WHITEHEAD INSTITUTE

2008 ANNUAL REPORT. A YEAR IN THE LIFE OF A SCIENTIFIC COMMUNITY EMPOWERED TO EXPLORE BIOLOGY'S MOST FUNDAMENTAL QUESTIONS FOR THE BETTERMENT OF HUMAN HEALTH.

CONTENTS

EDITOR & DIRECTOR
MATT FEARER

ASSOCIATE EDITOR
NICOLE GIESE

OFFICE OF COMMUNICATION AND PUBLIC AFFAIRS
617.258.5183
WWW.WHITEHEAD.MIT.EDU

DESIGN
HECHT DESIGN

INSIDE COVER MATTHEW SAELZLER **PAGE 1, 30** JOHN SOARES **PAGE 4, 10 (LEFT)** © FELICE FRANKEL, FROM "ENVISIONING SCIENCE, THE DESIGN AND CRAFT OF THE SCIENCE IMAGE (MIT PRESS) **PAGE 6** REPRINTED FROM CELL, 133/4, SA MANI , ET AL., THE EPITHELIAL-MESENCHYMAL TRANSITION GENERATES CELLS WITH PROPERTIES OF STEM CELLS, 704-15, COPYRIGHT 2008, WITH PERMISSION FROM ELSEVIER. **PAGE 7** J INFECT DIS. EM FRICKEL, ET AL. UNIVERSITY OF CHICAGO, PUBLISHER. © 2008 BY THE INFECTIOUS DISEASES SOCIETY OF AMERICA. ALL RIGHTS RESERVED. **PAGE 8** DUENNWALD ML, ET AL. IMPAIRED ERAD AND ER STRESS ARE EARLY AND SPECIFIC EVENTS IN POLYGLUTAMINE TOXICITY. GENES DEV. 2008 DEC 1. COPYRIGHT C 2008 BY COLD SPRING HARBOR LABORATORY PRESS. **PAGE 9** M WERNIG, ET AL. NEURONS DERIVED FROM REPROGRAMMED FIBROBLASTS FUNCTIONALLY INTEGRATE INTO THE FETAL BRAIN AND IMPROVE SYMPTOMS OF RATS WITH PARKINSON'S DISEASE. PNAS. 2008 APR 15. COPYRIGHT © 2008 BY THE NATIONAL ACADEMY OF SCIENCES. **PAGE 10 (RIGHT)** RT WHEELER, ET AL. DYNAMIC, MORPHOTYPE-SPECIFIC CANDIDA ALBICANS BETA-GLUCAN EXPOSURE DURING INFECTION AND DRUG TREATMENT. PLOS PATHOG. 2008 DEC;4(12). REPRINTED IN ACCORDANCE WITH THE CREATIVE COMMONS ATTRIBUTION LICENSE. PAGE 11 FROM Y LIN ET AL. GERM CELL-INTRINSIC AND -EXTRINSIC FACTORS GOVERN MEIOTIC INITIATION IN MOUSE EMBRYOS. SCIENCE. 2008 DEC 12;322(5908):1685-7. REPRINTED WITH PERMISSION FROM AAAS. **PAGE 14-29, 31-33** KELLY LORENZ **PAGE 34-45** JUSTIN KNIGHT

Background Image Tumor cells in a mouse model of human breast cancer developed in the lab of Whitehead Member Robert Weinberg.

PRESERVING THE MISSION, FACING THE FUTURE

David Page, Director

It's customary in this space to recount and reflect on the accomplishments of the year gone by. I'll certainly do so here—proudly—but in many important ways, 2008 was about positioning the Institute for years to come.

Many colleges, universities, and independent research institutions found themselves in dire fiscal positions at the close of 2008 and entered 2009 in operational crisis reflective of the global economic environment. Hiring freezes and large-scale workforce reductions have become the norm. Although Whitehead Institute is certainly not insulated from the impact of the downturn, I am pleased and somewhat humbled to report that the Institute remains financially strong and no less committed to scientific excellence.

Over the past two years, we have been engaged in a focused effort to increase efficiency and reduce our administrative costs, with the explicit goal of ensuring that as much of the Institute's revenue as possible directly supports Whitehead research. Our approach, which has resulted in a 10-percent reduction in operational expense, has been carefully considered. Every decision has been evaluated not just for its potential effects on our scientific mission, but also for possible consequences to the Whitehead community and its unique culture.

In some cases, our reductions in overhead have also yielded cultural benefits. This past year, we moved administrative departments that had for the past several years been housed in offsite office space back into our main building at Nine Cambridge Center. In so doing, we have eliminated significant rental expense while experiencing the kinds of gains in productivity, communication, and ideation that result from what I refer to as "random collisions" between scientific and administrative staff. This reunion of functions is contributing to a more cohesive and vibrant environment that will serve us well.

Our attention to fiscal discipline has also enabled us to take bold, definitive steps toward ensuring the Institute's scientific prowess for successive generations. In 2008, our Board of Directors approved the first phase of a multi-year plan to recruit new faculty to Whitehead. Phase one anticipates the hiring of two junior faculty members and one mid-career hire. Friends of the Institute know well that as Director, I have made faculty recruitment a priority. Our ability to recruit actively during a period of great economic uncertainty and staffing contraction elsewhere is an enormous competitive advantage for Whitehead.

"Our attention to fiscal discipline has enabled us to take bold, definitive steps toward ensuring the Institute's scientific prowess for successive generations."

Attracting the brightest young scientists requires more than simply posting job openings. We must constantly seek opportunities for improvement if we intend to contend for the best. Last year, we substantially increased compensation for our postdoctoral scientists through innovative enhancements to our salary and benefits plans. Postdocs play a critical role at Whitehead, fueling some of our most creative and productive research. At the same time, these young researchers often face the dual challenge of trying to launch their careers and establish families. Our ability to reward them financially, recognize their value to our community, and increase the Institute's appeal as a scientific workplace make this change in compensation one of our most important accomplishments of 2008.

Just before this report went to press, we received word that our efforts to improve the postdoc experience have not gone unnoticed. *The Scientist* magazine, which conducts an annual ranking of educational and research institutions, named Whitehead Institute the best place in the country for postdocs to work. The Institute, unranked until 2008 when we placed 14th, surged to the top of the list of 85 surveyed institutions. We view this news as solid affirmation of our commitment to the future of biomedical research.

In an environment as dynamic as Whitehead, change and transition are inevitable. 2008 delivered its share of both. In July, we suffered the loss of former Board Chair Alex d'Arbeloff. We all treasured Alex for his bold leadership, profound honesty, and intellectual rigor. Alex served as a mentor for me when I first assumed the directorship here, and I came to rely on him heavily during those first few years. His passing is a blow softened only by the news that Alex's wife, Brit, has joined our Board of Directors. Brit's support of and affection for the Institute are so strong that at times it seemed to me that she actually shared the position of Board Chair with Alex. Her wisdom, knowledge, experience, and good humor make her an outstanding addition.

At the close of 2008, we also welcomed Mark Lapman to the Board. Mark is a successful investment professional with advanced degrees in the humanities—perhaps the perfect combination for our times. Mark's energy and fresh perspective should inspire us.

Jonathan Goldstein, an MIT alumnus who as an undergraduate student worked in the lab of Whitehead Founding Director David Baltimore, became Chair of the Board of Associates (BOA). Jono, who will serve a concurrent term on the Institute's Board of Directors, takes over for outgoing BOA Chair Ellen Polaner. We're delighted to have Jono aboard. We will certainly miss Ellen's enthusiasm for our mission. I personally wish to thank her for her leadership of the BOA during a transitional time for that important group.

This past year, we said farewell to two long-serving Members of the Whitehead faculty. After 23 years here, Paul Matsudaira has taken over as Head of the Department of Biological Sciences at the National University of Singapore. We thank Paul for his contributions to Whitehead and wish him, his wife Maureen, and their two children well in this exciting new opportunity. In September, the Broad Institute, born out of the Whitehead/MIT Center for Genome Research, became an independent organization, and Whitehead relinquished the governance role it had held since the Broad's inception in 2004. At the same time, Broad Director Eric Lander formally left the Whitehead faculty. We view the establishment of this "new", independent Broad as the culmination of a natural evolution for this neighboring institution and are proud of the role Whitehead played in its creation. Whitehead faculty continue to collaborate with their peers at Broad in the pursuit of scientific discovery, and both institutions are the better for it.

In the pages that follow, you'll learn in greater detail why, despite a global economic malaise, we have every reason for optimism as we move through 2009. Our science has never been stronger or more impactful. Our faculty are continually recognized for their extraordinary achievements. We are the beneficiaries of remarkable philanthropy, most notably from Board Member Landon Clay and Board Vice Chair Susan Whitehead. And, regardless of one's political leanings, it was heartening to hear our new President declare during his inaugural address: "We will restore science to its rightful place and wield technology's wonders to raise health care's quality."

I'm extraordinarily grateful to our faculty, staff, friends, and supporters for continually validating this optimism and for helping us realize our potential on a daily basis.

Sincerely,

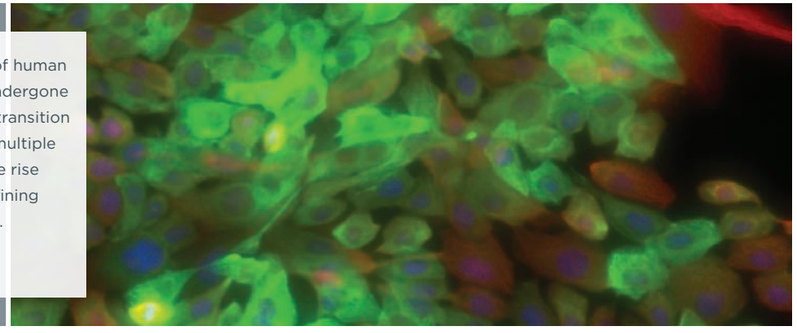
David C. Page
Director

IMAGE OF YEAST COLONY GROWN IN THE LAB OF MEMBER GERALD FINK © FELICE FRANKEL, FROM "ENVISIONING SCIENCE, THE DESIGN AND CRAFT OF THE SCIENCE IMAGE (MIT PRESS)

SCIENTIFIC ACHIEVEMENT

WHITEHEAD SCIENCE IS INSTITUTIONAL BEDROCK. IT IS OUR VERY CORE, A CORE FURTHER STRENGTHENED BY A HOST OF SIGNIFICANT RESEARCH FINDINGS EMERGING FROM INSTITUTE LABORATORIES IN 2008. MANY OF THE SCIENTISTS BEHIND THESE ADVANCES—AND LARGER BODIES OF WORK—WERE RECOGNIZED ACCORDINGLY DURING WHITEHEAD'S 26TH YEAR.

STEMMING A CANCEROUS TIDE



The multi-colored staining of human mammary cells that have undergone an epithelial-mesenchymal transition denotes the beginnings of multiple cell types. The ability to give rise to diverse cell types is a defining feature of certain stem cells.

CANCER

Recent research in the lab of Member Robert Weinberg has shown that cancer stem cells bestow on certain tumors the abilities to grow and spread to distant sites around the body. Such cells, though few in number within a tumor, have the unique yet devastating capability to self-renew and form new tumors elsewhere.

In 2008, scientists in Weinberg's lab discovered that some tumor cells undergo a shape change that enables them to break from the primary tumor, plant remotely, and seed new tumors. Known as an epithelial-mesenchymal transition (EMT), the process essentially produces cancer stem cells. Researchers realized they could induce EMT in cancer cells in the laboratory setting, allowing for creation of cancer stem cells to be screened for susceptibility to potential anti-cancer drugs.

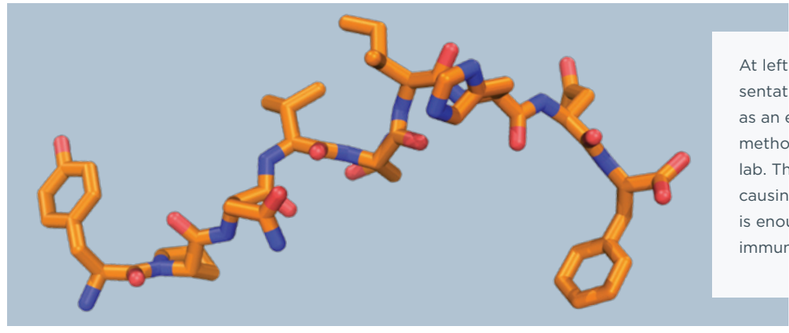
Then came the unexpected: inducing EMT in non-cancerous cells confers the desirable properties of adult stem cells. This remarkable finding may have significant implications for regenerative medicine, as it suggests a relatively simple route to producing adult stem cells for therapeutic purposes.

Says Weinberg: "This for us is a very exciting discovery, not only because of its unexpectedness but because it offers a route by which one could in principle generate unlimited numbers of stem cells committed to create a specific cell type. One could imagine, for example, that if one takes skin cells and induces them to undergo an EMT, they could become skin stem cells."

Those afflicted with mixed-lineage leukemia (MLL) typically face poor prognoses. Infants diagnosed with MLL seldom reach their first birthdays. The majority of MLL cases are caused by the fusion of two specific genes—*MLL* and *AF4*. This fusion results in production of a so-called fusion protein known to be intricately involved in the disease process. What was unknown, until now, is exactly how this protein disrupts normal cellular function. Researchers in the lab of Whitehead Member **Richard Young** recently discovered that this fusion protein, known as MLL-AF4, binds to more than 200 genes. In so doing, the targeted set of genes corrupts blood stem cell machinery, essentially turning blood cells cancerous. Genes within this identified set might one day become therapeutic targets.

Notes Young: "We think we've figured out a key piece of how this leukemia works."

ON THE DEFENSIVE



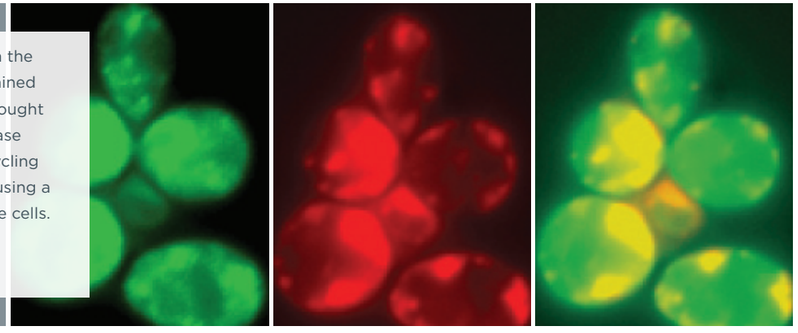
At left is a three-dimensional representation of a small molecule, known as an epitope, identified by a new method developed in the Ploegh lab. This epitope from the disease-causing parasite *Toxoplasma gondii* is enough to trigger a targeted immune response.

IMMUNE SYSTEM

Novel technologies refined in the lab of Whitehead Member Hidde Ploegh brought new clarity to the understanding of how the immune system responds to hostile invaders. Employing a sophisticated targeting method, researchers studying the parasite *Toxoplasma gondii* (which can cause the serious disease toxoplasmosis) were able to identify two specific epitopes—small portions of invading pathogens that trigger host defenses. A separate team of scientists in the lab pinpointed 19 such epitopes involved in the immune response to a form of mouse herpes virus, which bears similarities to the herpes virus that causes mononucleosis in humans. Identification of specific epitopes capable of triggering immune responses could bring new efficiencies to vaccine development strategies.

MicroRNAs—exceedingly small RNAs that modulate genetic expression and protein-coding —are coming under ever-increasing scrutiny as scientists continue to learn how diffuse, diverse, and relevant they are to myriad biological processes. In 2008, researchers in the lab of Whitehead Fellow **Fernando Camargo** discovered that a single microRNA, known as microRNA-223, plays a key role in regulating the mammalian immune system's first line of defense against infection. It turns out that microRNA-223, which is expressed only in a specific branch of the immune system, controls both the production and function of a class of defending cells called granulocytes. In mice modified to lack microRNA-223, researchers found excessive levels of granulocytes that proved to be over-aggressive in reacting to foreign stimuli. Moreover, these granulocytes continued their attack in the absence of infection, causing destructive inflammation in vital organs. The discovery of microRNA-223 could further the understanding of a variety of harmful inflammatory conditions.

OF FOLDING AND FINE TUNING



According to research from the Lindquist lab, a protein (stained red in the center image) thought to cause Huntington's disease clogs the cell's protein recycling system (stained green), causing a toxic buildup lethal to nerve cells.

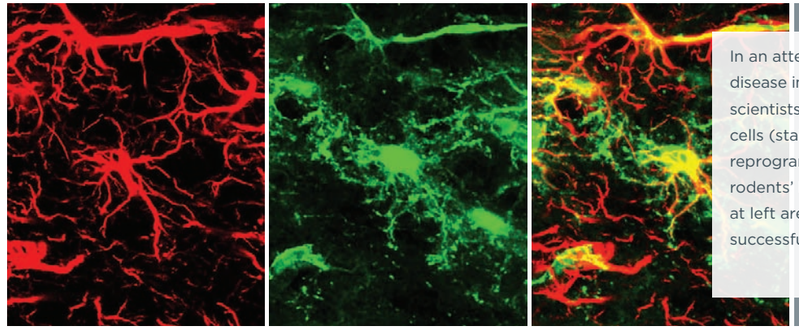
PROTEIN FUNCTION

The work in the Camargo lab described earlier helped inform aspects of a comprehensive microRNA study undertaken in the lab of Whitehead Member **David Bartel**. Scientists in Bartel's lab teamed up with researchers at Harvard Medical School to look at the protein output of genes targeted by specific microRNAs.

"This is the first time a large-scale data set has been used to observe the effect of microRNAs on the production of thousands of proteins," Bartel says. "Previous technology enabled us to only look at how microRNAs affect messenger RNAs." The study confirmed that, rather than behaving as blunt on–off switches, microRNAs actually fine tune protein expression, often in exquisitely delicate fashion. An individual microRNA may affect the levels of hundreds of proteins, but only in tiny amounts.

Huntington's disease, a devastating neurodegenerative disorder, is known to be linked to a mis-folded cellular protein. What remains a mystery, however, is how this protein inflicts the damage that leads to the death of neurons in the brain. In November, scientists in the lab of Whitehead Member **Susan Lindquist** discovered a mechanism that begins to explain how the misfolded protein can wreak neuronal havoc. Using yeast, rat, and mouse models of nerve toxicity and Huntington's disease, researchers found that the protein in question disrupts cells' normal protein degradation and disposal systems, leading to a destructive accumulation of other proteins that simply aren't meant to be retained inside the nerve cells. This finding implicates previously unsuspected cellular pathways, opening new areas for investigation.

UNSCHEDULED PROGRAMMING



In an attempt to treat Parkinson's disease in a rodent model, Whitehead scientists transplanted neural precursor cells (stained green)—derived from reprogrammed skin cells—into the rodents' brains. Cells stained yellow at left are those that matured successfully post-transplant.

STEM CELLS

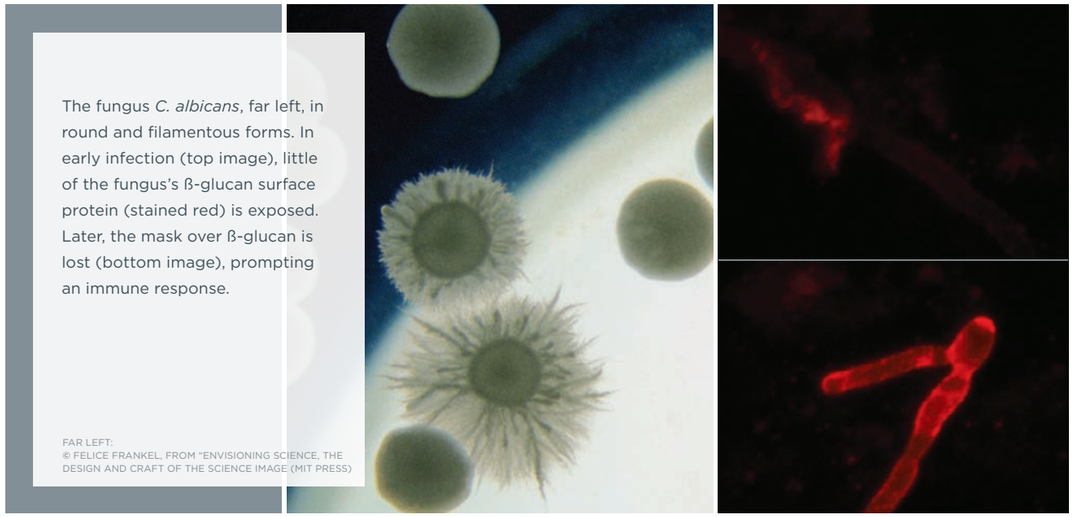
The lab of Member Rudolf Jaenisch maintained its leadership in cellular reprogramming—the process of reverting mature, fully differentiated cells to an embryonic stem cell-like state. Embryonic stem cells are pluripotent, having the ability to become any of the roughly 200 cell types in the body. Reprogrammed cells, known as induced pluripotent stem cells or iPS cells, have captured considerable attention, as they appear to harbor the therapeutic potential of embryonic stem cells without the need for embryos. In 2008, Jaenisch's lab fueled the excitement by using iPS cells to treat a rodent model of Parkinson's disease. Said Jaenisch: "It's a proof of principle experiment that argues, yes, these cells may have the therapeutic promise that people ascribe to them."

Since then, members of his lab have refined the reprogramming process, which, as first described, was problematic. Initial creation of iPS cells relied on viruses to insert four reprogramming genes into cellular DNA. One of these four genes is known to cause cancer, and viral insertions may also trigger virally-induced cancers. The original method is also remarkably inefficient, with roughly 1 in 1,000 cells reprogrammed. In a productive series of experiments in the latter half of 2008, Jaenisch lab members eliminated use of the *c-Myc* oncogene (one of the original reprogramming genes) in creating iPS cells; cut the number of viruses used in reprogramming from four to one; and devised a method that reliably reprograms not 1 in 1,000 cells but 1 in 20.

With all the focus on novel stem cell research, it's easy to forget that stem cell transplantation has been in clinical use for many years. Bone marrow transplants are in fact stem cell transplants. However, such procedures are complicated and may require lifelong immunosuppressive therapy for recipients. One of the impediments to successful transplantation is that blood-forming stem cells in the bone marrow—hematopoietic stem cells (HSCs)—are extremely rare. An estimated 1 in 10,000 blood cells is an HSC, and it is HSCs that transplant recipients require.

In 2008, scientists in the lab of Member **Harvey Lodish** identified a cocktail of growth factors that increases the number of HSCs in culture by a factor of 20. Such a result should in theory improve the odds for successful transplant. Lodish's work is slated for clinical testing in Singapore in 2009.

YEAST, UNMASKED



The fungus *C. albicans*, far left, in round and filamentous forms. In early infection (top image), little of the fungus's ß-glucan surface protein (stained red) is exposed. Later, the mask over ß-glucan is lost (bottom image), prompting an immune response.

FAR LEFT:

A tenuous détente exists in the cold war between the yeast *Candida albicans* and its human hosts. A healthy immune system largely keeps *C. albicans* at bay, allowing occasional breakthrough thrush or vaginal yeast infections. Most of the time, the yeast resides contentedly on our skin and in our intestines.

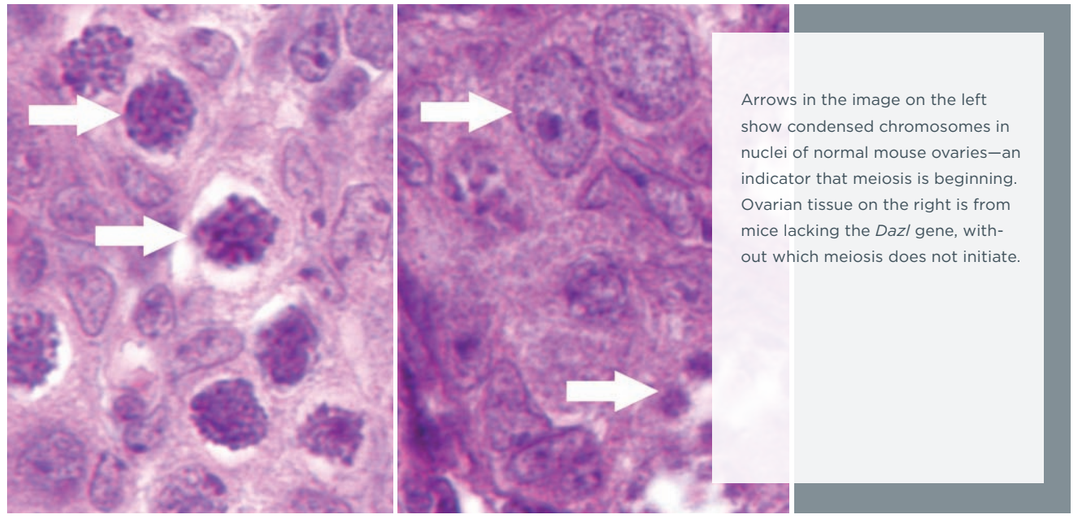
But if the immune system is weakened by drug therapy for cancer or organ transplantation, *C. albicans* seizes the opportunity, invades the bloodstream, and attacks vital organs.

C. albicans has two forms: a round, yeast form and an invasive, multi-celled filamentous form. Interestingly, a healthy immune system launches an attack when it detects a specific molecule on the cell's surface. This molecule is ß-glucan, a structural molecule that holds together the cell wall around the pathogen but also tags it for destruction by immune cells.

Robert Wheeler, then a postdoctoral researcher in the lab of Member **Gerald Fink**, was perplexed that fungi grown in the lab can mute immune responses by maintaining a dense sugar coating over ß-glucan. He asked whether this evasion mechanism functions during infection—in the face of immune response. Looking at fungal infections in mice, Wheeler found that ß-glucan is initially covered by a thin mask that prevents the immune system from launching a full-blown attack. Later during infection, it loses that mask and the immune system recognizes the assailant as foreign.

"We don't know why yeast takes off that mask," says Wheeler, who is now an Assistant Professor at the University of Maine. "Maybe it does it on purpose or maybe the immune system damages the mask to expose ß-glucan. That question is something we're following up on."

TWICE THE SIGNALING, HALF THE CHROMOSOMES



Arrows in the image on the left show condensed chromosomes in nuclei of normal mouse ovaries—an indicator that meiosis is beginning. Ovarian tissue on the right is from mice lacking the *Dazl* gene, without which meiosis does not initiate.

For reproductive and developmental biologists, few processes are more intriguing than those that regulate germ cells and their complex path to sexual differentiation. Possessed uniquely among all cells with the ability to halve their genetic material in preparation for the next generation, germ cells reside at the core of survival of sexually reproducing organisms.

"From the point of view of reproductive biology, this is as fundamental a juncture in an animal's life cycle as I can imagine," says Institute Director **David Page**, whose laboratory has been focused intently on meiosis; more specifically, on the *initiation* of meiosis, when the chromosomal halving commences. Researchers in the Page lab have been looking to settle a longstanding debate over whether meiosis is triggered by intrinsic factors within the germ cells themselves or by extrinsic signals coming from the cellular environment. They cracked the case this past year, proving through a series of experiments that *both* sets of signals are required to start the meiotic process.

Previous work in the Page lab had shown that in female mice, extrinsic signaling from the Vitamin A derivative retinoic acid (RA) induces expression of the gene *Stra8* (stimulated by retinoic acid), which in turn induces meiosis. It was an important finding, to be sure, but the scientists realized that because RA signaling is fairly ubiquitous in mammals at multiple phases of development, it alone could not explain something as specific as meiotic initiation.

They turned their attention to a gene known as *Dazl*, which had been shown to code for the germ-cell-specific protein DAZL, and discovered that intrinsic signaling from DAZL readies germ cells to respond to extrinsic RA signaling, which then triggers them to go meiotic. Two sets of signals, one fewer debate.

HONORS AND AWARDS

IAIN CHEESEMAN

Whitehead Member Iain Cheeseman was one of 11 scientists statewide to receive a competitive New Investigator Grant from the Massachusetts Life Sciences Center. The three-year grant supports his study of core proteins involved in cell division.

RUDOLF JAENISCH

Whitehead Member Rudolf Jaenisch received the 2008 Meira and Shaul G. Massry Prize recognizing his work in creating so-called induced pluripotent stem cells, or iPS cells. The Massry Prize is given annually to those making outstanding contributions to the biomedical sciences and the advancement of health. Jaenisch shared the prize with two other renowned stem cell scientists: Shinya Yamanaka of Kyoto University, and James Thomson of the University of Wisconsin-Madison School of Medicine and Public Health.

SUSAN LINDQUIST

Research in the area of protein folding earned Whitehead Member Susan Lindquist the Otto Warburg Medal from the German Association of Biochemistry and Molecular Biology. In awarding Lindquist the medal, the association president said, "Susan Lindquist's findings in the field of protein folding are groundbreaking." Lindquist also received the Genetics Society of America Medal in recognition of outstanding contributions to the field of genetics.

Harvard University presented Lindquist with a Centennial Medal, awarded to alumni of its Graduate School of Arts and Sciences deemed to have made outstanding contributions to society.

At the close of 2008, Lindquist, who is also a Howard Hughes Medical Institute (HHMI) investigator, won an HHMI Collaborative Innovation Award. HHMI established the award program to broaden its community of supported scientists. Lindquist leads a team of researchers, including Whitehead's Rudolf Jaenisch, investigating the mechanisms of neurodegenerative disorders.

HARVEY LODISH

The Massachusetts Life Sciences Center (MLSC) appointed Whitehead Member Harvey Lodish Chair of its Scientific Advisory Board. In this capacity, Lodish leads a group of scientists charged with developing a transparent, competitive, peer review process for grant applications and funding proposals to the MLSC. The Scientific Advisory Board will also make funding recommendations to the MLSC Board of Directors.

DAVID PAGE

Whitehead Director David Page was elected to the Institute of Medicine (IOM) of the National Academies. Election to the IOM recognizes individuals who have made major contributions to the advancement of the medical sciences, health care, and public health. Page is the fifth Whitehead Member in the IOM, joining Gerald Fink, Rudolf Jaensich, Susan Lindquist, and Robert Weinberg.

PETER REDDIEN

The W.M. Keck Foundation named Whitehead Member Peter Reddien a Distinguished Young Scholar in Medical Research. Reddien is one of five scientists across the country so honored by the foundation. The designation includes a five-year grant supporting Reddien's research on the mechanisms of regeneration in planaria flatworms.

DAVID SABATINI

Whitehead Member David Sabatini was appointed a Howard Hughes Medical Institute (HHMI) investigator. The appointment is a highly sought-after post that recognizes the nation's top biomedical scientists by providing long-term, flexible funding in support of creativity and intellectual daring. Sabatini, who was one of 56 scientists selected nationwide from a field of nearly 1,100 applicants, remains at Whitehead Institute while HHMI supports a large percentage of his research. Other HHMI investigators at Whitehead include Members David Bartel, Susan Lindquist, and David Page.

Whitehead Institute research on reprogramming cells was heavily cited in *Science* magazine's "Breakthrough of the Year" coverage. *The Scientist* magazine named Whitehead the best place in the country for postdocs to work—a validation of the Institute's commitment to improving the postdoc experience.

INSTITUTIONAL HONORS

In December, *Science* magazine named cellular reprogramming—the process of turning adult cells back into an embryonic stem cell-like state—as its Breakthrough of the Year for 2008. As part of its coverage, the magazine's editors compiled a list of 25 of the most important reprogramming papers from laboratories around the globe that were published during the year. Four of these seminal publications came from Whitehead Institute, which is clearly maintaining its leadership position in a field that, according to *Science*, is "moving faster down the highway of discovery than many had expected or dared to hope."

Just prior to publication, the magazine *The Scientist* named Whitehead Institute the best place in the country for postdoctoral researchers to work. Whitehead claimed the number one position in a survey of postdocs at 85 research institutions across the United States. In 2008, the first year in which Whitehead appeared in *The Scientist's* rankings, it placed 14th. Whitehead Director David Page, upon hearing of the Institute's surge to the top commented, "Our postdocs are and always have been the backbone of the Whitehead Institute...they deserve a first-class environment in which to work, train, and learn, and we will do our best to continue to enhance their experience here."

Although technically a 2009 honor for Whitehead, this top ranking is largely the result of a 2008 initiative, when the Institute bolstered compensation for postdocs through innovative improvements in salary and benefits packages. In announcing its rankings, editors at *The Scientist* cited Whitehead's renewed focus on postdocs, including generous benefits, interactions with high-caliber senior scientists, and a family-friendly environment that supports good work–life balance.

PRINCIPAL INVESTIGATORS

IT IS AN AUGUST COLLECTIVE, WHITEHEAD FACULTY: 14 MEMBERS, HAND-PICKED, ACCOMPLISHED, DECORATED. THEY ARE WORLD-CLASS SCIENTISTS WHO ALSO ARE GIFTED TEACHERS, MENTORS, AND LEADERS. THEIR INFECTIOUS PASSION AND COMMITMENT TO THEIR CRAFT CONTINUALLY DISTINGUISH THE INSTITUTE.

DAVID BARTEL

RESEARCH FOCUS

David Bartel's lab is determined to describe fully the roles microRNAs play in biological processes and the profound effects these tiny snippets of RNA have had on the evolution of myriad species. The Bartel lab was among the first to identify hundreds of these microRNAs and their effects on protein-coding genes in plants and animals. (It is the proteins that such genes code for that actually carry out cellular functions.)

In the Bartel lab, it's becoming clear that microRNAs are more integral to life than thought just a few years ago. Says Bartel: "We now know that more than half of protein-coding genes are targets of microRNAs."

2008 ACCOMPLISHMENTS

Using sophisticated high-throughput DNA sequencing, Bartel's lab determined that microRNAs are present in diverse animal species, including sponge, which is the simplest of all animals. These results indicate that microRNAs have been shaping gene expression for the past billion years; that is, throughout animal evolution. During 2008, the lab also used improved technical capabilities to examine the effects of a microRNA on the production of multiple proteins, discovering that a single microRNA alters levels of hundreds of cellular proteins, but often in a modest fashion, acting more as dimmer than an on–off switch.

THE FUTURE

The lab has discovered RNA interference—or RNAi, a process by which small RNAs naturally silence certain genes—in a close relative of baker's yeast and will be using this yeast for the genetic and biochemical study of RNAi.

DID YOU KNOW... *that David Bartel lived for three years in Mwamba, a small village in Zambia? Bartel was a volunteer in the African nation with a non-governmental development agency working to improve agricultural methods.*

IAIN CHEESEMAN

RESEARCH FOCUS

Iain Cheeseman's lab studies the kinetochore, a specialized complex of an estimated 80 to 100 proteins that assembles during cell division and couples chromosomes with thin protein filaments termed microtubules. Without proper attachment, microtubules are unable to drag the large chromosomes through the nucleus's viscous fluid and accurately divide the chromosomes between the two new cells. The penalty for a mistake is severe: cells with the wrong chromosomes often die or become cancerous.

2008 ACCOMPLISHMENTS

The kinetochore's proteins must bind to microtubules and also remain bound to the chromosome's centromere region. The centromere, where a human chromosome's arms pinch together to form an X or Y shape, contains highly compacted DNA intertwined with centromere-specific proteins. According to Cheeseman, while the mitosis field has focused on only one of these centromere proteins, CENP-A, it was unclear whether additional proteins were central to kinetochore formation and attachment to the chromosome. Working with collaborators in Japan, Cheeseman's lab found that a new group of human kinetochore proteins, the CENP-T/CENP-W complex, is also necessary for the kinetochore to hold on to the chromosome.

THE FUTURE

Cheeseman is fascinated by both sides of the kinetochore: the side nestled against the chromosome's DNA and the side receptive to protein microtubules. He is especially interested in understanding how these interfaces work and how such an incredibly complex and dynamic structure is so tightly regulated by the cell.

DID YOU KNOW... *that Iain Cheeseman often serenades the researchers in his lab? He has been known to croon impromptu ditties about microtubules and how he hopes his experiments will work.*

GERALD FINK

RESEARCH FOCUS

Gerald Fink's lab analyzes how microbes alter their cell surfaces to recognize each other but avoid detection by the immune system. In yeast this camouflage involves switching from one cell surface protein to another. Fink's work has uncovered a previously invisible network of non-coding RNAs that toggle the cell surface genes on and off, providing variation that confuses the immune system.

2008 ACCOMPLISHMENTS

Our immune system recognizes a signature surface feature of fungal cells, ß-glucan, which alerts the organism to the invader's presence. The fungal cells mask the ß-glucan, thus foiling the immune system's recognition system. Eventually, the immune system unmasks the fungal cells and mounts an immune response, but a sluggish response can lead to severe systemic infections. Fink's lab showed that an antifungal agent can speed the unmasking process. The Fink lab also demonstrated that certain cell wall genes are under the control of non-coding RNAs. Some of these RNAs are antisense, each with a sequence complementary to the expressed gene; others are found in the spaces between genes and switch the adjacent genes on and off. New sequencing methods have revealed that these non-coding RNAs are much more prevalent than previously suspected.

THE FUTURE

Fink is fascinated by non-coding RNAs. These RNAs come from DNA that does not code for proteins, but regulates proteins. So, what regulates these non-coding RNAs? Fink is working closely with David Bartel and Whitehead Affiliate Member David Gifford to answer this question.

DID YOU KNOW... *that Gerald Fink discovered a super-secret fishing hole somewhere off Cape Cod? When Fink took David Bartel there, he and his son caught 30 striped bass and bluefish. The normally mild-mannered Bartel was so excited that he fumbled the handoff of Fink's favorite fishing rod, which sank deep into the ocean.*

RUDOLF JAENISCH

RESEARCH FOCUS

A pioneer in cellular reprogramming—the process of turning mature, differentiated cells back to an embryonic stem-cell-like state, without the use of embryos—Rudolf Jaenisch is focused on developing highly efficient, consistently reliable methods for creating so-called induced pluripotent stem (iPS) cells.

2008 ACCOMPLISHMENTS

The Jaenisch lab garnered considerable attention for using iPS cells to generate neurons capable of treating a rodent model of Parkinson's disease. This was a groundbreaking, proof-of-principle experiment showing the remarkable therapeutic potential of iPS cells. Cells used in this research, however, were created using viral vectors to insert four reprogramming genes into cellular DNA—an approach that can eventually lead to development of cancerous tumors. During 2008, the lab was able to improve the reprogramming process by eliminating the use of a known-cancer causing gene. Researchers also showed that iPS cells can be created not just from skin cells, which had become a standard approach, but also from terminally differentiated cells in the immune system and from cells of various other tissue types.

THE FUTURE

The advances of 2008 have put the lab in position to study a variety of diseases using human iPS cells. Says Jaenisch: "We've assembled the tools to really make the iPS systems ready for disease study and for the creation of patient-specific cell types. The possibilities are much more real now."

DID YOU KNOW... *that Rudolf Jaenisch is an accomplished mountain climber who has trekked across a variety of peaks in Europe, Asia, and Africa? Although a fan of climbs in the Himalayas, he cites Mount Kenya as his favorite conquest.*

SUSAN LINDQUIST

RESEARCH FOCUS

Proteins are long, complex chains of amino acids that must fold into precise three-dimensional structures to perform their vital cellular functions properly. Susan Lindquist's lab studies the many unexpected ways in which the protein folding problem interfaces with biology in both health and disease.

2008 ACCOMPLISHMENTS

In Huntington's disease, toxic levels of misfolded proteins accumulate in brain cells. Studying protein behavior in yeast cells, Lindquist's lab found that a misfolded protein (huntingtin) clogs the cells' protein recycling system, which normally clears out misshapen huntingtin. Researchers observed the same phenomenon in mammalian nerve cells of the kind affected in Huntington's disease, confirming that compromised protein disposal leads to neurotoxicity. Cells can prevent some protein misfolding.

Heat shock proteins (HSPs) steer misfolded proteins into form, allowing the proteins to function normally. However, under stress (extreme temperature or toxin exposure), HSPs are overwhelmed, allowing mutant proteins into shapes that alter cellular and organismal function. In stressed mustard plants, Lindquist's researchers found that suppressing a key HSP affects traits like flowering and seed production. Such seemingly spontaneous changes in multiple traits may explain rapid evolution in response to environmental shifts.

THE FUTURE

Studying the molecular genetics of yeast, Lindquist is exploring how environmental change couples to the evolution of new traits. She is also investigating the number of prion proteins found in yeast and other organisms, suspecting that they are more common and more beneficial than researchers currently think.

DID YOU KNOW... *that Susan Lindquist is a ballroom dancer? She and her husband picked it up eight years ago and now like to tango and swing dance at home or wherever they can find a band.*

HARVEY LODISH

RESEARCH FOCUS

Current areas of interest in the Lodish lab include red blood-cell development, hematopoietic (blood-forming) stem cells, and the regulatory roles microRNAs play in development and function of muscle cells, fat cells, and several types of blood cells, including the B cells of the immune system. Much of the lab's work lies at the interface between molecular cell biology and medicine.

2008 ACCOMPLISHMENTS

Researchers in the lab devised a cocktail of growth factors that increases the number of human hematopoietic stem cells in culture by a factor of 20. It's a finding with the potential to improve success rates of bone marrow transplants. Scientists also identified microRNAs that affect drug resistance in certain types of leukemia, noting that when the level of one microRNA (miR-221) is increased in these leukemic cells, they respond to drug therapy. Other work has begun to implicate specific microRNAs whose down-regulation is associated with obesity.

THE FUTURE

According to Lodish, microRNA work will be front and center: "The exciting thing about microRNAs is that they really do play key roles in developmental processes. They have profound effects. We've been studying these developmental systems for years, and now all of a sudden we've discovered a whole new layer of regulation."

DID YOU KNOW... *that Harvey Lodish has twice officiated at marriage ceremonies of students in his lab? In fact, in February 2009, he presided at what is believed to be the first and only wedding ever held at the Institute itself. Says Lodish: "It's an honor to be asked to serve at such important life events."*

TERRY ORR-WEAVER

RESEARCH FOCUS

Cells may undergo certain important transitions in their lifetimes: dividing from one cell with a complete chromosome set into two cells, each with complete sets (mitosis); dividing from one cell with a complete chromosome set to produce eggs or sperm with half a set (meiosis); and changing from unfertilized egg to fertilized egg to embryo. Terry Orr-Weaver studies the precise controls needed for these steps to occur properly.

2008 ACCOMPLISHMENTS

As a female human embryo develops, all its eggs are created and enter meiosis. But the process stops halfway through, and the eggs await a trigger at puberty that nudges them to ripen and move to a second meiotic hiatus, awaiting fertilization. In many organisms, the egg is filled with templates for meiosis-regulating proteins, but these templates must not produce proteins until the right developmental time.

In fruit flies, the Orr-Weaver lab analyzed at the molecular level how these protein templates are stalled and discovered a protein complex that exquisitely jumpstarts them.

The Orr-Weaver lab is also deciphering the first step of cell division—the replication of a cell's DNA. Although much of this process is understood, little is known about replication regulation in animals. In six DNA replication sites in fruit fly ovaries, the lab found strikingly different mechanisms controlling each site. Until now, researchers had thought only one mechanism regulates the initiation of DNA replication.

THE FUTURE

Surprised by the variety of DNA replication controls, Orr-Weaver is investigating how other cell types regulate the process. She is also delving deeper into the processes that manage meiosis.

DID YOU KNOW... *that Terry Orr-Weaver enjoys playing the piano? She is currently perfecting Beethoven's Sonata #8 Rondo.*

DAVID PAGE

RESEARCH FOCUS

Institute Director David Page has long been at the forefront of research into mammalian sex chromosomes. While perhaps best known for exposing the previously unappreciated complexity of the human Y chromosome, his work in elucidating how germ cells halve their chromosomes and commit to becoming either egg or sperm may prove no less important in the field of reproductive biology.

2008 ACCOMPLISHMENTS

The Page lab found another piece of the puzzle of how germ cells enter meiosis (the halving of chromosomes) in preparation for production of sperm or egg. The lab had previously discovered in mouse studies that the gene *Stra8* (stimulated by retinoic acid) is required to initiate meiosis. In 2008, researchers determined that even before *Stra8* expression can trigger meiosis, another gene known as *Dazl* must produce a protein that paves the way for *Stra8* expression. These results confirm that meiotic initiation occurs through a complex pathway of signals that is slowly becoming clearer.

THE FUTURE

"I look back a decade and realize that we never could have guessed the answers we have today," says Page, who believes the *Dazl-Stra8* story has several chapters yet to be told. "They're the two central players, and we're about to greatly expand their job descriptions."

DID YOU KNOW... *that David Page met his wife of 23 years while working at a hospital in Liberia? David and future spouse, Elizabeth, were medical students at the time. On her first day, Elizabeth encountered an active hornets' nest while attempting to move into a hospital residence hall. A chivalrous Page cleared the hornets' nest. Says Page, "That has not been a metaphor for our relationship!"*

HIDDE PLOEGH

RESEARCH FOCUS

For Hidde Ploegh, exploring the intricacies of the immune system has been a lifelong pursuit. Along the way, he and scientists in his lab have devised novel methods to study the various cellular and molecular mechanisms of the system's responses to foreign invasion. His interest in drawing from other scientific disciplines, including chemistry and chemical and mechanical engineering, fuels innovation in his lab's immunology research.

2008 ACCOMPLISHMENTS

Researchers developed a unique "microengraving" system allowing them to depict how individual cells in the immune system respond to vaccinations. The system quickly and efficiently generates important data on B cells, including their number, whether they are actively producing antibodies to a vaccine challenge, and the specificity of antibodies produced.
A second discovery concerns the manner in which incoming pathogens are handled by certain Toll-like receptors, which are proteins that focus on microbial macromolecules. Ploegh and colleagues solved the longstanding mystery of how and why lysosomes, intracellular organelles usually charged with disposal of unwanted materials, are involved in the activation of some of these Toll-like receptors.

THE FUTURE

Beyond continued investigation of the immune response, Ploegh is collaborating with Whitehead Members Rudolf Jaenisch and Richard Young in developing new models for the study of infectious diseases, making use of nuclear transplantation technology to generate mice that are better suited to study the interplay between a host and its pathogens.

DID YOU KNOW ...*that Hidde Ploegh is an avid sport fisherman? He co-owns a fishing boat named* The Rampage, *upon which he cruises the Atlantic on summer days in the hunt for striped bass, bluefish, and bluefin tuna.*

PETER REDDIEN

RESEARCH FOCUS

How stem cells can be utilized for regeneration is an issue of great scientific interest. Getting at the root of this problem requires understanding how stem cells function, how cellular and tissue regeneration occur, and how a body part regrows with correct identity. The Reddien lab studies these topics in planarians, flatworms with the amazing ability to regrow any severed body part—including nervous system, muscles, skin, and intestine.

2008 ACCOMPLISHMENTS

Reddien's lab identified multiple genes that regulate neoblasts, the planarian stem cells responsible for regeneration. Because stem cell regulation occurs in all animals, Reddien's work in planaria may ultimately provide insight into regeneration and stem cells in higher animals, including humans.

Reddien's lab found that a Wnt signaling pathway triggers a tail to grow on the back end of the worm. When this pathway is blocked, the back end grows a head instead. Wnt signaling is important to the life of all animals. The lab determined the mechanism by which Wnt signaling makes the regeneration polarity decision, involving action of Wnt proteins at wounds. This role for Wnt signaling provides some of the first insight into how the process is regulated at the molecular level.

THE FUTURE

By studying planarian stem cells, the Reddien lab is identifying the mechanisms that regulate the Wnt signaling pathway and control multiple genes that are turned on specifically in those stem cells.

DID YOU KNOW... *that Peter Reddien was a remote-control racing car champion as a high school senior and college freshman? At the height of his remote racing career, he was on the U.S. team and placed first in Texas, 23rd in the country, and 45th in the world?*

DAVID SABATINI

RESEARCH FOCUS

Regulation of cell growth is essential for proper development and to prevent cancer, which results from rampant overgrowth of cells. David Sabatini studies the components of a cellular system that triggers growth (known as TOR, or target of rapamycin) and how this system is controlled.

2008 ACCOMPLISHMENTS

Sabatini's lab found a potential drug target for cancers caused by a mutation in the PTEN gene. Tumors resulting from PTEN deficiency depend on a particular protein complex in the TOR system. When that protein complex is disabled in a mouse cancer model, tumor formation is blocked, but normal tissues are not affected—an ideal result for a cancer drug.

The TOR system is also involved in normal cell growth. The Sabatini lab discovered a key component that links nutrition to the "grow" command, a connection that greatly puzzles researchers. When the so-called Rag family of proteins senses the presence of the nutrients for protein-building (amino acids), Rag alters the location of part of the TOR system within the cell. This relocation signals the cell to grow.

THE FUTURE

Despite a better understanding of how growth signals are transmitted through the cell, Sabatini still does not know what actually senses the amino acid nutrients. Also, similar pathways involved in cell growth have been documented with cancer-causing mutations. Although no such mutations have been found in this nutrient-sensing pathway, Sabatini is searching for connections between this pathway and cancer.

DID YOU KNOW... *that David Sabatini's garden is smaller than his office, but is home to several large, unusual trees, including a spiky monkey puzzle tree and a "Bigleaf Magnolia", with 30-inch leaves?*

HAZEL SIVE

RESEARCH FOCUS

In the Sive lab, developing embryos of frogs and zebrafish serve as tools for the study of early brain and craniofacial development. Within the complexity of brain formation may lie clues to the genesis of mental health disorders, including schizophrenia and autism.

2008 ACCOMPLISHMENTS

Scientists in the Sive lab identified a previously undescribed bending mechanism in the formation of zebrafish brains. As the brain develops, sheets of cells must bend and fold the brain so that it can "pack" into the skull. All cell sheets have two sides, the apical side and the basal side. A considerable body of research has characterized the changes that take place among the cells of the apical side of the sheet, but researchers in the Sive lab have discovered that cellular constriction on the basal side ("basal constriction") occurs actively and plays a critical role in one of the most important early bends in the brain.

THE FUTURE

"Our challenge now is to figure out how cells know to basally constrict and what genes are required for the process," Sive says of this latest discovery. "Whatever results we obtain will be novel, and that's a very exciting place to be."

DID YOU KNOW... *that Hazel Sive believes that biology has a soundtrack? In a recent interview on National Public Radio, Sive explained that the earliest embryonic cell divisions appear to her as though they're moving to the beat of Pink Floyd's "Another Brick in the Wall", and that nerve cells seem to fire to the score of the Who's rock opera "Tommy".*

ROBERT WEINBERG

RESEARCH FOCUS

Long at the fore of cancer research, Robert Weinberg has in recent years turned an intense eye to the processes by which cancerous tumors invade surrounding tissue and metastasize to distant sites in the body. Much of this work has implicated so-called cancer stem cells, relatively rare cells within a tumor that have the ability to self-renew and seed new tumors.

2008 ACCOMPLISHMENTS

Researchers in the Weinberg lab determined that certain tumor cells are able to tap into a normal embryonic pathway that allows them to undergo an important morphological change. This change in shape not only allows these cells to separate from their neighbors, it also confers on them the properties of stem cells. The finding adds a crucial piece to the metastasis puzzle. Moreover, these same researchers soon realized that the same pathway can be induced in non-cancerous cells to generate healthy stem cells.

Says Weinberg: "Perhaps surprisingly, studies of the origins of human cancers are leading us toward new ways of creating normal human stem cells."

THE FUTURE

Much of the focus in the lab now is on exploiting last year's unexpected results. "I hope we'll figure out a formula by which we can propagate epithelial cells in culture to create epithelial stem cells," Weinberg says, adding that this pursuit will likely further the understanding of the workings of cancer stem cells.

DID YOU KNOW... *that in addition to being an accomplished gardener and a passionate genealogist, Bob Weinberg physically built his own cabin in New Hampshire? He began work on his special hideaway in 1976, saying it became "habitable" in 1977. Over the years he's expanded the place (himself, of course) and added a few creature comforts but insists the place retains its rustic charm.*

RICHARD YOUNG

RESEARCH FOCUS

Humans are made up of hundreds of types of cells, each with a special job. How cells are programmed to do these jobs and stick with the program is unknown. The Young lab has taken on the challenging task of discovering how hundreds of regulatory genes control these programs in clinically important cells.

2008 ACCOMPLISHMENTS

The lab recently completed a draft map of embryonic stem cells' main regulatory circuitry. This guide helps researchers predict how to keep embryonic stem cells in their undeveloped state or to develop them into any cell type. Working with the Jaenisch lab, Young also improved the efficiency of converting adult cells into embryonic stem cell-like cells, called induced pluripotent stem (iPS) cells.

Working with MIT Biology Professor Phillip Sharp, Young found that the machinery that normally slides forward along DNA to produce RNA can also run backward. Young says that running backward may allow the machinery to sweep the DNA clean of proteins that promote or inhibit gene expression. Or there could be another reason—right now, it's another mystery for the Young lab to investigate.

THE FUTURE

In addition to extending the map of embryonic stem cell circuitry, the Young lab is trying to discover what keeps a cell as a particular type of cell, for example, what keeps a heart cell from changing into a blood cell or a neuron.

DID YOU KNOW... *Richard Young is an adrenaline junkie? He was an award-winning giant slalom ski racer in high school, an accomplished marksman in later years, and continues today as a mountaineer who dreams of tackling the world's highest peaks.*

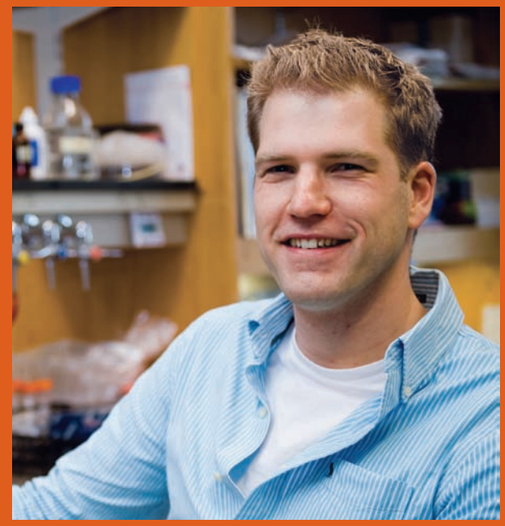
WHITEHEAD FELLOWS

THEY REPRESENT THE FUTURE OF BIOMEDICAL RESEARCH: A SMALL GROUP OF PROMISING YOUNG SCIENTISTS SUPPORTED BY THE INSTITUTE AND ENCOURAGED TO PURSUE THEIR RESEARCH AS CREATIVELY AS THEY DARE. FREE FROM TEACHING RESPONSIBILITIES, THEY EXPLORE UNDER THE TUTELAGE OF FACULTY, INSPIRED BY THE KNOWLEDGE THAT THE WHITEHEAD FELLOWS PROGRAM HAS LAUNCHED A NEW GENERATION OF SCIENTIFIC LEADERS.

THIJN BRUMMELKAMP

Thijn Brummelkamp investigates the Hippo pathway, a chain of cellular signals that regulates organ and tissue size. Brummelkamp has found that when an organ's cells have too much of a specific Hippo pathway gene (YAP1), the organ can quadruple in size. Uncontrolled cell growth and increased tissue size are hallmarks of cancer, and the Hippo pathway is overactive in about one-third of cancers. Although the Hippo pathway appears to be an important factor in tumor formation, Brummelkamp is working to clarify what remains a poorly understood role.

Brummelkamp's lab is also studying genes that have a hand in a variety of human diseases. This research includes genetic variations in cancer as well as a look at certain genes that infectious agents such as influenza virus and toxic bacteria use to enter a cell. By characterizing how genes function in diseases, Brummelkamp is narrowing down how and which therapeutics might best exploit disease-specific genetic traits.



FERNANDO CAMARGO

Like his colleague Thijn Brummelkamp, Fernando Camargo studies how the Hippo signaling pathway regulates tissue growth. Camargo also focuses on the development of blood cells. Both of his areas of research have important links to cancer. When a tissue or organ grows out of control, cancerous tumors can form. When blood cell development goes awry, the body produces inordinate numbers of certain cell types, resulting in various leukemias. Camargo recently determined that in healthy cells, the gene MEF2C directs cells to develop into B cells, T cells, and natural killer cells, instead of red blood cells or other types of white blood cells. When too little or too much of the gene is expressed, the balance of blood cells is disrupted, causing leukemia. Although the connection between MEF2C and leukemia was known previously, Camargo identified it as a pivotal point in blood cell development.

ANDREAS HOCHWAGEN

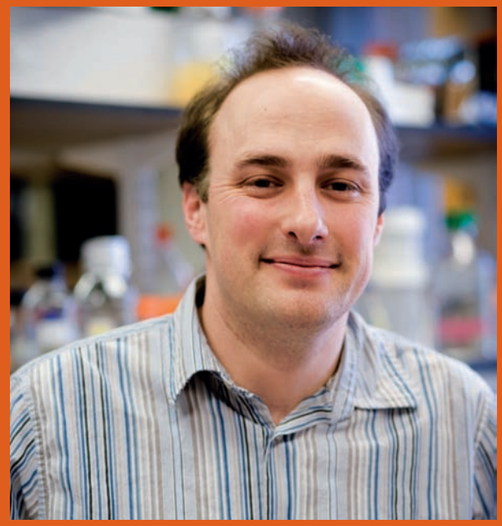
Our cells have remarkable quality-control mechanisms designed to ensure normal function. Despite such mechanisms, the complex cellular division processes of mitosis and, in the case of germ cells, meiosis, may still go awry. Improper chromosomal and DNA breaks occur, often with dire consequences. Andreas Hochwagen has been studying double-stranded (DS) DNA breaks, known to be among the most problematic errors. DS breaks are difficult for a cell to repair, and flawed reparations can lead to deletions of genetic material or improper sequences upon rejoining of the DNA. The results? Potential gene mutations, chromosomal abnormalities, and birth defects. Most recently, the Hochwagen lab has discovered that a "checkpoint" kinase known as ATR plays a key role in blocking inappropriate DS breaks. Hochwagen believes that this function of ATR will shed important new light on the possible origins of Down syndrome and related birth defects.

KATE RUBINS

The Rubins lab is bringing novel technology and improved field infrastructure in Africa to its investigation of monkeypox virus. The virus, which Kate Rubins describes as a "high-consequence human pathogen," causes infection with epidemic potential. To better understand the dynamics of infection, Rubins has established a lab in the Democratic Republic of Congo, enabling her to collect blood samples during outbreaks. Using the samples, she's able to identify viral genetic variation using sophisticated genetic sequencing. Rubins notes that monkeypox infections are caused not by a single virus, but by a "cloud of viruses" with thousands of individual virus genomes. Each genome may undergo a series of changes to elude immune system defenses. The lab's large-scale sequencing and microarray analysis will provide a clearer picture of what's actually happening genetically during viral transmission and perhaps ultimately yield clues to epidemic prevention.

PAUL WIGGINS

Lest you think chemists and geneticists have all the fun, Paul Wiggins combines physics with these "traditional" techniques to probe the connection between structure and function at larger scales. Wiggins and coworkers have developed a new technique to deduce the forces needed to maintain the shape of cellular organelles. These organelles are enclosed in their own membranes, some of which have labyrinthine shapes essential to organelle function. To investigate the connection between forces and membrane conformation, Wiggins and coworkers use a tool called optical tweezers to tug on beads bound to the membrane. These beads are then trapped and manipulated by a focused laser beam. By recording the force needed to shape the membrane a certain way, Wiggins can calculate the force needed to create similar convolutions in an organelle's membrane. The lab is using similar tools and techniques to investigate the mechanism of chromosome organization.



DEFNE YARAR

Since graduate school, Whitehead Special Fellow Defne Yarar has been fascinated by a ubiquitous, overachieving protein known as actin. This protein comprises a key part of the cellular architecture known as the actin cytoskeleton, which plays a central role in cellular movement and division, as well as in muscle cell contraction. For Yarar, one of actin's more intriguing roles is in endocytosis, a process during which a cell's outer membrane folds inward to engulf external matter in a membrane-enclosed pouch. Endocytosis is important for providing certain nutrients to a cell and is a key activity among the cells of the nervous system. Yarar describes her examination of endocytosis as "a global, systematic look at its mechanisms." Yarar says this approach has recently uncovered a surprise finding, which she hopes to publish in 2009. At this writing, she's not sharing details, but it's probably a safe bet that actin is involved. Stay tuned...

COMMUNITY EVOLUTION

THE INSTITUTE MOVES TO RHYTHMS ALL ITS OWN. AS IN THE LIFE OF ANY ORGANISM, THE PASSAGE OF TIME BRINGS CHANGE—SOME EXPECTED, SOME UNFORESEEN. EACH YEAR DELIVERS DISCOVERIES, EVENTS, AND TRANSITIONS THAT SHAPE THE WHITEHEAD COMMUNITY. 2008 WAS NO EXCEPTION.

INSTITUTE NEWS

FACULTY DEPARTURES

In his 23 years at the Institute, **Paul Matsudaira** advanced the study of quantitative biophysics, often through the development or enhancement of microanalytical technologies. He was integral in the formation of MIT's biological engineering department, served as founding director of the Keck Facility for Biological Imaging at Whitehead, and then oversaw the Whitehead/MIT BioImaging Center. Along the way, he became heavily involved in the Singapore–MIT Alliance, an educational collaboration among the National University of Singapore (NUS), Nanyang Technological University, and MIT. His ties to Singapore strengthened at the close of 2008, when he left Whitehead to run the department of biological sciences at NUS and to become founding director of a new biological imaging center there.

Longtime Member **Eric Lander** formally left the Whitehead faculty in September 2008. Lander's departure coincided with the announcement that the Broad Institute—which spun off from the Whitehead/MIT Center for Genome Research—is becoming an independent organization. Whitehead no longer holds a governing role in Broad, while Harvard University and MIT still have a hand in its governance. Whitehead Director David Page describes Lander's transition and the Broad's independence as appropriate evolutionary outcomes. "The Whitehead model has always been to identify and attract excellence, nurture it, and allow it to flourish," Page says. "This 'new' Broad Institute stands as a testament to the wisdom of this model." Lander, who has served as Broad's Director since its inception in 2004, had been a Whitehead Member since 1989.

At the close of 2008, Whitehead Fellow **Hui Ge** joined Cambridge biotechnology start-up Proteostasis Therapeutics as the company's head of bioinformatics and systems biology. Ge says of her four years at Whitehead, "My time here really helped me to become an independent scientist." In wishing Ge a fond farewell, Institute Director David Page lauded her "extraordinary intelligence, intellectual curiosity, and collaborative approach to biological problems."

(Clockwise from top) Member Gerald Fink addressed a gathering of students who later took to the labs of the Institute during the Whitehead Spring Lecture Series for High School Students. Institute outreach extends to high school teachers, who attend an annual seminar series and, in the fall of 2008, participated in the Boston Stem Cell Science Education Symposium.

PUBLIC OUTREACH

The Institute engages in a number of programs designed to educate the public on the latest advances in biomedical research and to serve as a community resource on science and science policy issues. Among the most popular is the Whitehead Spring Lecture Series for High School Students. The three-day event, conducted during spring vacation, encourages students to explore the facts behind science headlines and to consider how the latest findings will affect their own lives.

In 2008, some 100 students attended *Cell Wars: The Battle between Infectious Agents and Their Hosts*. The series took participants on a journey into how researchers are tackling some of biology's most challenging issues around infectious disease, such as how the immune system distinguishes friend from foe and how viruses evade normal immune response. The program featured lectures from leading scientific experts in the fields of immunology, virology, and yeast genetics. Students were also treated to lab tours at Whitehead and neighboring facilities, including those housed at nearby biotechnology companies. During each day of the program, students lunched with young Whitehead scientists, hearing firsthand about the diverse paths a scientific career may take. The program concluded with a panel discussion of public health issues associated with emerging infections.

Another important initiative is the Whitehead Seminar Series for High School Teachers, which provides a framework for educators to incorporate new ideas into their classrooms. In 2008, more than 80 teachers participated in the series entitled *Controlling Genes*, an examination of DNA packaging, transcription factors, microRNAs, and other regulatory mechanisms. The start of the academic year in the fall brought with it a new series for teachers, *Pursuing the Promise: Advances in Stem Cell Science*.

In November, Whitehead hosted the Boston Stem Cell Science Education Symposium. This innovative event aimed at high school teachers and junior college professors was produced in collaboration with the Harvard Stem Cell Institute, the Broad Institute, the Massachusetts Biotechnology Council, the Biotechnology Institute, and the National Academy of Sciences.

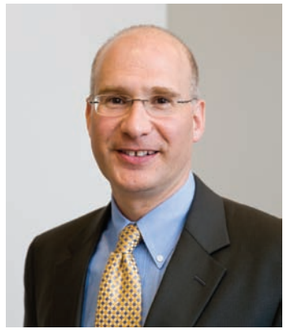
BOARD AND PHILANTHROPY NEWS

BOARD AND PHILANTHROPY NEWS

At the close of 2008, **Brit d'Arbeloff,** an ardent and longtime Whitehead supporter, accepted an invitation to join the Institute's Board of Directors. Brit, who earned a Master's degree in mechanical engineering from MIT, holds the distinction of being the first woman to receive a BS in mechanical engineering from Stanford University. Brit's formal ties to the Institute date to 1997, when she joined the Board of Associates.

Brit d'Arbeloff

MIT alumnus **Jonathan Goldstein,** who as an undergraduate worked in the lab of Whitehead Founding Director David Baltimore, became Chair of the Board of Associates—an appointment that carries with it a corresponding term on the Institute's Board of Directors. Jono, as he's known, holds an MBA from Harvard Business School and is currently Managing Director of the private equity firm TA Associates, where he evaluates healthcare, technology, and service-related businesses.



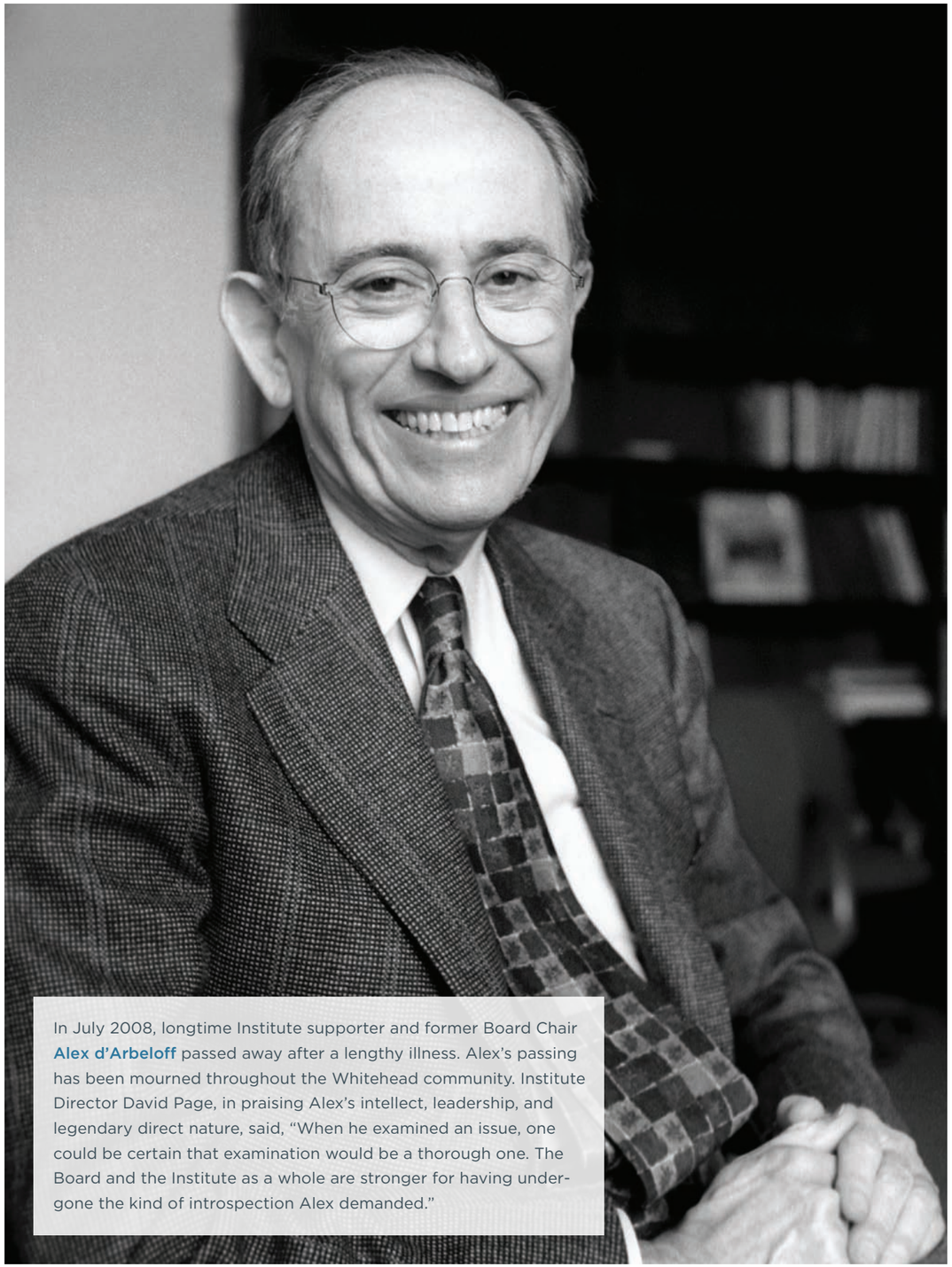
Jonathan Goldstein

Boston-based investment professional **Mark C. Lapman** was elected to the Board in December 2008. Mark is currently Chief Executive Officer of Independence Investments, where he has worked since the firm's incorporation in 1982. He holds an undergraduate degree from the University of Maryland and a Master's from Harvard University, where he also earned his PhD in Russian and East European history.

The Institute's recently launched *Stem Cell and Regenerative Biology* Initiative received a welcome infusion in December. Board Vice Chair **Susan Whitehead** pledged to donate $500,000 to the campaign over the next five years. Susan's generosity will help propel stem cell research across the Institute. Board member **Landon Clay** announced an extraordinary gift of $15 million, which will fund a research collaboration among the laboratories of Members Hidde Ploegh, Rudolf Jaenisch, and Richard Young.

Mark C. Lapman

"We are profoundly grateful for these remarkable donations, viewing them as acts of what Jack Whitehead once called 'enlightened philanthropy'," says Institute Director David Page. "Clearly, these are commitments to the power and potential of basic biomedical research and the belief that such research, as performed here, is among the best in the world."



In July 2008, longtime Institute supporter and former Board Chair **Alex d'Arbeloff** passed away after a lengthy illness. Alex's passing has been mourned throughout the Whitehead community. Institute Director David Page, in praising Alex's intellect, leadership, and legendary direct nature, said, "When he examined an issue, one could be certain that examination would be a thorough one. The Board and the Institute as a whole are stronger for having undergone the kind of introspection Alex demanded."

HONOR ROLL OF DONORS

WHITEHEAD INSTITUTE RECOGNIZES WITH DEEPEST GRATITUDE THOSE INDIVIDUALS, ORGANIZATIONS, FOUNDATIONS, AND CORPORATIONS WHO LENT THEIR SUPPORT SO GENEROUSLY IN FISCAL YEAR 2008, BETWEEN JULY 1, 2007 AND JUNE 30, 2008.

FOUNDER'S CIRCLE

$100,000 and above

Landon and Lavinia Clay
Alex* and Brit d'Arbeloff
Charles Ellis and Linda Lorimer
The Levien Foundation
Drs. Joan and Herman Suit

DIRECTOR'S CIRCLE

$50,000 and above

Arthur and Carol Brill
Peter Hecht and Kristina Jones
Peter S. and Kathryn S. Kim
David H. Koch
Harvey and Pamela Lodish
Peter and Renée Whitehead
Susan Whitehead

LEADER'S CIRCLE

$25,000 and above

Anonymous
Paul and Andria Heafy
Matthew D. Nichols and Katrina Burton-Nichols
Ellen and Leonard Polaner

BENEFACTOR'S CIRCLE

$10,000 and above

Endre A. Balazs and Janet L. Denlinger
Philip and Eve Cutter through the Goldhirsh Foundation
Mr. and Mrs. Robert G. Dettmer
G.S. Beckwith Gilbert and Katharine S. Gilbert
Amy and Jimmy Haber
Gregory E. Moore and Wynne W. Szeto
Matt and Mauny Plum
Clayton and Julianne Rose
Mitchel Sayare
Dr. and Mrs. Daniel Vapnek
John L. and Adelaide W. Zabriskie

PATRON'S CIRCLE

$5,000 and above

Madeleine Condit
Garey V. Ellis and Tomora-Lutreast Ellis
Dr. Orrie M. Friedman
Ansbert Gadicke, MPM Capital, LP
Kaia and Jonathan Goldstein
George and Daphne Hatsopoulos
Russell M. Jaffe
Mary Ellen Johnson and Richard Goeltz
Dr. and Mrs. Lawrence C. Pakula
James W. and Patricia T. Poitras
Gabriel and Samantha Schlumberger
Paul and Francine Tramontano
Harold and Anna S. Ullian Charitable Foundation: Steven A. Meyer; Robert Snider; Eliot Snider, Trustees

MEMBER'S CIRCLE

$2,500 and above

Anonymous (2)
Noubar Afeyan, Flagship Ventures
Alison Andrews
Lucy Aptekar
Mr. and Mrs. Thomas R. Armstrong
Neal Baer, MD and Gerri Smith
Lorraine and Emanuel Balkin
Dr. Barry A. and Mrs. Barbara Berkowitz
David and Arlene Brook
John and Susan Brooks
George and Judith Carmany
Neil and Martha Chayet
Alex and Dorleen Crutchfield
Bob and Winnie Curry
Patricia and Robert Denn
Michael and Barbara Eisenson
Anthony B. Evnin
Douglas M. Fambrough
Lora and Charles Farkas
Matthew and Jacqueline Fearer
Peter Feinstein and Miriam Weinstein
R. John Fletcher, Fletcher Spaght, Inc.
Kenneth Fong, Kenson Ventures, LLC
Mr. and Mrs. James W. Fordyce
Richard and Catherine Foster
Peter A. Glicklich
Mr. and Mrs. Thomas Gochberg
Karl Handelsman
Beverly P. Head
Don and Margery Hetzel
James Heywood
Bonnie and Lester Hochberg
Marianne and James Howard
Candace and W. Michael Humphreys
Evan and Cindy Jones

Paul Joskow and Barbara Chasen Joskow
Jerome and Judith Koch
Fannie E. Rippel Foundation: Laura Landy
Earl and Barbara Lewis
Gordon N. Litwin
Monaise and Angus MacDonald
George McCabe
Thomas N. McCarter
Terry and Carolyn McGuire
David and Franny Mitchell
Martin A. Mullins
Joe and Kathy O'Donnell
Dorothy Ornitz
David and Elizabeth Page
Joy Gail Raywid
Philip R. and Nancy L. Reilly
R. Rudolph Reinfrank
Carlyn Ring
Scott and Patty Rocklage
Neal and Sharon Rodin
Roger Sametz, Sametz Blackstone Associates, Inc.
Ruth Scheuer, JD and James Scheuer, MD
Arthur and Yvette Schleifer
Schooner Foundation
Parag Shah
James P. Sherblom, Seaflower Associates
Mr. and Mrs. Malcolm L. Sherman
Mr. and Mrs. R. Gregg Stone
Henri Termeer, Genzyme Corporation
John and Jean Travia
Mr.* and Mrs. Jeptha H. Wade
Drs. Barbara Wallner and Richard L. Cate
Robert A. Weinberg and Amy Shulman Weinberg
Ira and Phyllis Wender
Justin Wender and Deborah Goldfrank
Robert F. Wright

FRIEND'S CIRCLE

$1,000 and above

Anonymous
John E. Abele
Alchemy Foundation
Edith and Henry Allen
E.S. Anderson
David Bartel and Jan Preheim
Paul Berg
Thomas S. Caldwell, Caldwell Asset Management
Lawrence and Susan Daniels
Paul W. Douglas
Richard Goldsby and Barbara Osborne
Lawrence and Tina Haut
John R. Kennedy
Allan and Joan Kleinman
Kristine S. Langdon
Sam J. Lehr
Frank and Amy Linde
Mary and Nelson Luria
Eve and Nick Nichols
Lois Peerce
Jean-Jacques Pierrat, French Government
Hidde Ploegh and Anne Mahon
Marcia Radosevich
Elisabeth A. Raleigh
David E. Redlick
Margaret Sand
Eugenia and Robert* Seamans, Jr.
Stephen and Bessie Seiler
Phillip and Ann Sharp
Christine d'Arc Taylor
Arnold N. and Inge T. Weinberg

SUPPORTERS

Other Gifts

Giovanni Bosco
Sheldon Buckler
David Chao and Julia Zeitlinger
Dr. Shoumen Datta
Roslyn Daum
William Dietrich and Rebecca Mosher
Don S. Doering
David and Marion Ellis
John and Adrienne Erickson
Carlos and Ruth Gimeno
Rebecca Henderson
Craig and Heather Hill
Rakesh K. Jain
Victoria Kaplan
Ramunas and Skirma Anna Kondratas
Rosalind Lichter
Brigitte D. Linz
Albert Meyer and Irene Greif
Jill and Todd Milne
Dr. George M. Milne
Ken and Laura Morse
Mr. and Mrs. Edward W. Probert
William S. Reardon
Eliot and Ruth Snider
Joan and Thomas Steitz
Mr. and Mrs. Richard D. Stone
Bob Talanian
Laurie and Peter Thomsen
Lila and Benedict Wallis
Stephanie S. Watowich
Dr. Dorothy S. Zinberg

IN HONOR & MEMORY OF GIFTS

In honor and memory of friends and loved ones, Arthur Brill and Carol Tobin

Honorary Gifts

In honor of Susan Lindquist, Madeleine Condit
In honor of Charles L. Meyer, Adrienne and Jack Erickson
In honor of William Nachtigal, Adrienne and Jack Erickson
In honor of Jack Kaufold, Adrienne and Jack Erickson
In appreciation of Arthur Brill, the Rodenfels Family Foundation, Inc.
In honor of husband Arthur Brill, Carol R. Tobin

In Honor of Samantha Schweitzer and Gabriel Schlumberger

Benjamin Brainard
Marion Dorer
Paula and Doug Eads
Jane and Bill Grenawalt & Family
Zandy Hillel and Janis Taube, in memory of Sandra Meyer Schweitzer
Georgette Levis, in memory of Sandra Meyer Schweitzer
Tajlei Levis and Jonathan Canter
Mark Quinlan
Renee Ryan
Christine Wasserstein, in memory of Sandra Meyer Schweitzer

Memorial Gifts

In memory of Hatsuyo M. Hayashida, Adrienne and Jack Erickson
In memory of Vivian Howard, Richard and Helen Gates
In memory of Margarita Subotky, Peter A. Glicklich
In memory of Vivian Howard, James Howard and family
In memory of Francis S. Levien and Janice C. Levien, The Levien Foundation

In Memory of Norman Hascoe

Allan and Nancy Bernard
Arthur and Carol Brill
Robert and Patricia Dettmer
Mario J. Gabelli
The Goergen Foundation Inc.
Landmark Charitable Foundation, Inc.
James Lash and S. Deborah Jones
Oivind Lorentzen, Jr.
Susan E. Lynch
The Morales Family
Sally Swanson
Arnold N. and Inge T. Weinberg

MATCHING GIFTS

American Express
Capital Guardian Trust
Goldman Sachs & Co.
Robert Wood Johnson Foundation

* Deceased

RESTRICTED GIFTS

Liliana and Hillel Bachrach Fund for Stem Cell Research at Whitehead Institute

Liliana and Hillel Bachrach

Clay Fellows Fund

Landon and Lavinia Clay

Genzyme Postdoctoral Fellowship

Genzyme Corporation

RNAi Selection Web Server

Ambion, Inc.

Dharmacon, Inc

CORPORATE AND FOUNDATION SUPPORT

Anonymous

Abcam Inc.

Advanced Medical Research Foundation

Agencourt Bioscience Corporation

Agilent Technologies

Rita Allen Foundation

American Cancer Society

American Diabetes Association

Amgen, Inc.

Applied Biosystems Inc.

Battelle National Biodefense Institute

BD Biosciences

The Beez Foundation

Biogen Idec Foundation, Inc.

Bioline Inc.

The Breast Cancer Research Foundation

Broad Institute

Canadian Institutes of Health Research

Children's Tumor Foundation

Jane Coffin Childs Memorial Fund for Medical Research

Deshpande Center for Technological Innovation

Ellison Medical Foundation

Fisher Scientific Inc.

Anna Fuller Fund

Howard Hughes Medical Institute

ISC BioExpress

The W.M. Keck Foundation

The Sidney Kimmel Foundation for Cancer Research

Charles A. King Trust

Susan G. Komen for the Cure

The LAM Foundation

Leukemia and Lymphoma Society

Life Sciences Research Foundation

Lonza Walkersville, Inc.

Virginia and D.K. Ludwig Fund for Cancer Research at MIT

March of Dimes

Massachusetts Institute of Technology

G. Harold and Leila Y. Mathers Charitable Foundation

The Medical Foundation

Merck Research Laboratories

Millipore Corporation

Novartis Institutes for BioMedical Research

Open Biosystems, Inc.

Perkin Elmer Life Sciences, Inc.

Pressure BioSciences, Inc.

Qiagen, Inc.

Rett Syndrome Research Foundation

Fannie E. Rippel Foundation

Roche Diagnostics Corporation

Damon Runyon Cancer Research Foundation

Sage Science Corporation

Searle Scholars Program

Sigma-Aldrich Biosciences

Singapore / MIT Alliance

Richard and Susan Smith Family Foundation

Stanley Medical Research Institute

Alexander and Margaret Stewart Trust

Union Biometrica, Inc.

VWR International, Inc.

Helen Hay Whitney Foundation

Bradley Zankel Foundation, Inc

Each of our donors is important to us. Please notify us of any omissions or errors.

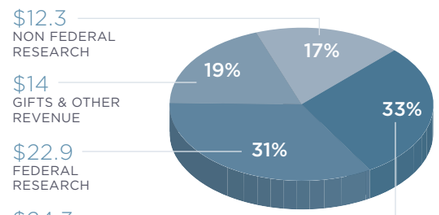
FINANCIAL SUMMARY

WHITEHEAD INSTITUTE'S CONTINUED FINANCIAL STRENGTH ENABLES ITS COMMITMENT TO BEST-IN-CLASS SCIENCE, EVEN IN THE MIDST OF AN EXTRAORDINARILY DIFFICULT ECONOMIC CLIMATE. THE GENEROUS SUPPORT OF INDIVIDUALS, CORPORATIONS, AND FOUNDATIONS REMAINS AN IMPORTANT INGREDIENT IN WHITEHEAD'S RECIPE FOR FISCAL STABILITY, WHILE THE QUALITY OF WHITEHEAD RESEARCH ALLOWS THE INSTITUTE'S FACULTY AND ASSOCIATED SCIENTISTS TO COMPETE SUCCESSFULLY FOR FEDERAL AND NON-FEDERAL FUNDING. AT THE SAME TIME, INSTITUTE ADMINISTRATION IS PARING OPERATING COSTS IN AN ONGOING EFFORT TO ALLOCATE A GREATER PROPORTION OF EVERY DOLLAR DIRECTLY TO RESEARCH.

REVENUES & SUPPORT

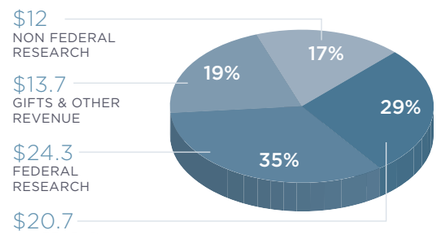
IN MILLIONS

2008



2008 TOTAL
$73.5

2007

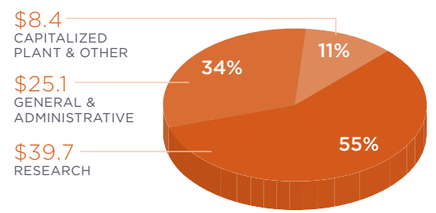


2007 TOTAL
$70.7

EXPENDITURES & DISBURSEMENTS

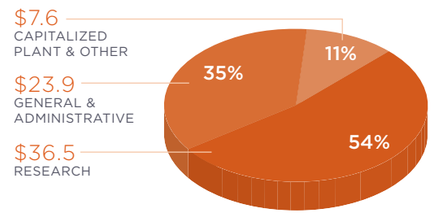
IN MILLIONS

2008



2008 TOTAL
$73.2

2007



2007 TOTAL
$68

LEADERSHIP

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 the full range of normal faculty duties.

Faculty achievements Whitehead faculty includes the recipient of the 1997 National Medal of Science (Weinberg), seven members of the National Academy of Sciences (Fink, Jaenisch, Lindquist, Lodish, Orr-Weaver, Page, and Weinberg), six fellows of the American Academy of Arts and Sciences (Fink, Jaenisch, Lindquist, Lodish, Ploegh, and Weinberg), five members of the Institute of Medicine (Fink, Jaenisch, Lindquist, Page, and Weinberg), and four Howard Hughes Medical Institute investigators (Bartel, Lindquist, Page, and Sabatini).

SITED FOR SCIENCE

Whitehead Institute was constructed in the early 1980s on a vacant lot on the northern edge of the MIT campus, strategically placed in proximity to the physical resources of MIT's Department of Biology. Today, the Institute is at the nexus of a vibrant biomedical "supercluster." The Broad Institute, along with the David H. Koch Institute for Integrative Cancer Research at MIT, McGovern Institute for Brain Research at MIT, and the Picower Institute for Learning and Memory at MIT, have emerged or expanded since Whitehead's founding, and promising biotech startups now sit alongside such industry leaders as Biogen Idec, Genzyme, and Novartis. It is an unprecedented concentration of talent; a neighborhood where innovation and discovery are the norm.

Whitehead Institute

Whitehead Institute for Biomedical Research Nine Cambridge Center Cambridge, Massachusetts 02142-1479