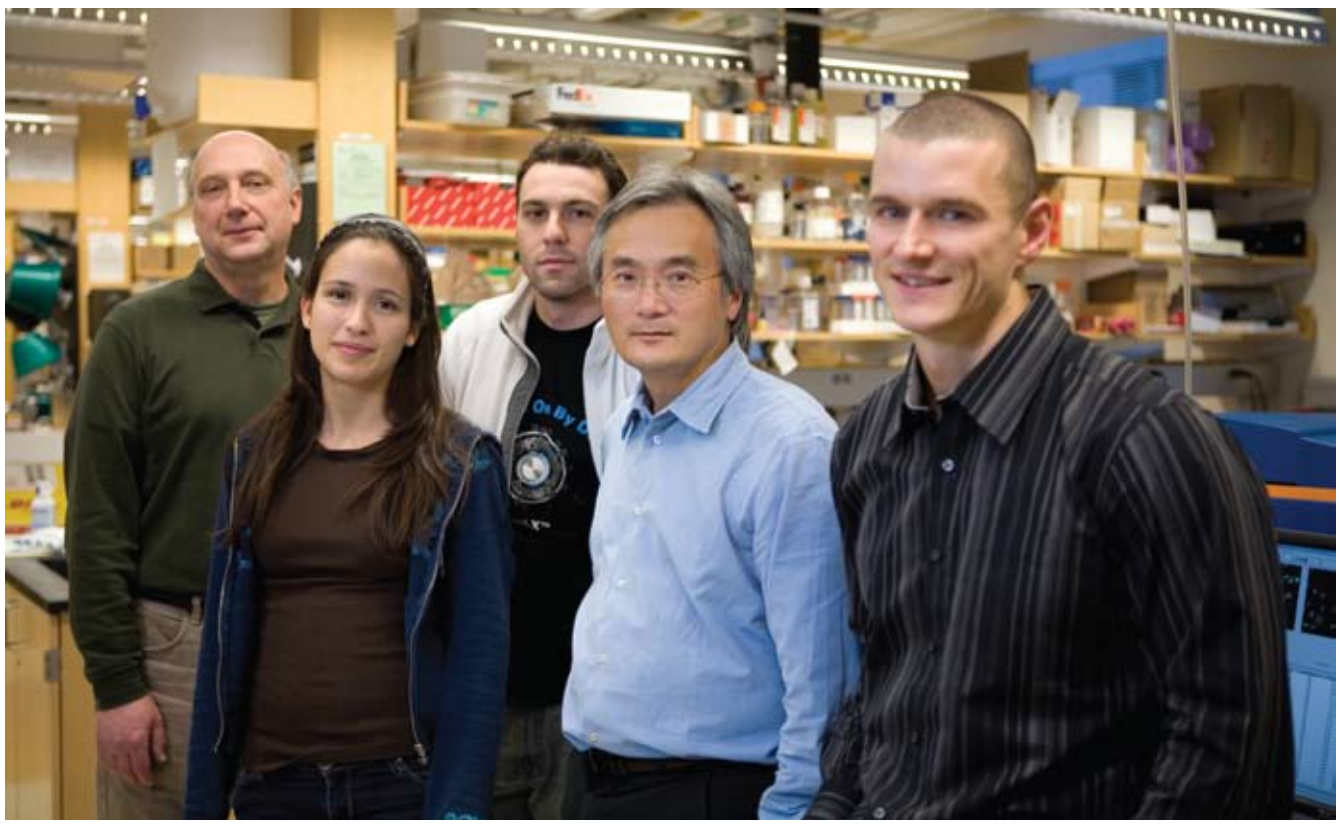
RECENT SCIENTIFIC ACCOMPLISHMENTS

In 2007, researchers in the lab and their colleagues created the first fluorescent sensor that measures the forces involved in cell movement. Previously, researchers who wanted to know how much force is exerted when cells travel needed to place the cells on an instrument that bends or flexes and then calculate the force. In contrast, the fluorescent sensor simply changes colors to show how much force is applied. In other recent work, scientists developed a computational model of a cell moving in three dimensions, overcoming the limits of two-dimensional models that ignore obstacles in the cell's way.

CURRENT TRENDS IN THIS FIELD

"Biomechanics is one of the emerging areas in cell biology, and it's in a lot of the papers you see at the subcellular and cellular levels," says Matsudaira. "Now we're down at the level of how a cell generates force, or how molecular assemblies within a cell generate force. The challenges are so new that you have to develop the techniques in order to ask the questions."

"People typically think of how a cell works in terms of chemistry. But mechanics is just as vital. Everything in life is about movement. If it doesn't move, it's probably dead." — **PAUL MATSUDAIRA** (second from right)



WHITEHEAD MEMBER

Terry Orr-Weaver

FOCUS OF RESEARCH

The Orr-Weaver lab discovers genes and proteins crucial for cell division, focusing on genes and proteins important for DNA replication in the mother cell as well as those critical for the division of chromosomes between the daughter cells. She uses the fruit fly, which her work has shown is a powerful model for cell division in humans.

RECENT SCIENTIFIC ACCOMPLISHMENTS

One of the most difficult aspects of studying DNA replication is finding a way to visualize and isolate the sites at which DNA replication starts. The Orr-Weaver lab has exploited particular biological contexts in the fruit fly that permit the scientists to analyze DNA replication at specific sites in the DNA. This has allowed researchers to decipher mechanisms governing the initiation of replication and to uncover a link between proteins needed for transcription and gene expression and the process of DNA replication. They have identified direct functions in the process of initiation of DNA replication for several proteins affected in cancer cells.

CURRENT TRENDS IN THIS FIELD

The interface between the fields of developmental biology and the cell cycle has become accessible as discoveries in each field have identified key regulatory genes. This makes it possible to now determine how cell cycle regulators are subjected to developmental signals and how control of cell division affects cell differentiation into distinct cell types.

"Gene discovery is one of the most important post-genomic fields of research. It's a crucial area of biology—to find out what all of these unknown genes do."

— TERRY ORR-WEAVER
(center)

WHITEHEAD MEMBER

David Page

FOCUS OF RESEARCH

Mammalian females are born with all of their eggs, but males can produce sperm only after puberty; the difference between the female and male embryonic development is practically unknown. Some researchers in the Page lab are deciphering at a molecular level how mammalian germ cells can develop into eggs in a female or sperm precursors in males. Other lab members are sequencing the Y chromosome of the chimpanzee, which may give us new insight into the evolution and role of the human Y chromosome. The lab also is working on the genetic basis for male infertility, which is often due to deletions in the Y chromosome.

RECENT SCIENTIFIC ACCOMPLISHMENTS

The Page lab found that one gene (*Stra8*) is needed to trigger germ cells to develop into eggs or sperm. "Understanding the embryonic foundations of human fertility at a molecular level is our biggest contribution in the past year," says Page.

CURRENT TRENDS IN THIS FIELD

Reproductive biology was transformed fairly late by the DNA revolution, and some areas of the field are still quite sleepy, says Page, whose lab's biggest overall contribution "has been to bring intellectual respect to the Y chromosome and to put it on the map." However, reproductive genetics and development make up an extremely dynamic field that touches on many inherently controversial areas, including cloning and stem cell research.

"The change in thinking about the Y chromosome caused by our research is very gratifying."

— **DAVID PAGE**
(center)

WHITEHEAD MEMBER

Hidde Ploegh

FOCUS OF RESEARCH

Looking at the devious methods that viruses use to sidestep our immune responses, the Ploegh lab is learning about how the immune system functions at the cellular and molecular levels. Lab members are also using chemistry to create new tools that more precisely track protein movement in a cell. The work will advance many aspects of cellular research.

RECENT SCIENTIFIC ACCOMPLISHMENTS

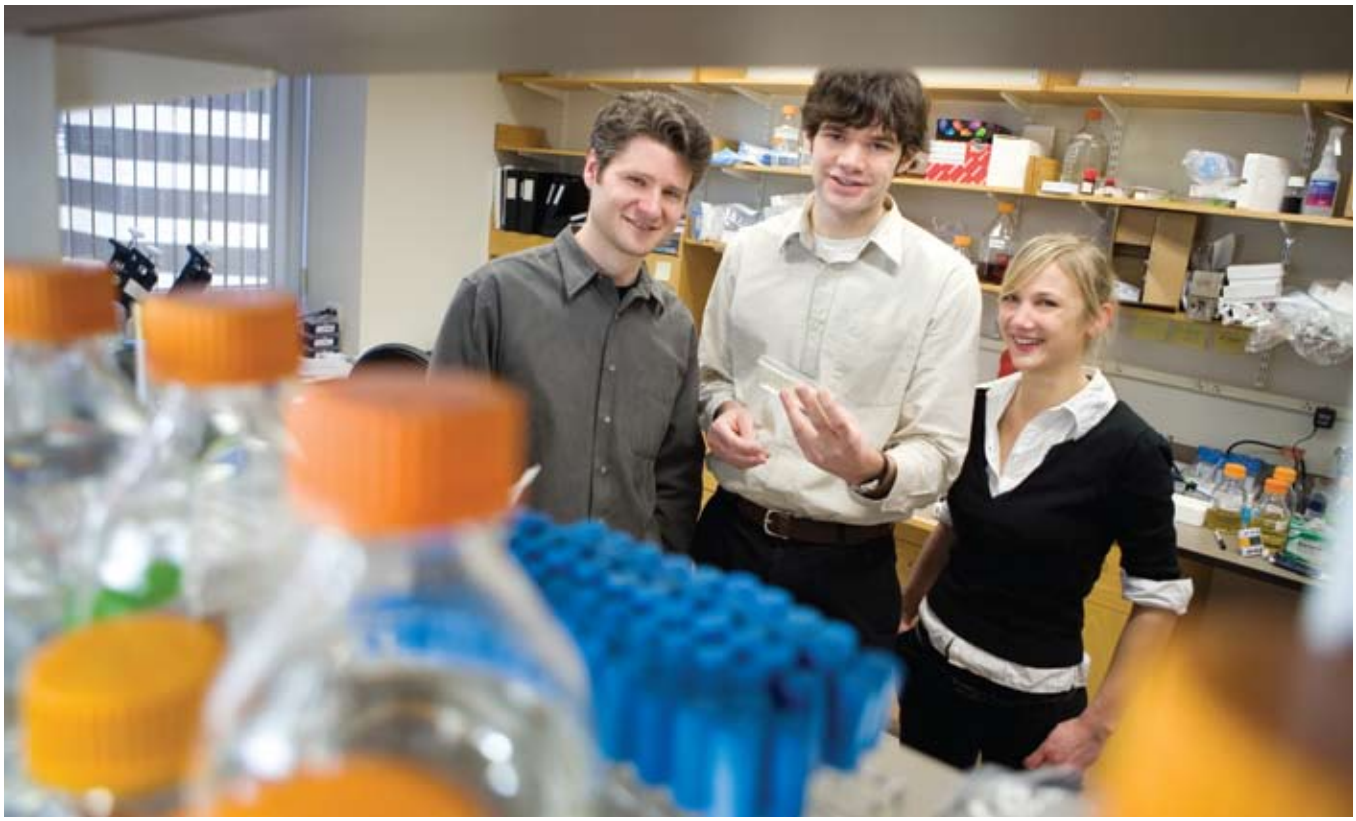
Researchers have created a new way of attaching "tags" to proteins in the cell. These tags are small molecules that glow or add color to a protein, allowing concentrations of the protein to be seen. The new method makes it easier to add tags more precisely to selected proteins. Additionally, researchers solved the complex structure of a recently discovered protein that is found in a wide range of herpes viruses and that may be a good target for drug development.

CURRENT TRENDS IN THIS FIELD

Ploegh believes that progress in biology in general drives progress forward in all parts of the field. For example, certain methods to knock down gene expression that were not possible 10 years ago have had a ripple effect on how research is conducted throughout all of biology. "Therefore, my area of biology marches in lockstep with the rest of biology," says Ploegh.

"Oftentimes, the use of viruses has been very helpful to illustrate aspects of basic biology. For example, from our line of research in herpes viruses stems a whole series of experiments that concern protein quality control in general, not necessarily within the context of a virus infection, but of a normal, cell biological principle."

— **HIDDE PLOEGH**
(left)



WHITEHEAD MEMBER

Peter Reddien

FOCUS OF RESEARCH

Reddien investigates how the flatworm planarian *Schmidtea mediterranea* uses stem cells called neoblasts to regenerate new heads, new tails or entire new organisms from a tiny fragment of its body. Developing RNA interference strategies for exploring gene function, his lab has helped establish planaria as a viable and powerful molecular system for studying regeneration.

RECENT SCIENTIFIC ACCOMPLISHMENTS

The lab found that the gene *Smed-beta-catenin-1* is crucial in determining whether planaria, when cut, will produce a head or tail at a particular site. "Based upon observations, we hypothesized that *Smed-beta-catenin-1* processes specify head-to-toe polarity in the tissues of most if not all animals," says Reddien.

CURRENT TRENDS IN THIS FIELD

Planaria were a classic model for studying regeneration but had not been employed much in the molecular genetic era. "This requires all sorts of innovation and trouble-shooting in the lab," says Reddien. "That's part of the excitement." He believes the biggest payoff will be in understanding the basic biology of stem cells and the general principles of regeneration—not just in planaria but in most or all multicellular animals.

"Early in college I took a required biology class and realized that with a little bit of knowledge you could ask questions that were lacking in answers and were at the forefront of current research."

— **PETER REDDIEN** (center)

WHITEHEAD MEMBER

David Sabatini

FOCUS OF RESEARCH

The Sabatini lab focuses on the mechanisms that regulate cell growth–controlling organ size, body size and even the size of different units within the cell. "Some of the pathways that control size also are involved in diseases and are important pathways for targeting cancer therapy," Sabatini notes. To study these growth pathways, he adds, "we had to invent some new technologies, which took on a life of their own." These tools include genome RNA interference libraries, high-throughput cell-based microarrays and cell-analysis imaging software.

RECENT SCIENTIFIC ACCOMPLISHMENTS

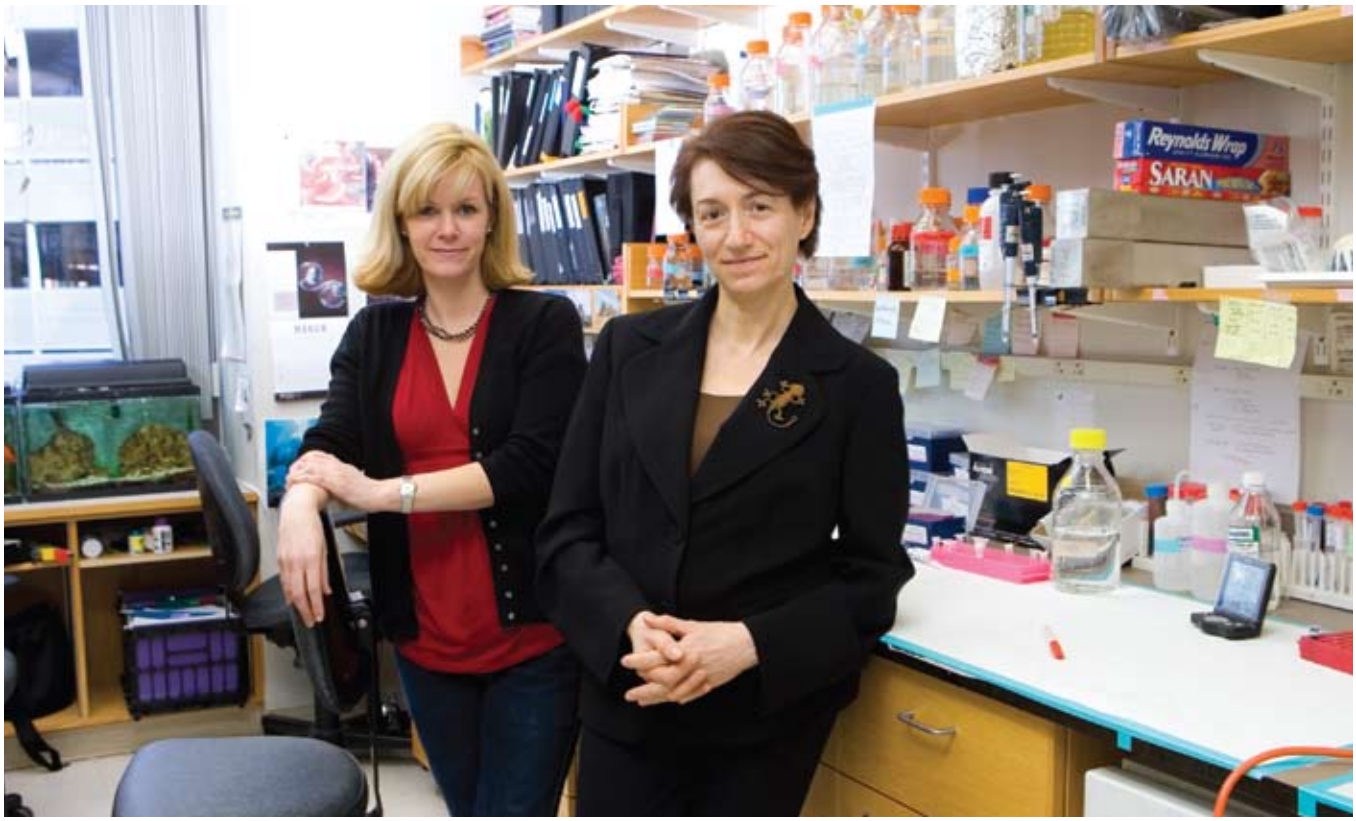
The most important achievements have been in investigating the growth pathway called the mammalian target of rapamycin (mTOR), which senses information about the environment to regulate cell growth—and turns out to be a master regulator of many fundamental cell processes. "One of the biggest contributions has been understanding the pieces of this pathway and showing that their function matters for diseases, in particular cancer," Sabatini says.

CURRENT TRENDS IN THIS FIELD

The pace of these studies is dramatically accelerating due to new technologies including high-throughput RNA interference screens and more sensitive mass spectrometry. Also, there has been an influx of researchers studying these growth systems because of their correlation to disease. "The field has become more competitive, but I'm happy because it's generated a lot more interest," he says.

"I'm proud of having good people in my lab and seeing them succeed after they've left Whitehead. Mentoring people is the most satisfying part of my career."

— **DAVID SABATINI**
(center)



WHITEHEAD MEMBER

Hazel Sive

FOCUS OF RESEARCH

Looking at development in zebrafish and frogs, the Sive lab is deciphering how the brain develops into its specific structure, how the very front of an animal develops organs associated with the face, and which genes may underlie certain birth defects and neurodevelopmental disorders.

RECENT SCIENTIFIC ACCOMPLISHMENTS

Researchers documented how early brain structure develops, using the zebrafish as a model, with an emphasis on the brain ventricular system, a kind of circulatory system deep within the brain. They showed that a mutation in one gene (*sfpq*) caused abnormal midbrain and hindbrain development in zebrafish embryos. The problems noted in these fish indicate that *sfpq* is necessary for normal brain development in zebrafish and possibly other vertebrates. Additionally, using the frog model, the Sive lab described development of the "primary mouth", the first opening between the outside and the gut of the embryo, that is found in all multicellular animals and is essential for eating.

CURRENT TRENDS IN THIS FIELD

In the last five years, Sive and her lab have changed the way researchers look at brain development. As she explains, the vertebrate brain starts as part of a hollow tube. Researchers have devoted much effort to ask how the tube forms, but no one has asked why the nervous system needs to be a tube. Sive lab members hypothesize that the fluid contained in the tube, the cerebrospinal fluid, is essential for normal brain development.

"We started a new field—brain morphogenesis—and we're literally rewriting the textbooks."

— HAZEL SIVE
(right)

WHITEHEAD MEMBER

Robert Weinberg

FOCUS OF RESEARCH

How does cancer spread? How do epithelial and stromal cells, the two primary types of cells found in mammalian tissue, interact in tumors? And what's the role of cancer stem cells, which may fuel the ability of many solid tumors to renew and spread? These are among the questions being tackled by the Weinberg lab.

RECENT SCIENTIFIC ACCOMPLISHMENTS

In 2007, researchers in the Weinberg lab created a line of cancer stem cells that could aid breast cancer research. After being injected with just 100 of these cells, mice develop tumors that metastasize. In another line of research, scientists found compelling evidence that some breast cancer cells recruit normal adult stem cells from the bone marrow and force them to secrete a protein that fosters cancer cell movement and invasion. Additionally, the lab demonstrated that a single microRNA can directly regulate a gene implicated in human cancers.

CURRENT TRENDS IN THIS FIELD

When Weinberg founded his lab 30 years ago, "the disease of cancer was quite a mystery," he says. "We didn't understand what it was, and why cancer cells misbehaved and why tumors behaved the way they do. And now the great majority of the details have come into view. It's much more founded on a coherent logical structure rather just than a hodgepodge collection of phenomena."

"The conceptual foundation of cancer biology is now laid. I think that almost everything we believe now will remain true 10, 20 or 30 years from now. We will build on it, but future discoveries will not obviate or nullify what we now believe."

— ROBERT WEINBERG
(left)

WHITEHEAD MEMBER

Richard Young

FOCUS OF RESEARCH

The Young lab is mapping the regulatory circuitry that controls cell state and differentiation. This is an extraordinarily complex undertaking—scanning the genomes of our cells with sophisticated new technologies and discovering how close to 20,000 genes are coordinately controlled. Many human diseases, ranging from autoimmune conditions to obesity and cancer, are caused by defects in this regulatory system. One of the lab's goals is to map the regulatory circuitry of both healthy and diseased cells, and to use this information to reprogram cells for regenerative medicine, which offers hope that one day we could use an individual's own healthy cells to replace damaged or diseased cells and tissues.

RECENT SCIENTIFIC ACCOMPLISHMENTS

"Just within the last several years we've succeeded in creating maps of the core regulatory circuitry of human embryonic stem cells," says Young. In 2005 and 2006, his lab and collaborators discovered how key transcription factors (proteins that act as master regulators for gene expression) give embryonic stem cells their unique attributes.

CURRENT TRENDS IN THIS FIELD

"This is an important new biological frontier that wasn't a part of the research landscape half a decade ago, because we didn't have the key technologies to map how regulators control our genomes," says Young. "Mapping circuitry in embryonic stem cells and induced pluripotent stem cells is at the frontier of regenerative medicine."

"In very innovative, challenging areas, like trying to map the human genome's regulatory circuitry, even incremental new understanding can have a major impact across many scientific fields."

— **RICHARD YOUNG**
(center)

Whitehead Fellows

Whitehead Fellows are young researchers who skip the postdoctoral stage of their training and are given the space and resources to run their own labs and pursue independent research, without teaching responsibilities.

WHITEHEAD FELLOW

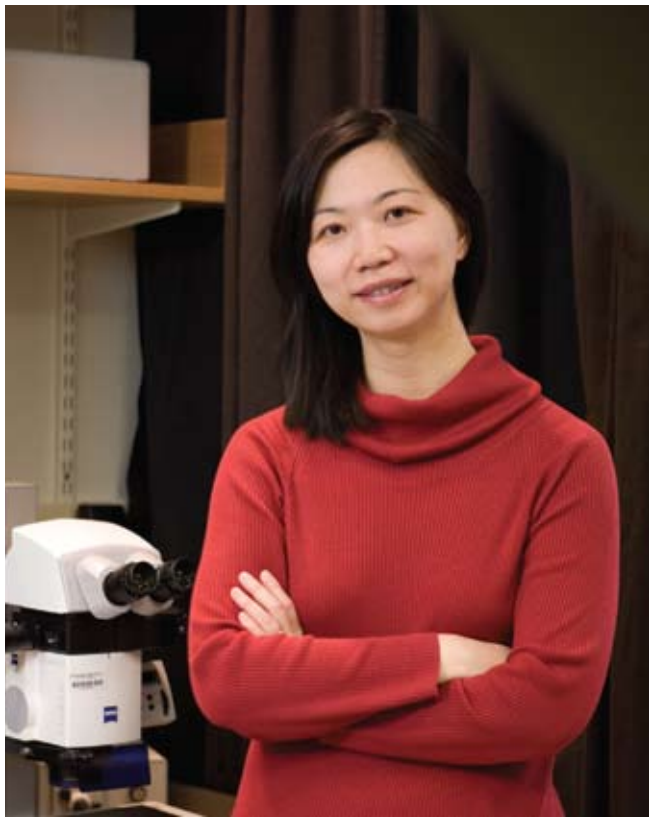
Thijn Brummelkamp

Thijn Brummelkamp focuses on cancer research. He uses functional genetic approaches, such as RNA interference screens, to identify genes that affect the growth and survival of cancer cells and how they respond to therapeutics. More recently he became interested in the links among organ size, stem cells and cancer. Together with Whitehead Fellow Fernando Camargo, he showed that all can be affected by the *YAP1* gene. When the gene was over-expressed for 30 days in mice, liver size quadrupled. Brummelkamp and his colleagues also have found that *YAP1* is normally expressed in the stem cell compartment of the intestine and that activation of *YAP1* leads to expansion of undifferentiated progenitor cells. Because *YAP1* expression has such important effects, the Brummelkamp lab now is figuring out how and where in the body it is turned on and off.

WHITEHEAD FELLOW

Fernando Camargo

In molecular terms, how do blood cells and immune cells develop? Fernando Camargo and his colleagues study hematopoietic stem cells—the cells found in bone marrow that give rise to mature blood cells. The lab is working to identify genes that are crucial in blood stem cell renewal and differentiation and that also are involved in the development of leukemia and lymphoma. Recently, his lab identified a microRNA critically involved in the regulation of immune responses, which may lead to the development of more targeted therapies for cancers. Additionally, in collaboration with the Brummelkamp lab, Camargo is studying the Hippo signaling pathway, which regulates the size and growth of organs and tissues, and influences cell regeneration and possibly cancer.



WHITEHEAD FELLOW

Hui Ge

Around the world, researchers are probing how thousands of genes and their proteins interact during embryonic development in the tiny worm *C. elegans*. Like early explorers of a distant continent, the scientists report back the information they uncover. Hui Ge acts like a cartographer, compiling millions of snippets of information from the *C. elegans* explorers and using computational methods to map how all of the gene information fits together with the protein information. To check the accuracy of her map, the Ge lab predicts how a protein or gene will act in a certain situation and then tests the prediction in live worms. This work illuminates many previously unknown relationships between numerous proteins and genes.

WHITEHEAD FELLOW

Andreas Hochwagen

Broken chromosomes are a hallmark of cancer progression and a variety of genetic diseases. Under some developmental circumstances, however, tightly controlled break formation in chromosomes is beneficial for the organism. For example, during meiosis, the cell division that creates eggs and sperm in humans, chromosome breaks serve to ensure proper chromosome transmission and increase genetic diversity in the offspring. In 2007, the Hochwagen lab developed a new method to precisely locate the sites of meiotic chromosome break formation using yeast as a model organism. The resulting break profiles provided fundamental new insights into the transmission of small chromosomes and showed that chromosome ends serve as key regulators of this process. These findings have important implications for our understanding of Down syndrome, which is caused by incorrect meiotic transmission of chromosome 21.

WHITEHEAD FELLOW

Kate Rubins

The Rubins lab targets poxviruses, a class that includes smallpox, monkeypox, cowpox and vaccinia (the virus from which the classic smallpox vaccine is developed). Probing the strategies that these viruses employ to sidestep and weaken host defenses, Rubins seeks insights about their mechanisms of pathogenesis as well as the mysterious processes of immunity they highlight. Her work investigating these pathogens balances basic lab science and clinically oriented biomedical research. In one project, she conducts field studies of monkeypox in the Democratic Republic of Congo. She also analyzes tissue culture models of vaccinia and works with U.S. Army researchers to develop therapies for victims of the Ebola virus.

RUBINS: SAM OGDEN

WHITEHEAD FELLOW

Paul Wiggins

Paul Wiggins is in search of elegance, more specifically an elegant and quantitative explanation for how gene expression is affected by the structure of chromatin (the complex of DNA and protein that makes up chromosomes) and the conformation of chromosomes. To encapsulate the human genome into the nucleus, the cell tightly condenses its two meters of DNA into a package tens of microns across. This dramatic condensation of the genome appears to be intimately connected to gene expression. Combining data describing the chromatin structure and the physical and genomic position of genes, Wiggins expects to find a few basic rules that can predict the role of chromatin structure in gene regulation and chromatin condensation.

WHITEHEAD FELLOW

Defne Yarar

Without actin, you would be a puddle on the floor. Dynamic networks of this protein provide structure for your cells and allow them to move and divide. They also play a key role in endocytosis—a process in which the cell membrane folds inward, engulfing materials from outside the cell. Endocytosis is an important mechanism for the basic business of cells, including the uptake of nutrients, immune system function and cell regulation. However, endocytosis also can be subverted by pathogens for entry into the cell. Problems with endocytosis can result in diseases such as familial hypercholesterolemia and certain cancers. Analyzing how actin networks perform in this process, Yarar hopes to better understand this fundamental pathway that allows the cell to take up many kinds of nutrients and to participate in certain forms of cell regulation.

WIGGINS: SAM OGDEN; YARAR: JUSTIN KNIGHT

Celebrating Whitehead's silver anniversary

When Edwin C. "Jack" Whitehead decided to found a biomedical research institution, he wanted this to be an act of "enlightened philanthropy" that would start with an entirely open mind about the institution's goals and structure.

Jack Whitehead's decade-long quest ended triumphantly in 1982. Partnered with Nobel laureate David Baltimore and many other allies, he launched Whitehead Institute as an independent institution focused on basic biomedical research and formed with a unique teaching affiliation with MIT.

In 2007, Whitehead Institute celebrated its 25th birthday with events for scientists, staff and friends.

Notably, 120 of the Institute's closest friends attended the 25th Anniversary Board of Associates Colloquium in November. Attendees enjoyed presentations by all Whitehead Directors past and present, a keynote address on cancer by Whitehead Member Robert Weinberg, and informal scientific salons with many Institute scientists and distinguished colleagues.

Additionally, special projects commemorated the Institute's history, including an anniversary website and an exhibit at the MIT Museum.

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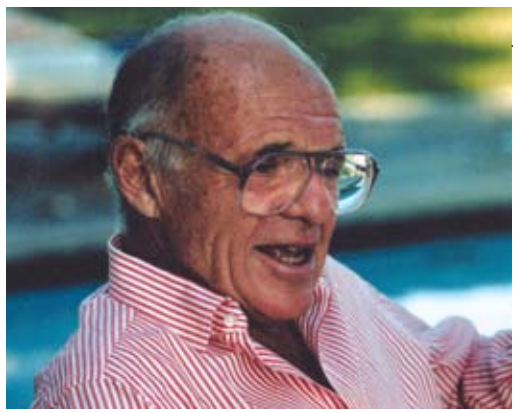

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1 On a rainy March afternoon in front of 9 Cambridge Center, confetti cannons help the Institute staff kick off the birthday celebrations.

2 Senator Edward Kennedy, Governor Deval Patrick, Victoria Kennedy and David Page chat at the Whitehead silver anniversary gala, which was held at the Boston Museum of Fine Arts in November.

3 At the 25th Anniversary Colloquium, Whitehead Member Harvey Lodish (second from left) discussed "Biopharmaceutical Companies of the Future" with BOA members Barry Berkowitz, Ansbert Gadicke and Don Hetzel.

4 You can find reminiscences about philanthropist extraordinaire Jack Whitehead at www.wi.mit.edu/about/25th, along with a video about his Institute's creation.

JUSTIN KNIGHT

New members join Board

Three longtime members of the Whitehead Board of Associates joined the Whitehead Board of Directors in 2007.

Arthur W. Brill, an attorney with Roberts and Holland, LLP, joined the Whitehead Board of Directors in March. Brill was heavily involved in the initial formation and organization of Whitehead Institute, and he represented the family and estate of Jack Whitehead for more than 25 years. He has served as Secretary of the Whitehead Corporation since 1981 and will continue in that role.

Peter M. Hecht, chief executive officer of Ironwood Pharmaceuticals, Inc. (formerly Microbia) was elected to the Board in June. Co-founding the company in 1998, Hecht has assembled and integrated the company's growing team of industry-leading "drug hunters," raised $231 million and driven the execution of the company's strategy. Prior to founding the firm, Hecht was a postdoctoral researcher in the lab of Whitehead Member Gerald Fink. He earned a BS in mathematics and an MS in biology from Stanford University, and he holds a PhD in molecular biology from the University of California at Berkeley. Hecht serves on the Leadership Council for the David H. Koch Institute for Integrated Cancer Research at MIT.

David H. Koch is an executive vice president and a board member of Koch Industries, Inc., which owns a diverse group of companies with more than $90 billion in revenues, 80,000 employees, and a presence in nearly 60 countries. Koch also is chairman of the board and chief executive officer of Koch Chemical Technology Group, LLC, a wholly owned subsidiary of Koch Industries. Koch is an extraordinary philanthropist who has made significant gifts to a wide variety of organizations and programs that further cancer research, enhance medical centers and support educational institutions, as well as to programs that sustain arts and cultural institutions. He is the prime contributor to the David H. Koch Institute for Integrative Cancer Research at MIT, where he earned BS and MS degrees in chemical engineering. Koch was named to the Board in December 2007 and began active service in 2008.

Senior administrators appointed

Martin A. Mullins started as vice president at Whitehead Institute in August. In that position, he is responsible for running the Institute's administration.

Previously, Mullins held the positions of vice president of technology licensing at Georgetown University; associate vice president for licensing at Case Western Reserve University; and senior licensing manager and interim director of the Office of Technology Licensing & Industry Sponsored Research at Harvard Medical School. Prior to moving to the U.S., Mullins, an Irish native, held positions at Eli Lilly & Co. and at the Irish government's Industrial Development Agency. He holds a BS and an MS in biochemistry from University College Cork.

Marianne Howard was promoted to the new position of associate vice president for administration. In her new role, Howard has assumed line management responsibility for information technology, environment health and safety, physical plant and the library. She also retains her position as director of human resources.

Patricia F. Denn has joined Whitehead as director of development. Denn has had 23 years of development experience, first as director of external relations at the Fletcher School of Law and Diplomacy at Tufts University and then as director of foundation relations/principal foundation gifts at Northeastern University. She also taught writing and literature at several colleges and universities. Denn received an AB in American literature from Brown University and an MA in English from the University of California at Irvine.

Landon and Lavinia Clay are sponsoring the work of Hidde Ploegh and other Whitehead researchers

Positive results for philanthropic gifts

Whitehead Institute benefited immensely from generous private donations from longtime Board of Associates members in 2007.

Landon T. Clay, founder and managing member of East Hill Management, and his wife, Lavinia, gave $10 million to establish the endowed Clay Laboratory Fund and the Clay Chair, which currently is supporting the lab and the professorship of Whitehead Member Hidde Ploegh. The gift is the largest to the Institute since its founding.

The Clays also gave $1 million this year to establish the Clay Fellows Program, which will fund three postdoctoral researchers per year over a three-year period, working in the Ploegh lab and potentially with collaborating labs. The Clay Fellows Program will enable postdocs to develop as independent researchers while also contributing to the advancement of the principal investigator's work.

Under a $4 million bequest from the estate of Margaret Sokol, Whitehead Institute established its first endowed chair, the Margaret and Herman Sokol Chair in Biomedical Research. The first holder of the chair is Gerald Fink, a Whitehead Founding Member. "Margaret and Herman Sokol were enormously supportive of Whitehead from the very first days," comments Whitehead Director David Page. "This extraordinarily generous gift will allow further progress in the basic research that was so important to them."

Liliana and Hillel Bachrach have pledged $1 million to fund stem cell research at Whitehead. In recognition of this gift, the Liliana and Hillel Bachrach Stem Cell Bank at Whitehead Institute has been permanently designated. The fund will support novel research in the Whitehead Human Embryonic Stem Cell Facility to isolate and propagate new embryonic stem cell lines from donated surplus *in vitro* fertilization embryos and from adult cells reprogrammed to be pluripotent stem cells. Liliana Bachrach is a member of the Whitehead Board of Associates Executive Committee, the Development Committee of the Board of Directors and Whitehead's Stem Cell Working Group. Hillel Bachrach is managing partner of 20/20 Health Care Partners, LLC.

9CC renovations

Whitehead's 9 Cambridge Center building is always being reconfigured to support research. But during the 25th anniversary year of 2007, the building's lobbies and the McGovern Auditorium were remodeled, and previously stored pieces of art from the Institute's collection were put on display for all to enjoy.

Explaining biology at the cutting edge

One of Whitehead Institute's core missions is to share the understanding of biomedical research with other scientists, students, teachers and the public.

In March, the Whitehead/Museum of Science public lecture series drew hundreds of attendees to hear three talks by Whitehead Members about evolution's cornerstone role in biomedical research.

The Whitehead drama fest, a public event featuring films and skits about biology plus artists talking about their creations that address scientific themes, debuted in April.

Also that month, 140 students attended the high school student lecture series, learning how researchers are unraveling the molecular mysteries of cancer. The event included laboratory tours and lunches with young Whitehead researchers.

In October, the annual scientific symposium, on "Regeneration in Biology and Medicine," drew about 1,000 registrants. Speakers from Whitehead and other research organizations presented overviews of cutting-edge work in stem cells and tissue regeneration.

Throughout the academic year, the high school teacher lecture program brought in biology high school and community college educators to hear world-class investigators talk on "The Awesome Power of Genetics."

The BiologyWeek newsletter (biologyweek.wi.mit.edu) alerted the local biomedical research community to scientific presentations throughout Greater Boston. And Whitehead spread news worldwide about research advances via its external website (www.whitehead.mit.edu) and *Paradigm* magazine.

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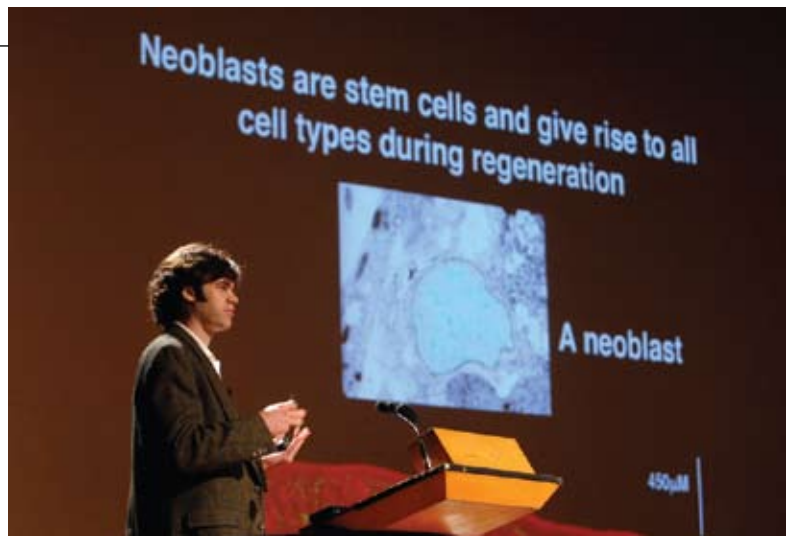

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1 At the Whitehead scientific symposium, MIT Institute Professor and Whitehead Board Member Robert Langer discusses innovations in tissue engineering.

2 Duke University's Kenneth Poss, right, another symposium speaker, chats about zebrafish regeneration over lunch with postdocs.

3 Whitehead Member Peter Reddien describes progress in understanding how planarian worms regenerate after they have been chopped up.

JUSTIN KNIGHT

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4 Postdoc Jennifer Gutzman displays some of the zebrafish whose brain development is studied in Whitehead Member Hazel Sive's lab.

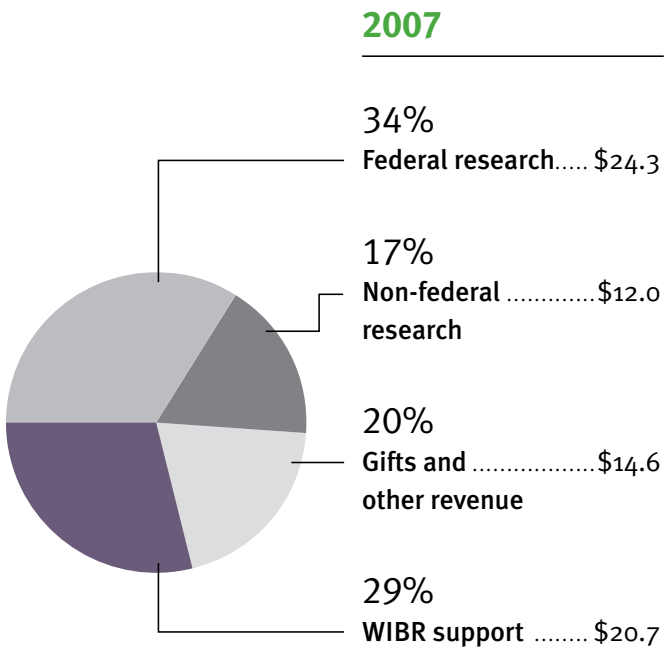
5 Young Whitehead researchers (on the left) partner with high school biology teachers throughout the academic year.

Financial summary

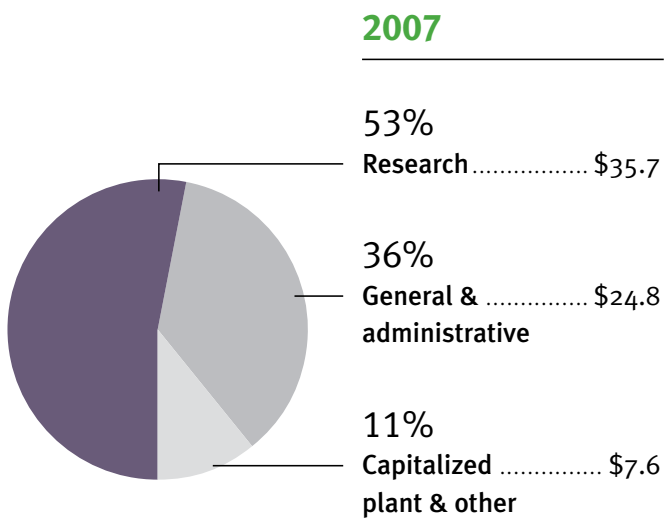
Whitehead Institute's commitment to best-in-class research remains unwavering, even in the face of a challenging federal funding environment. Drawing upon its own endowment and the generous support of individuals, corporations and foundations, the Institute has been able to keep pace with the rapidly escalating costs associated with maintaining—and defining—the state of the art. Institute administration is now focusing on streamlining operations, helping to ensure that a larger proportion of every dollar will directly support Whitehead science.

The future for Whitehead research is extraordinarily bright, firmly supported by the Institute's solid financial foundation. Going forward, major efforts, such as the recently launched Stem Cell and Regenerative Biology Initiative, will be underwritten by a mix of new partnerships, additional funding sources and the kind of resourcefulness that has long been a Whitehead hallmark.

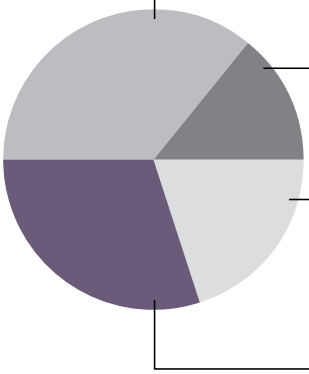
Revenues and support (in millions)



Expenditures and disbursement (in millions)



2006



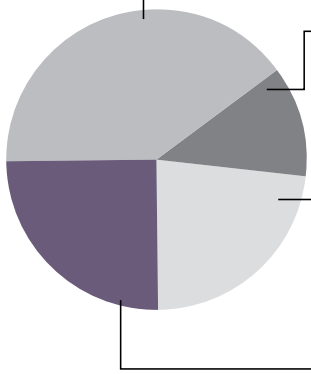
36%
Federal research..... $26.6

14%
Non-federal research $10.4

20%
Gifts and other revenue $14.5

30%
WIBR support $21.8

2005



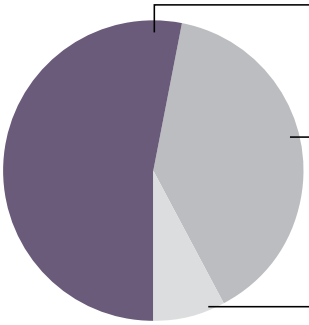
40%
Federal research..... $26.5

12%
Non-federal research $8.1

23%
Gifts and other revenue $15.2

25%
WIBR support $16.6

2006

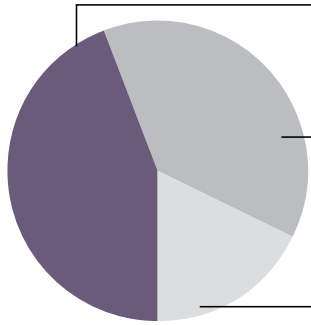


53%
Research..... $34.4

39%
General & administrative $25.4

8%
Capitalized plant & other $5.3

2005



44%
Research..... $29.2

38%
General & administrative $24.8

18%
Capitalized plant & other $11.5

Leadership

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Faculty and Fellows
Whitehead principal investigators are world-class scientists working at the frontiers of biological research. Under the Institute's close affiliation with Massachusetts Institute of Technology, Whitehead Members also are members of MIT's biology department or other MIT departments.

The Whitehead Fellows program allows exceptionally talented young scientists to set up independent research programs without undertaking normal faculty duties.

Faculty honors
Whitehead faculty includes the recipient of the 1997 National Medal of Science (Weinberg), eight members of the National Academy of Sciences (Fink, Jaenisch, Lander, Lindquist, Lodish, Orr- Weaver, Page and Weinberg), seven fellows of the American Academy of Arts and Sciences (Fink, Jaenisch, Lander, Lindquist, Lodish, Ploegh and Weinberg) and three Howard Hughes Medical Institute investigators (Bartel, Lindquist and Page).

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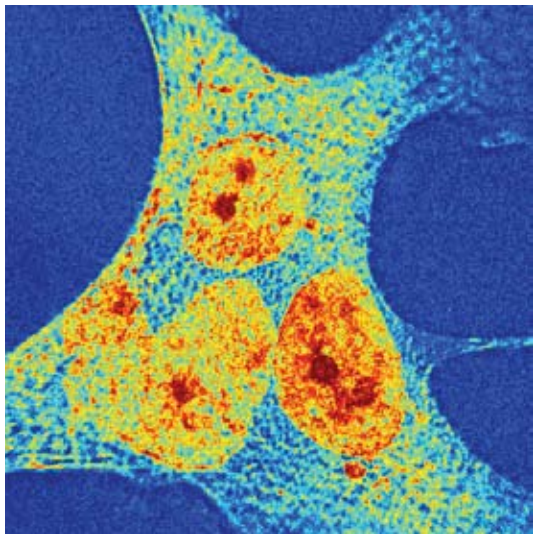
BELOW: Taken by a deep-ultraviolet microscope, this image shows how the mass of nucleic acids is distributed in a mouse macrophage (a kind of immune cell). Image by Benjamin Zeskind, Paul Matsudaira's laboratory.



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At the 25th anniversary kickoff event, Founding Member Robert Weinberg debuts a time capsule that will store Whitehead artifacts.

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