

Whitehead Institute
2010 ANNUAL REPORT

A vertical strip on the right side of the page features a microscopic image of cells. The cells are stained with various fluorescent dyes, appearing in shades of red, green, and blue. The staining highlights different cellular components, possibly nuclei and membranes. The overall appearance is that of a biological specimen under a fluorescence microscope.

ON THE VERGE...

WHITEHEAD INSTITUTE

Fueled by insatiable curiosity, unparalleled intellect, and a culture of collegiality, Whitehead Institute scientists are driven to contribute meaningfully to their chosen fields of study. Each year, they deliver. Impressively. 2010 was no exception. And yet, something's different. The pace of discovery is accelerating. The progress is real. Critical breakthroughs with the potential to improve human health appear closer than ever. We are:

ON THE VERGE...

contents

Carefully Scripting a Sequel	1
Scientific Achievement	3
Honors and Awards	12
Principal Investigators	15
Whitehead Fellows	32
Community Evolution	34
Honor Roll of Donors	36
Financial Summary	41
Leadership	42

COVER IMAGE Most cells in the body have two copies of each chromosome. But some cells, including the sub-perineurial glia cells (nuclei labeled green) encasing this larval fruit fly brain lobe, have an increase in DNA copy number. By studying cells like these, Whitehead Member Terry Orr-Weaver investigates how and why cells increase or decrease copies of their DNA.

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images Cover Yingdee Unhavaithay (Orr-Weaver lab) **PAGE 2** Chelsea Backer (Cheeseman lab) and Jen Gutzman (Sive lab) **PAGE 4** Reprinted with permission from Macmillan Publishers Ltd: *Nature Medicine*, "Musashi-2 regulates normal hematopoiesis and promotes aggressive myeloid leukemia". Kharas MG, Lengner CJ, Al-Shahrour F, Bullinger L, Ball B, Zaidi S, Morgan K, Tam W, Paktinat M, Okabe R, Gozo M, Einhorn W, Lane SW, Scholl C, Fröhling S, Fleming M, Ebert BL, Gilliland DG, Jaenisch R, Daley GQ. Aug;16(8):903-8, copyright 2010. **PAGE 5** Jacob Hanna (Jaenisch lab) **PAGE 6** Adapted with permission, *Development*, Gutzman and Sive, Mar 1, 2010, 137: 795-804. **PAGE 7** "MicroRNA miR-125b causes leukemia". Bousquet M, Harris MH, Zhou B, Lodish HF. *Proc Natl Acad Sci U S A*. 2010 Dec 14;107(50):21558-63. **PAGE 9** "HIF1alpha synergizes with glucocorticoids to promote BFU-E progenitor self-renewal". Flygare J, Rayon Estrada V, Shin C, Gupta S, Lodish HF. *Blood*. 2011 Mar 24;117(12):3435-44. **PAGE 11** Reprinted with permission from Macmillan Publishers Ltd: *Nature*, "mTORC1 controls fasting-induced ketogenesis and its modulation by ageing". Sengupta S, Peterson TR, Laplante M, Oh S, Sabatini DM. Dec 23;468(7327):1100-4, copyright 2010. **PAGE 12** Ryan K Morris Photography/National Science & Technology Medals Foundation. **PAGE 14** Dan Wagner (Reddien lab) **PAGE 16** Michael Nodine, Bartel lab and *Genes and Dev*. **PAGE 17** Chelsea Backer (Cheeseman lab) **PAGE 18** Alex Esteban (Fink lab) **PAGE 19** Alberto Salguero Quiles. **PAGE 20** Yuxiong Feng (Gupta lab) **PAGE 21** Reprinted from *Cell*, Mar 6;136(5), Soldner F, Hockemeyer D, Beard C, Gao Q, Bell GW, Cook EG, Hargus G, Blak A, Cooper O, Mitalipova M, Isacson O, Jaenisch R, "Parkinson's disease patient-derived induced pluripotent stem cells free of viral reprogramming factors", 964-77, 2009, with permission from Elsevier. **PAGE 22** Sebastian Treusch (Lindquist lab) **PAGE 23** Bill Wong (Lodish lab) **PAGE 24** Yingdee Unhavaithay (Orr-Weaver lab) **PAGE 25** Yueh-Chiang Hu (Page lab) **PAGE 26** McGehee AM, Strijbis K, Guillen E, Eng T, Kirak O, et al. (2011) "Ubiquitin-Dependent Control of Class II MHC Localization Is Dispensable for Antigen Presentation and Antibody Production". *PLoS ONE* 6(4): e18817. **PAGE 27** Lucila Scimone and Mansi Srivastava (Reddien lab) **PAGE 28** Reprinted from *Mol Cell*, Jun 11;38(5), Yip CK, Murata K, Walz T, Sabatini DM, Kang SA, "Structure of the human mTOR complex I and its implications for rapamycin inhibition", 768-74, 2010, with permission from Elsevier. **PAGE 29** Ellie Graeden, Sive lab. **PAGE 30** Christina Scheel (Weinberg lab) **PAGE 31** Reprinted from *Cell*, Mar 18;144(6), Young RA, "Control of the embryonic stem cell state", 940-54 (2011), with permission from Elsevier. **PAGE 40** Jared Owen (Reddien lab) **PAGE 43** Zuzana Keckesova (Weinberg lab)

FROM THE DIRECTOR

Carefully Scripting a Sequel



During 2010, I enthusiastically accepted an appointment by our Board of Directors to a second five-year term as Director of Whitehead Institute. Being entrusted once again with the leadership of such an extraordinary institution demands both deep reflection and refinement of vision.

Five years ago, I was singularly, perhaps even obsessively focused on junior faculty recruiting. As many of you observed, my colleagues and I approached this challenge with diligence and deliberation. We conducted exhaustive searches annually. More than once we chose not to extend offers, not only because it is our obligation to recruit the best of the best, but because these hiring decisions have implications for Whitehead Institute that can endure for decades.

The stakes are high, but our track record has been exceptional. During my first term, we brought Peter Reddien and Iain Cheeseman to Whitehead. It's been a pleasure witnessing both demonstrating the vast potential we first sensed in them. Last year, we welcomed Mary Gehring and Piyush Gupta to our faculty, and already each has made valuable contributions to our culture and community.

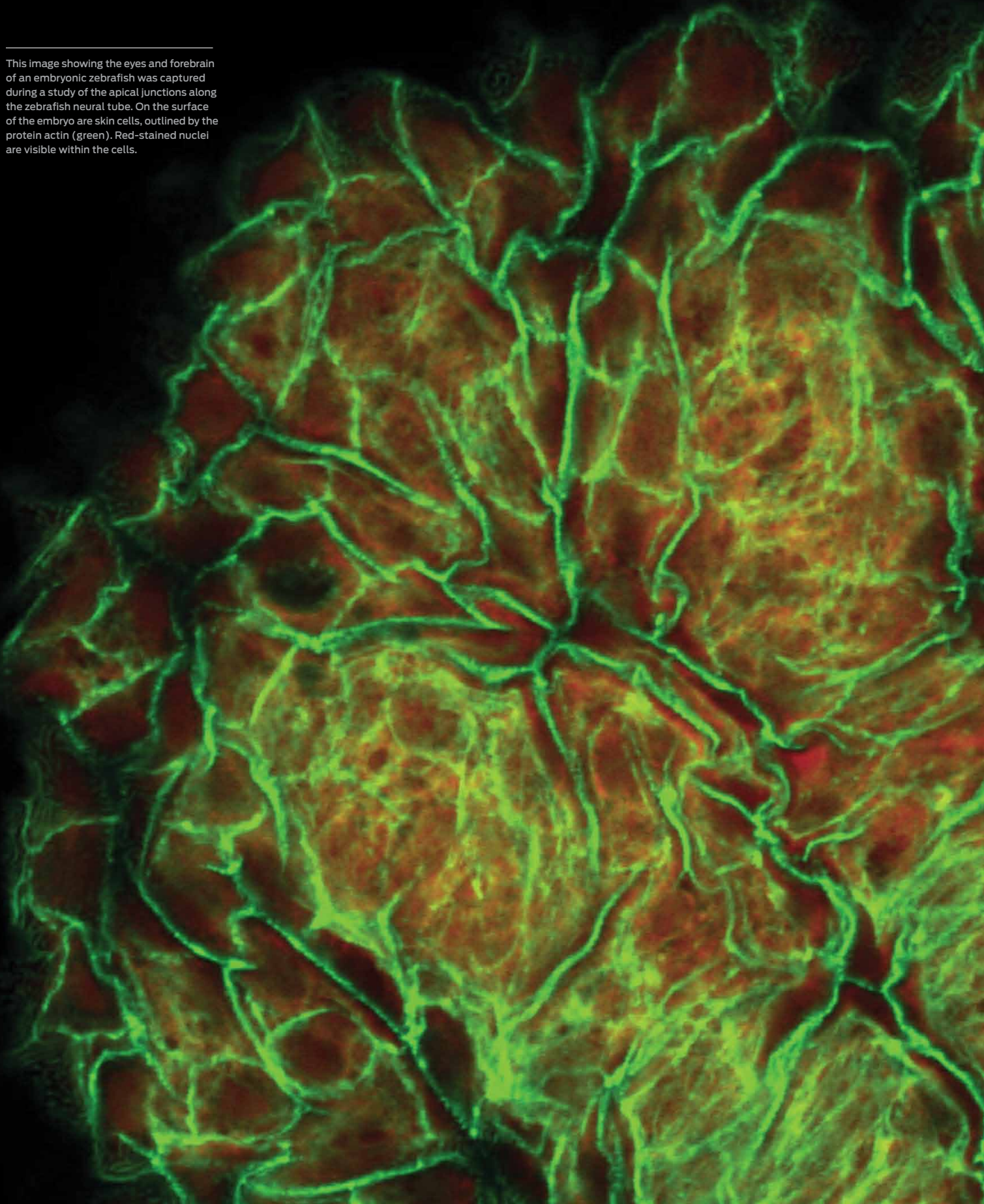
With such a critical component of our future success solidified, we are now—in keeping with a theme of this report—on the verge of formalizing long-range plans to enable us to build upon our considerable momentum. Our faculty is currently engaged in a strategic scientific planning process that is guiding rigorous, forward-looking financial analysis. Rest assured that our commitment to basic science will remain unchanged. Rather, we are thinking holistically about how best to position the Institute to capitalize in the long term on the many opportunities presented by our researchers and by the enabling breakthrough technologies employed in their labs. I look forward to updating you on our progress on this front.

Continued success is not guaranteed, of course, but as you read herein about our latest research achievements and resulting accolades, you'll see why I like our chances. As Director, I'm reminded daily how fortunate Whitehead Institute is to benefit from such a unique blend of brilliant scientists, dedicated staff, and passionate friends and supporters. I'm most grateful for the contributions of each.

A handwritten signature in blue ink that reads "David C. Page". The signature is fluid and cursive.

David C. Page

This image showing the eyes and forebrain of an embryonic zebrafish was captured during a study of the apical junctions along the zebrafish neural tube. On the surface of the embryo are skin cells, outlined by the protein actin (green). Red-stained nuclei are visible within the cells.



Scientific ACHIEVEMENT

High-impact research. It is the very essence of Whitehead Institute and has been from day one. Findings emerging from Institute laboratories are driving advances in our understanding of molecular and developmental biology, cancer, genetics, genomics, immunology, stem cells, and beyond. Fittingly, such scientific excellence continues to garner recognition globally.

Cancer

PAUSING AND PROLIFERATION

During a massive study of DNA transcription and gene expression in embryonic stem cells, researchers in the lab of Whitehead Member **Richard Young** made a surprising discovery that not only reveals one of the mechanisms behind uncontrolled cell growth in cancers, but also offers clues how to prevent it.

In the simplest model of gene expression, DNA is transcribed into RNA that encodes for a gene. If that gene codes for a protein, the result of transcription is a unit of messenger RNA that is translated to produce a protein that will perform a biological process within the cell. During transcription, the enzyme RNA polymerase unzips DNA's double helix to create a complementary RNA strand. But to initiate transcription, RNA polymerase has to be recruited to the proper start site by proteins known as transcription factors. The process has been well documented, but during their reexamination of it, Young lab scientists found, quite unexpectedly, that other factors actually stop transcription in its tracks just after it begins.

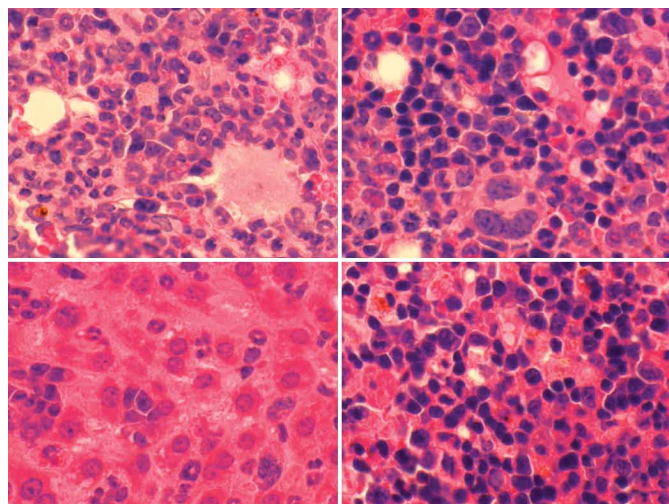
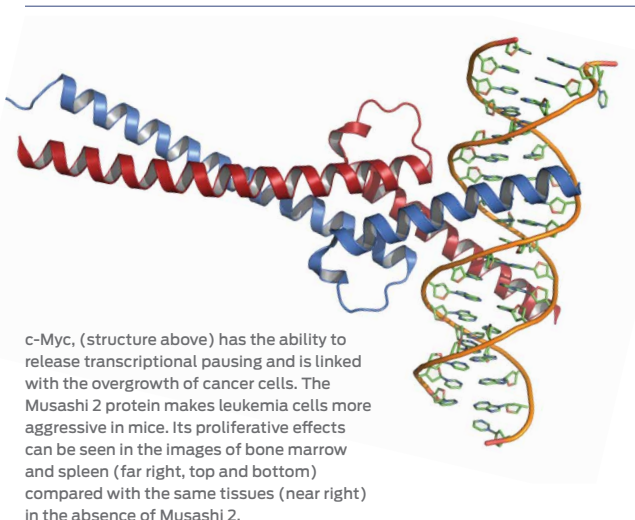
Young likens this phenomenon to a car in which the engine is running with the transmission in neutral. Something has to kick it into gear. It turns out that for a surprisingly large number of genes in embryonic stem cells, that "something"

is the transcription factor c-Myc. This pause-release role for c-Myc is significant, as many of c-Myc's targets are genes in highly proliferative cells. Over-expression of c-Myc is a hallmark of a host of tumors, and it now appears that c-Myc's ability to release transcriptional pausing is linked with the hyper-proliferation seen in cancer cells. Young and colleagues are now searching for drugs that could disrupt c-Myc's activity.

"Clearly, cancer cells are able to exploit mechanisms that normally operate in embryonic stem cells," he says. "Further understanding of embryonic stem cell control mechanisms will give us additional insights into human disease mechanisms."

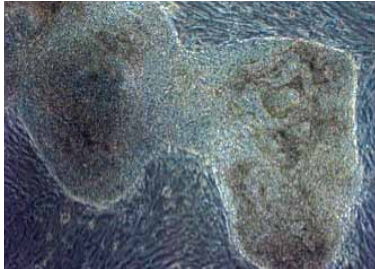
In other studies of cellular proliferation, scientists in the lab of Whitehead Founding Member **Rudolf Jaenisch** identified a protein that, when present in high levels, is associated with increased cell replication, decreased maturation, and multiple cancer-related cellular pathways in human leukemias.

Collaborating with the Children's Hospital Boston lab of former Whitehead Fellow George Daley, the Jaenisch researchers discovered that, when exposed to the protein Musashi 2, acute myeloid leukemia and chronic myeloid leukemia cells become more stem cell-like and more aggressive.

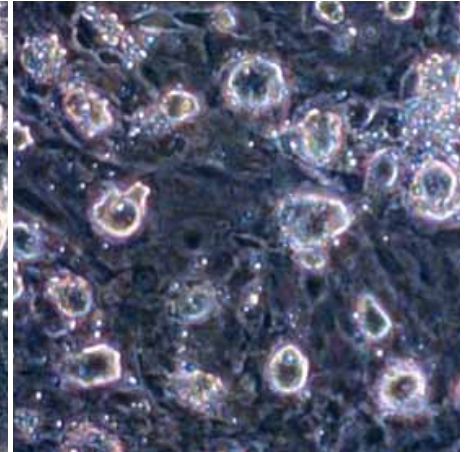
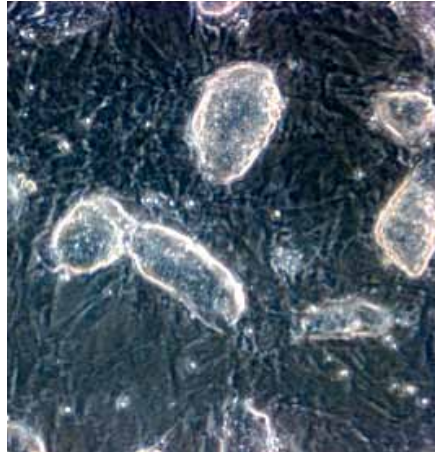


Stem Cells

THE PURSUIT OF NAÏVETÉ



In addition to important biological differences, human embryonic stem (ES) and induced pluripotent stem (iPS) cells are shaped differently. The human cells (above) are large and flat, while mouse cells (right) are smaller and ball-like. The converted, more pluripotent human cells (center) more closely resemble the mouse cells, both biochemically and morphologically.



Few scientific discoveries have generated as much excitement as the creation of embryonic stem cell-like cells without the use of embryos. The breakthrough, sending mature, fully differentiated adult cells back to the pluripotent state characteristic of embryonic stem (ES) cells via the insertion of a few genes—the process of generating induced pluripotent stem (iPS) cells—ushered in an era of cellular reprogramming and dreams of advances in personalized regenerative medicine in the absence of the moral and ethical debates that accompany human ES cell research.

Amid the enthusiasm, however, a new debate has emerged over whether iPS cells are truly identical to ES cells. It's an issue that must be addressed before iPS cells can safely be used in humans. A number of recent studies comparing the two cell types have found differences in gene expression. Whether such variation could be problematic in clinical applications is unknown.

Whitehead Founding Member **Rudolf Jaenisch** suspects that the differences observed thus far are attributable to the varied methods labs around the world employ when creating and maintaining iPS cells. Jaenisch has spent the past several years advancing the state of the art in deriving and culturing iPS and ES cell lines.

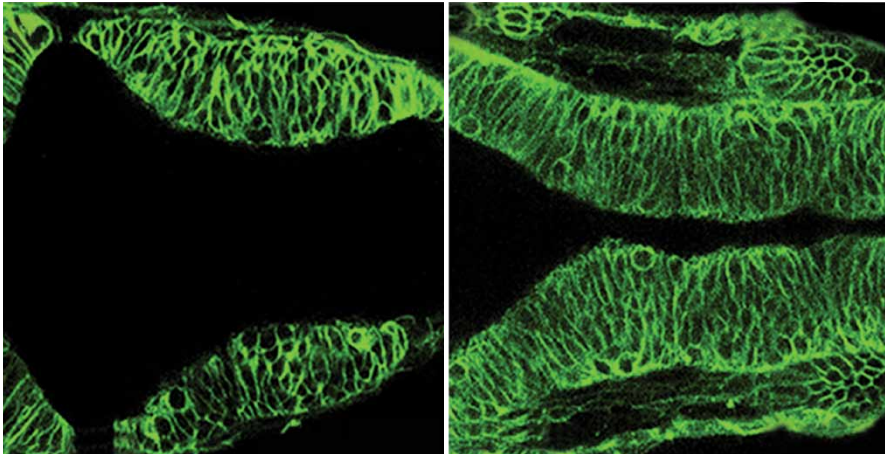
During 2010, his lab succeeded in pushing human iPS and ES cells to a state of pluripotency that had only been attainable in mouse ES cells. Over the years, researchers have had a relatively easy time manipulating and preventing differentiation (maturation beyond the base pluripotent state) in mouse ES and iPS cells. But human ES and iPS cells have important biological differences that make them notoriously difficult to work with. Researchers often refer to mouse ES and iPS cells as “naïve,” while human ES and iPS cells, which teeter on the verge of differentiation, are more mature and are referred to as being “primed” for differentiation. Jaenisch scientists engineered a cocktail of four small molecules that bring about the much-desired base pluripotent state in the human cells.

Says Jaenisch: “I think this really opens things up and gives us the possibility to define the biological properties of these new cells.”

In related work, the lab discovered that oxygen levels present during the culturing of human ES cells can affect their pluripotency. ES cells cultured at a low oxygen level mimicking that found *in vivo* remain in a state of enhanced pluripotency. Jaenisch believes deriving cells under such conditions represents a new standard.

Evolution and Development

TRACKING TRAITS, TAKING SHAPE



During vertebrate embryonic brain development, the neural tube fills with fluid to form cavities called ventricles. In the hindbrains of normal zebrafish (left), the fluid pushes the ventricle walls (green) apart. In zebrafish with a genetic mutation (right), the ventricle walls do not stretch enough to allow ventricular expansion.

The classical view of evolution states that species evolve over time—usually extended periods of time—through the natural selection of beneficial traits that are then passed to the next generation. How then to explain the rapid changes in phenotype seen in a variety of organisms, changes that seem to short-circuit traditional evolution?

It's a question that has long fascinated Whitehead Member **Susan Lindquist**, and during 2010, her lab provided a compelling possible answer. By studying the levels and activity of heat shock protein 90 (Hsp90) in more than 100 strains of yeast exposed to varying degrees of environmental stress, researchers in the Lindquist lab discovered that, when inhibited, Hsp90 can have almost immediate, profound effects on the phenotypes of the yeast. Crossing these strains resulted in the emergence of the new traits in the progeny and, intriguingly, roughly half of the new traits proved beneficial to the organism, while the remainder were detrimental. It appears that when the cellular reservoir of Hsp90 is depleted under stressful conditions, correlation with phenotypic variation is at its strongest.

Says Lindquist: "We can now show that the stress of environmental change and selective pressures can actually influence how evolutionary processes occur."

Evolution's manifestations, of course, play out in organismal development, when the genome shaped over time is translated from fertilized egg through embryogenesis and eventually to adulthood.

One of the critical junctures in vertebrate development is the formation of the embryonic brain. By tracking this process in zebrafish embryos, scientists in the lab of Whitehead Member **Hazel Sive** discovered a mechanism known as epithelial relaxation, which allows for the expansion necessary for proper brain morphology. The vertebrate brain, including that of fish and humans, forms from a tube known as the neural tube. During brain development, the center of the neural tube fills with embryonic cerebrospinal fluid (eCSF), to form a system of cavities known as brain ventricles.

The mere presence of eCSF, however, is not enough to ensure that the ventricles fill properly. In the Sive lab, researchers found that fish with a mutation in the gene *mypt1* have brain ventricles whose walls are too stiff to allow them to fill. Knowing that *mypt1* and its protein product normally function to regulate the motor protein myosin, which itself causes cellular contraction and rigidity, they concluded that ventricle wall relaxation (through suppression of myosin) is necessary for proper expansion and brain development.

MicroRNAs

WHAT A LITTLE RNA CAN DO

Over the past decade, scientists have come to realize that tiny strands of RNA known as microRNAs have played critical roles in the evolution of plants and animals and can have dramatic, widespread impact on biological functions through their regulatory effects on gene expression.

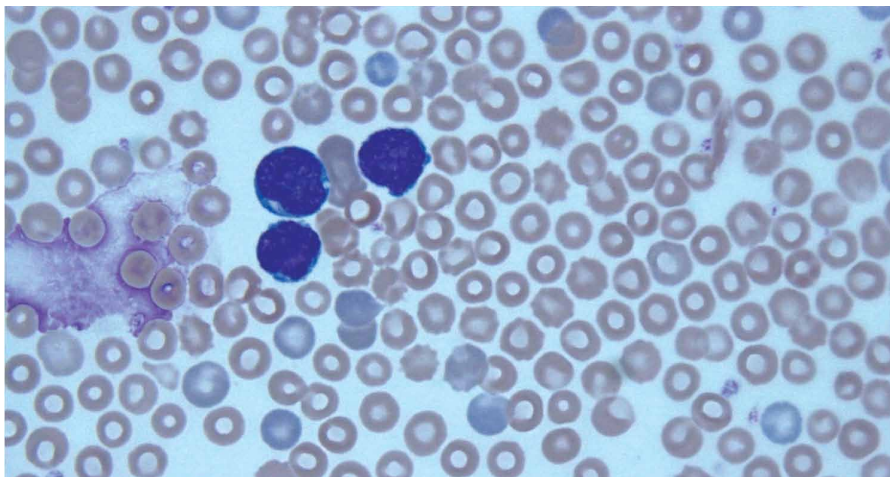
MicroRNAs suppress protein production by targeting messenger RNAs (mRNAs) of protein-coding genes. To create a protein, a cell uses an mRNA template that is copied from a gene. A cellular machine called a ribosome then translates this mRNA template into a chain of amino acids that form the protein. Until recently, it was unclear at exactly what point in this process microRNAs act to suppress protein production. Were they rendering the mRNAs less efficient or somehow degrading the mRNAs themselves?

During 2010, the lab of Whitehead Member **David Bartel**, a leading authority on small RNAs, found proof microRNA activity in fact reduces overall levels of mRNA, which in turn leads to lower levels of protein production. The finding not only clarifies the manner in which microRNAs influence gene regulation but also establishes the study of mRNA levels as a valid approach to identifying which genes a microRNA is regulating.

While Bartel was elucidating how microRNAs function, scientists in the lab of Whitehead Member **Harvey Lodish** were uncovering the potentially harmful effects a single microRNA can have when overexpressed.

Knowing that a little-studied genetic mutation in leukemia patients can lead to the overexpression of a microRNA known as miR-125b, Lodish lab researchers set out to determine whether miR-125b could actually cause leukemia. They injected into mice cells with the mutation in question, leading to as much as 90 times the normal expression of miR-125b. Between 12 and 29 weeks post-injection, half of the mice died having developed one of three different types of leukemia.

In a follow-on experiment, researchers transplanted a group of mice with bone marrow cells containing the known leukemia-causing mutation *BCR-ABL* and another group with cells harboring the *BCR-ABL* mutation and the miR-125b overproduction mutation. All transplanted mice developed leukemia, but mice receiving the dual mutation died a full two weeks before the others. Taken together, the results show that overexpression of miR-125b can not only cause leukemia, but also (in the presence of other associated mutations) accelerate disease progression. Whether miR-125b represents a viable therapeutic target remains to be seen.



A blood sample from a mouse overexpressing miR-125b, which developed B-cell acute lymphoid leukemia (B-ALL). In B-ALL, immature white blood cells, called lymphoblasts (dark purple), proliferate so wildly that they overflow from their usual location in the bone marrow into the blood stream.

RESEARCH STORIES

OVERCOMING ANEMIA

LIKE RED BLOOD-CELL PRODUCTION ON STEROIDS, ONLY BETTER...

For cancer patients on chemotherapy and kidney disease patients on dialysis, recombinant DNA technology developed in the 1980s delivered an important, often life-saving advance that remains in use today.

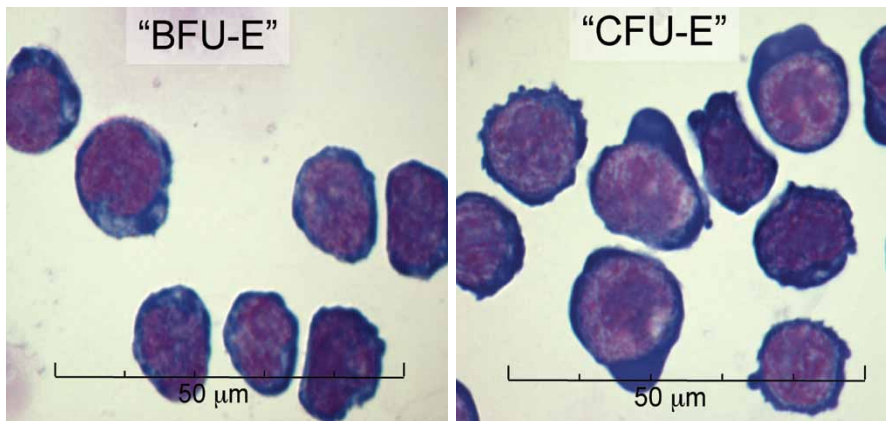
As a consequence of treatment, these patients frequently develop severe, chronic anemia. Simply put, they suffer from an insufficient number of red blood cells, which supply essential oxygen to tissues throughout the body. Anemia occurs from a breakdown in erythropoiesis, the complex, multi-step process that forms red cells.

A key player in erythropoiesis is the hormone erythropoietin (EPO), which normally stimulates red blood-cell production at one of the early stages of the process. Exogenous EPO, produced recombinantly in mammalian cell culture, was introduced in the United States in 1989 (Amgen's Epogen) as a treatment for anemia in dialysis patients, while other so-called EPO-stimulating agents (ESAs), emerged later to treat anemia in chemotherapy patients and patients with chronic kidney disease.

However, anemia in many of these patients eventually becomes EPO-resistant, while a number of other types of anemia never respond to EPO therapy. The result is a significant unmet medical need, one that Whitehead Founding Member [Harvey Lodish](#) and his lab have been striving to address.

In pursuing the problem, the lab looked to the rare blood disorder Diamond Blackfan anemia (DBA), whose patients lack a sufficient number of EPO-responsive cells. DBA can be managed with the use of corticosteroids such as prednisone or prednisolone, leaving Lodish researchers to wonder how these steroids actually affect erythropoiesis.

They began by purifying from mouse fetal liver cells two known progenitors of red blood cells: burst-forming unit erythroids (BFU-Es) and colony-forming unit erythroids (CFU-Es). During erythropoiesis, BFU-Es produce CFU-Es, which EPO then stimulates to generate the pro-erythroblasts that eventually become red blood cells. Because both of these progenitors divide numerous times before maturing, they have a limited ability to self-renew. Intriguingly, researchers observed that when BFU-Es and CFU-Es were exposed in vitro to a corticosteroid, only BFU-Es responded—dividing 13 times, rather than the standard nine times, before maturing into CFU-Es. These additional cell divisions ultimately led to a 13-fold increase in red blood-cell production.



During red blood cell production, burst-forming unit erythroids (BFU-Es) give rise to colony-forming unit erythroids (CFU-Es). BFU-Es (left) are mostly nucleus surrounded by very little cytoplasm. CFU-Es (right) are larger than BFU-Es and have more cytoplasm that sometimes bulges out from the cell.

During their study, lab members noticed something else: 83 genes in BFU-Es whose expression was stimulated by the corticosteroid. Upon closer examination they found promoter regions on these genes rich in binding sites for a transcription factor known as hypoxia-induced factor 1-alpha (HIF1-alpha), which itself is activated under conditions of oxygen deprivation. Knowing that a class of drugs referred to as prolyl hydroxylase inhibitors (PHIs) can trigger HIF1-alpha activation, researchers speculated that a PHI might act synergistically with a corticosteroid to promote increased BFU-E division, CFU-E production, and, ultimately, erythropoiesis.

As hypothesized, when they added a corticosteroid and a PHI to mouse BFU-Es in culture, the cells produced 300 times more red blood cells than did cells without exposure to the drugs. The same experiment with adult human BFU-Es showed a 10-fold increase in red blood-cell production when BFU-Es were exposed to the combination of a PHI and corticosteroid.

The finding provides hope for improved treatment for DBA patients, many of whom currently suffer from a host of corticosteroid-induced side effects, including decreased bone density, immunosuppression, stunted growth, and cataracts.

“If you could lower the dose of steroids so DBA patients would get just a little bit, and then add on this kind of drug, a PHI, that would boost the effect, maybe you could get around the steroids’ side effects,” says Johan Flygare, a postdoctoral scientist in the Lodish lab. “That’s what we’d like to see.”

Moreover, this novel approach to boosting erythropoiesis by extending the self-renewal of BFU-Es—resulting in creation of more EPO-responsive cells—could lead to therapeutic advances for other disorders of red blood-cell deficiency.

“There are a number of anemias that are much more prevalent than DBA and that cannot be treated with EPO either, such as anemias from trauma, sepsis, malaria, and certain genetic abnormalities,” says Lodish. “We’ll have to see whether these treatments will work in those.”

SCIENCE FOR THE AGES

CELLULAR PATHWAY OFFERS CLUES TO SLOWING THE RAVAGES OF TIME

Most of us are all too aware of the telltale signs of aging. Graying hair, wrinkling skin, slowing metabolism—and the extra pounds that often accompany it—are virtual certainties as the years mount. These manifestations are easy enough to observe, but they tell us little about what’s happening below the surface, at the cellular level, to bring about these changes.

Enter Whitehead Member **David Sabatini** and his lab, whose recent research is shedding new light on the multifaceted process we know simply as “aging.” Sabatini’s lab studies the interplay among nutrients, cell growth, and metabolism and their relationships to aging and such human diseases as cancer and diabetes. At the core of much of the lab’s research is the cellular pathway known as TOR (target of rapamycin), which has been shown to be a key player in controlling the growth of cells.

Sabatini has spent a significant portion of his career focused on TOR, discovering several years ago that the mammalian version of the pathway (mTOR) includes two major protein complexes: mTORC1 and mTORC2. Since then, the lab has identified links between each of these complexes and a variety of cellular processes. Most recently, lab members discovered an association between increased mTORC1 activity and a drop in ketone production, which is a well-defined physiological trait of aging in mice.

“This is the first time anyone has shown genetically that the mTORC1 pathway in mammals affects an aging phenotype,” Sabatini says. “It provides us with a molecular framework to study an aging-related process in deeper detail.”

Previous research had shown that when mTORC1 activity is blocked in a variety of animals, including worms, flies, and mice, they tend to live longer. Although an increased lifespan was an indication that mTORC1 is involved in aging, it failed to clarify mTORC1’s precise role in the process. In fact, lifespan is considered a poor proxy for studying aging, as it is not always a cause of death.

Intent on understanding what mTORC1 is actually doing here, researchers looked to the process of ketogenesis, the ability to produce ketones. During sleep or other times of low carbohydrate intake, the liver converts fatty acids to ketones, which are vital sources of energy during fasting. For reasons that remain unknown, the ketogenic response to fasting declines as animals age.

To determine whether mTORC1 mediates ketogenesis in mice, lab members induced mTORC1 hyperactivity in the livers of fasting mice. They found that while most blood and liver metabolite levels were unchanged, ketone levels fell precipitously, thereby establishing that mTORC1 activation suppresses ketogenesis.

The next challenge was to find exactly where mTORC1 was acting. Knowing that peroxisome proliferator-activated receptor alpha (PPAR-alpha) activates liver ketogenesis, the researchers attempted to jumpstart the process by stimulating PPAR-alpha. Interestingly, ketone levels failed to increase—a clear indication that mTORC1 was thwarting PPAR-alpha.

“That now places mTORC1 as the master regulator of ketogenesis,” says Shomit Sengupta, a former graduate student in the Sabatini lab who is now a Research Fellow at Harvard Medical School. “It could be one of many inputs for PPAR alpha. That’s unclear right now. But mTORC1 is sufficient and necessary to suppress PPAR-alpha and ketogenesis.”

It was an important finding, but it still didn’t formally connect mTORC1 to the aging-related decline in ketogenesis. Sabatini and Sengupta theorized that if mTORC1 activation is responsible for lower ketone levels caused by aging, then stimulating mTORC1 in older mice shouldn’t affect their already low ketone levels. The approach, they figured, would be like trying to turn off a light that has already been switched off.

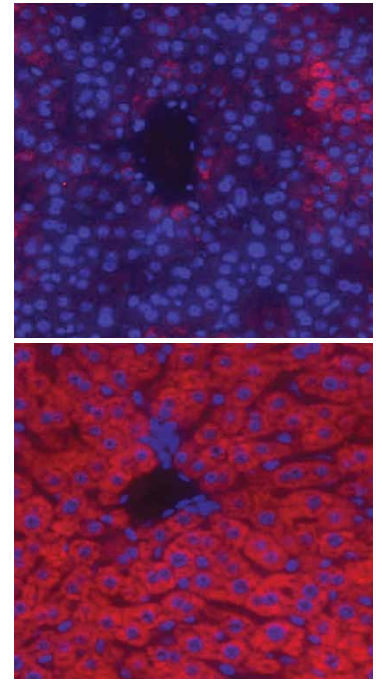
Sengupta compared the ketone production of old and young mice during fasting. While activating mTORC1 during fasting reduced ketone production in the young mice, ketone levels in the old mice stayed at their same low levels. Sengupta then decided to inhibit mTORC1 activity in very young mice and track ketogenesis over time. As these mice aged, they did not experience the normal drop in ketone production, confirming that continual inhibition of the mTORC1 pathway prevents the aging-induced decline in ketogenesis.

So, could suppression of mTORC1 be akin to a drink from the fountain of youth? Many have suggested that that the drug rapamycin, an mTOR inhibitor used to treat cancer and to prevent organ transplant rejection, might have anti-aging properties.

“Rapamycin definitely has lots of anti-aging hype,” says Sabatini. “Having worked with that molecule a lot, I’m not sure I would take it for long periods of time just in the hope of slowing down aging.”

Instead Sabatini is focused on a host of more practical, though less provocative matters, including why ketogenesis is suppressed by aging and how aging seems to activate mTORC1.

“We know enough of what’s upstream of mTORC1 that I think now we can test different components and ask which one is sort of acting funny in its aged state.”



Cells sense nutrients through a signaling pathway regulated by mammalian target of rapamycin (mTOR). In livers of mice fasted for 24 hours (top), the activity of mTORC1 (red), a protein complex containing mTOR, is almost undetectable; subsequent feeding results in high activation of mTORC1 (bottom). For visualization purposes, the cells’ DNA was also stained (blue).

HONORS AND AWARDS



Whitehead Member Susan Lindquist receives the National Medal of Science from President Barack Obama in the East Room of the White House. Lindquist was one of 10 scientists to receive the medal in 2010.

IAIN CHEESEMAN

In early April, Whitehead Member Iain Cheeseman was awarded a Young Investigator grant from the Human Frontier Science Program (HFSP). The grant will fund a team, including Cheeseman, to study how a structural scaffold of proteins, called the spindle matrix, prepares a cell for cell division. The collaboration is headed by Helder Maiato, from the Institute for Molecular and Cell Biology at the University of Portugal, and also includes Matthias Weiss, from the Cellular Biophysics Group at the German Cancer Research Center in Heidelberg, Germany. The team will receive \$350,000 per year for the next three years. Cheeseman is the first Whitehead researcher to be awarded the competitive Young Investigator grant. Founded in 1989 by an international group of scientists and politicians and headquartered in France, HFSP supports basic research on complex biological mechanisms through multiple grants and fellowships, including the Young Investigator grants.

In December, Cheeseman learned he would become the recipient of the 2011 R.R. Bensley Award, one of four Young Investigator Awards bestowed by the American Association of Anatomists (AAA). The Bensley award honors a cell biologist who has completed his or her

highest degree in the past ten years, advanced the field of anatomy, and published papers that substantially impacted his or her field. In announcing the award, AAA described Cheeseman as "...actively involved in pioneering the rapidly developing interface between [the study of proteins] and cell biology, which is likely to revolutionize the field."

GERALD FINK

Whitehead Founding Member Gerald Fink was awarded the 2010 Genetics Prize of The Peter and Patricia Gruber Foundation for his groundbreaking research in yeast genetics. Gruber Genetics Prize Laureates are chosen by a board of prestigious geneticists seeking to honor a researcher whose work "provides new models that inspire and enable fundamental shifts in knowledge and culture" and "whose contributions in their respective fields advance our knowledge and potentially have a profound impact on our lives." One of Fink's greatest contributions to the field of genetics is transformation, a revolutionary technique enabling the insertion of a gene from any organism into a yeast cell, causing the yeast cell to produce the protein coded by the inserted gene. This advance allows scientists to study specific genes and to produce large amounts of compounds used in vaccines, antibiotics, and even biofuels. Fink received the

prize, which includes \$500,000 and a gold medal, in November 2010, at the annual meeting of the American Society of Human Genetics, where he also gave a lecture. The inaugural Gruber Genetics Prize was awarded in 2001 to another Whitehead Institute Founding Member, Rudolf Jaenisch, for his work in creating the first transgenic mouse used to study human disease.

RUDOLF JAENISCH

In December, Massachusetts General Hospital (MGH) named Whitehead Founding Member Rudolf Jaenisch a recipient of the 2011 Warren Triennial Prize. By tradition, the prize is awarded to two scientists, and Jaenisch shares the prize with Kyoto University's Shinya Yamanaka. "We are delighted to be able to honor the groundbreaking work of Drs. Yamanaka and Jaenisch," says Daniel Haber, MD, PhD, chair of the MGH Executive Committee on Research. "Their research has opened up a new direction for the future of medicine." Awarded every third year, the Warren Prize, which includes a \$50,000 award, honors scientists who have made outstanding contributions in fields related to medicine.

SUSAN LINDQUIST

Whitehead Member Susan Lindquist received the 2010 National Medal of Science at a special ceremony at the White House in November. As a recipient of our nation's highest scientific honor, Lindquist was lauded "for her studies of protein folding, demonstrating that alternative protein conformations and aggregations can have profound and unexpected biological influences, facilitating insights in fields as wide-ranging as human disease, evolution,

and biomaterials." Lindquist was one of 10 scientists to receive the medal in 2010 and is now Whitehead Institute's second National Medal of Science recipient. Founding Member Robert Weinberg was so honored in 1997. Two current members of Whitehead's Board of Directors have also received the Medal: Phillip Sharp in 2004 and Robert Langer in 2006.

Her protein folding work has also earned Lindquist the prestigious Max Delbrück Medal. Named after physicist and biologist and Nobel Prize winner (1969) Max Delbrück, the medal has been awarded annually to outstanding scientists since 1992. Lindquist is the fourth Whitehead Member to receive the Max Delbrück Medal. Others include Rudolf Jaenisch (2006), Eric Lander (2001), and Robert Weinberg (1996).

Capping off a November to remember, Lindquist was awarded the Mendel Medal by the Genetics Society in the U.K. The Genetics Society recognizes distinguished geneticists for their lifetime achievements in genetics with the Mendel Medal. In bestowing the honor, Genetics Society President Veronica van Heyningen stated: "Susan Lindquist has produced groundbreaking work on how genes and their protein products interact with environmental changes. This is a most important area for many different types of disease from cancer to neurodegeneration. This interface may be one of the most likely to respond to novel drug development. Dr. Lindquist is the major pioneer in exploring this area."

In May, Harvard University awarded Lindquist an honorary Doctor of Science degree at its commencement exercises.

Lindquist, who received her PhD in biology from Harvard, was recognized both for her studies of protein folding and for her continuing investigations into the connections between genomics and medicine.

HARVEY LODISH

At the close of 2010, Whitehead Founding Member Harvey Lodish received the American Society of Hematology (ASH) Mentor Award, in recognition of "the significant impact he's made in the training and career development of many physicians and scientists in the field of hematology." ASH noted that Lodish, who received the award in the Basic Science category, provided guidance and support to more than 150 students and postdoctoral fellows since joining the MIT faculty in 1968. The society added that many of Lodish's trainees have attained successful academic careers, leadership roles in their fields, and prestigious awards, including a Nobel Prize and two Lasker Awards.

Whitehead Member Peter Reddien's lab studies planarians, small flatworms with the amazing ability to regenerate any tissue in the body. Here, the anatomy of an adult planarian is highlighted, including the nervous system (magenta), intestinal cells (green), and the muscular pharynx (yellow).



Principal
INVESTIGATORS

David BARTEL

PREDICTING THE PAIRINGS AND POTENTIAL OF microRNAs



ON THE VERGE...

"We're on the verge of knowing all the microRNAs that are consequential in humans and model animals, and now we're working on a more complete understanding of the mRNAs that they pair with. Knowing both the miRNAs and the 3' UTRs of each species helps us to more accurately predict which microRNAs are influencing which genes." **David Bartel**

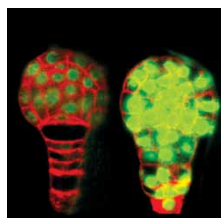
The Bartel lab continues to enhance our understanding of the important roles that RNA snippets known as microRNAs have played throughout evolution, the impact they have on biological processes via regulation of gene expression, and the precise ways in which they exert their effects.

Scientists have known that microRNAs influence gene function by targeting messenger RNAs (mRNAs) of protein-coding genes. mRNAs carry the information for protein production. Generally, the result of an interaction between microRNA and mRNA is decreased protein production, but whether this result in mammals is achieved by using the mRNA less efficiently or by degrading the mRNA has been an open question. Employing a technique known as ribosome profiling, the lab discovered that most of the drop in protein production is attributable to a drop mRNA levels.

The finding provides greater insight into microRNA behavior in mammals while validating an approach for future studies. Bartel notes: "We're more confident that you can learn which genes are regulated by a microRNA simply by looking at effects on mRNA levels, which is much easier to do than looking at effects on protein levels."

In other work, the lab conducted a comprehensive search for microRNAs in mice. By sequencing 60 million small RNAs, researchers confirmed the authenticity of nearly 400 genes and identified more than 100 previously unknown microRNA genes. Hundreds of proposed microRNAs were not found, and follow-up experiments confirmed that nearly all of these missing microRNAs were not authentic. The findings, which indicate that some older estimates of the number of microRNA genes were too high, bring a new level of confidence to the accuracy of the catalog of mouse and—by extension—mammalian microRNA genes.

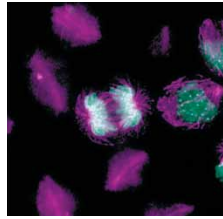
The lab also recently devised a high-throughput method to identify the terminal end of mRNAs, known as the 3' untranslated region or 3' UTR. They applied their method in the worm *C. elegans*, which has long been a model for the study of higher organisms. Because microRNAs and other gene-regulation molecules often interact with the mRNA 3' UTRs, identifying the 3' UTRs is important for predicting which mRNAs are being regulated and how.



During embryonic plant development, microRNAs prevent early gene expression and enable pattern formation. In these embryos, the target of microRNA 156 is labeled green. In the normal plant (left), most of the target is repressed, whereas a mutant (right) that cannot make microRNAs has an overabundance of the target.

Iain CHEESEMAN

CHROMOSOME SEGREGATION AT ITS CORE



During cell division, protein filaments, called microtubules (purple), latch onto chromosomes (green) by attaching to the kinetochores (light blue), which are partially integrated into the chromosomes. Once properly affixed to the kinetochores, the microtubules pull the chromosomes to opposite sides of the cell.

ON THE VERGE...

"In the lab we've defined key unanswered questions or challenges. These are larger, overarching issues that maybe we'll answer in a couple of years, or maybe it will take us 15 years. I think we're on the verge of solving the first challenge on our list, which is how do you direct the assembly of a kinetochore anywhere on the chromosome?"

Iain Cheeseman

The ultimate goal of cell division is to end up with two cells containing identical copies of the parent cell's DNA. The risks are high during this complicated process: if a cell has too many or too few copies of a gene, it could die or become cancerous. Upon entering cell division, the parent cell replicates its DNA and then bundles it into identical, tightly packed sister chromatids that are glued together, forming an X-shaped chromosome. During cell division, protein filaments reach out from opposite sides of the cell and try to grab onto the sister chromatids at their junction, called the centromere. These filaments, known as microtubules, eventually latch onto the kinetochore, a protein complex that is partially integrated into the centromere. Once attached, the microtubules pull on the sister chromatids until the microtubules break the glue holding the chromatids together and drag the chromatids to opposite ends of the parent cell.

Yet little is known about one of the most critical parts of the process: how a cell "knows" that a pair of sister chromatids are attached correctly to properly positioned microtubules. The Cheeseman lab recently demonstrated that an enzyme known as Aurora B plays a key role in this process. Aurora B resides within the centromere and adds phosphate molecules to the kinetochore if it is within a certain distance from the enzyme. When microtubules attach to a pair of sister chromatids, they tug the chromatids in opposite directions. The increased tension pulls part of the kinetochore away from Aurora B. The harder the filaments pull, the farther the kinetochore is lifted out of Aurora B's phosphorylation range. At the same time, another enzyme, called protein phosphatase 1 (PP1) removes the kinetochore's phosphates outside of Aurora B's range. The presence of a small number of phosphates indicates that the microtubule/kinetochore attachment is strong, while too many phosphates signal the microtubule to detach and try again.

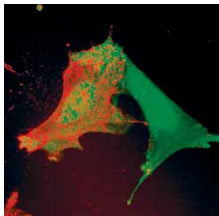


Gerald FINK

CRACKING THE GENOMIC CODE IN THE ABSENCE OF CODING

ON THE VERGE...

"With the aid of developing technologies, I think we really are on the verge of understanding how genomes evolve and what forces, beyond viruses and retrotransposons, are at work. We know the roles of non-coding RNAs are expanding, but are there any general rules involved? How do you gain genes and lose them? And what are the selective pressures that mold our genomes? These and other questions remain." **Gerald Fink**



Animals have proteins on the surface of their white blood cells that recognize infectious pathogens and trigger an immunological response. The mouse fibroblast on the left has been altered to express the protein *dectin-1* (red) on its surface, which is crucial for fungal recognition, while the cell on the right lacks *dectin-1*.

How much information is in our genomes? In his quest to answer this question, Gerald Fink has uncovered non-coding RNAs (ncRNAs) that don't specify a protein. Although it has been known for some time that there are 6,000 genes in yeast, each of which specifies a protein-encoding RNA, the Fink lab has identified ncRNAs, molecules that do not code for proteins but instead serve to regulate gene expression. These ncRNAs have now been discovered in organisms from bacteria to humans.

The Fink lab recently identified two such ncRNAs that control expression of a single gene that controls whether the yeast forms spherical cells or morphs into thread-like filaments. Fink suspected that these ncRNAs were acting like a toggle to turn the adjacent filamentation gene on or off without any fundamental change to the underlying DNA sequence. This work implicates ncRNAs as molecules key to epigenetic control in which cells with the identical DNA sequence may stably express the same gene differently.

Fink is now collaborating with a physicist at MIT who has developed imaging techniques capable of visualizing these ncRNA molecules in a single cell. These novel imaging techniques have enabled Fink and colleagues to show that the ncRNAs are in the nucleus where they contribute to switching between the yeast and filamentous form by modulating transcription factor localization.

Fink says that the ncRNAs may promote the formation of loops in the DNA that alter the expression of the adjacent gene. "We think these non-coding RNAs stabilize the ability of non-coding regions to come together to turn genes on," he notes. "Some loops may enhance the expression of a gene, whereas other loops may suppress expression. We are pretty sure that this looping promotes gene expression, or suppresses it, by associating factors that bind DNA at otherwise distant sites."

The lab has also investigated the mechanisms that silence retrotransposons, "selfish" DNA parasites that move about the genome and wreak havoc by inserting themselves into important genes. RNA interference (RNAi), which recognizes specific structural features of these retrotransposons, provides a defense against these inconsiderate invaders. However, baker's yeast, *Saccharomyces cerevisiae*, does not have the RNAi defense system, which has prompted the question: How could an organism evolve without this protection? Fink, working with Whitehead Member David Bartel, has uncovered a second system in yeast and many other RNAi-less organisms that would kill any yeast strain that maintained RNAi. Thus, yeast is in a precarious state, unable to harbor the RNAi system and therefore, susceptible to genome instability from retrotransposons.

Mary GEHRING

GETTING TO THE ROOT OF EPIGENOMIC CHANGE

ON THE VERGE...

“We know that gene imprinting is one consequence of the large-scale epigenomic changes that occur during seed development and formation of gametes. But I think that these epigenetic changes probably have other functions that we’re currently unaware of. I hope we’re on the verge of understanding how the genome of the egg and sperm cells is epigenetically altered and its functionality changes. As of now, our understanding of these epigenetic questions has just scratched the surface.

Mary Gehring

Plant biologist Mary Gehring is focused on epigenetics—the study of changes in phenotype and gene expression caused by mechanisms other than alterations to an organism’s underlying DNA sequence. Such changes, which constitute the epigenome, can be passed from one generation to the next. One epigenetic modification is the addition of a methyl chemical group to particular genes in a process called DNA methylation, which can subsequently control the expression of certain genes.

Until recently, researchers have studied a developing plant’s epigenome by processing the entire plant, thereby muddling together all of the cell types and their respective epigenetic differences. To identify methylation differences in specific cells, like egg and sperm, the Gehring lab is creating *Arabidopsis* plants that have chemical tags tacked onto only the cells selected for study. By sorting for the tagged cells and analyzing them, Gehring is determined to elucidate how the plant epigenome changes from fertilization through development.

Gehring’s lab is also looking at a particular aspect of the epigenome that is linked to an organism’s parents. During fertilization, the plant seed receives a copy of each gene from the mother and a copy from the father. In flowering plants and mammals, the expression of certain genes is determined by whether the copy of the gene, called an allele, comes from the father or mother. In some cases, only the mother’s allele is expressed, and in other cases, only the father’s. This phenomenon is called genomic imprinting. In earlier work, Gehring identified about 200 potentially imprinted genes in *Arabidopsis* seeds. Now her lab is trying to discern what role these genes may play in seed development, how imprinting is conserved in different *Arabidopsis* strains and closely related species, and what epigenetic mechanisms control gene imprinting.



With a rapid life cycle and one of the smallest plant genomes (only 157 million base pairs; humans have more than 3 billion base pairs), *Arabidopsis thaliana* is exceptionally well-suited to being a genetic model organism. Gehring is creating transgenic *Arabidopsis* lines whose reproductive cells are labeled with a chemical tag called biotin.

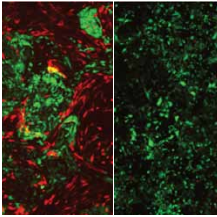
Piyush GUPTA

STEM CELLS FOR BETTER AND FOR WORSE

ON THE VERGE...

"We now have tools that enable us to systematically identify the genetic networks that control normal stem cell and cancer stem cell biology. I think we are going to be in a position where we will be able to probe for the genes involved in these processes in a much more comprehensive way. And we're looking forward to the time when we have a better picture of how those genes are working to control stem-differentiation decisions."

Piyush Gupta



The Gupta lab identified a small molecule that kills stem-like cells (red), leaving non-stem-like cells (green) unharmed. Before the molecule is added to this sample of breast epithelial cells, both cell types flourish (left). Six days later, only non-stem-like cells remain (right).

Piyush Gupta studies the Dr. Jekyll and Mr. Hyde personas of stem cells: the Jekyll-like normal stem cells that maintain our blood, intestines, skin, and myriad other tissues; and the Hyde-like cancer stem cells that drive tumor formation, resist treatment, and promote metastasis.

Little is known about cancer stem cell biology, especially how cancer stem cells differ from more differentiated cancer cells. The Gupta lab is identifying the genes that are essential for cancer stem cell maintenance and survival by exploiting recently-discovered small molecules that target cancer stem cells but not differentiated cancer cells. Using RNA interference (RNAi) to identify genetic interactions with these selective molecules, the lab is learning more about the genes that maintain cancer cells in a stem-like state, preventing them from differentiating into more specialized states. Some of these genes could also control normal stem cell biology.

The Gupta lab is also analyzing normal adult stem cells, specifically in epithelium. This cell type lines the outer surfaces of many tissue types in the body. Using RNA interference (RNAi) screens, the lab is mapping the genetic networks that control normal stem cell biology. Gupta's lab will then contrast the genes important for cancer stem cell biology with the genes important for normal stem cell biology to gain a greater understanding of both cell types.

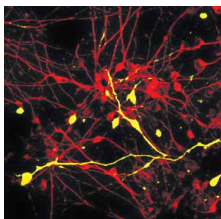
Rudolf JAENISCH

HOLDING CELLULAR REPROGRAMMING TO A HIGHER STANDARD

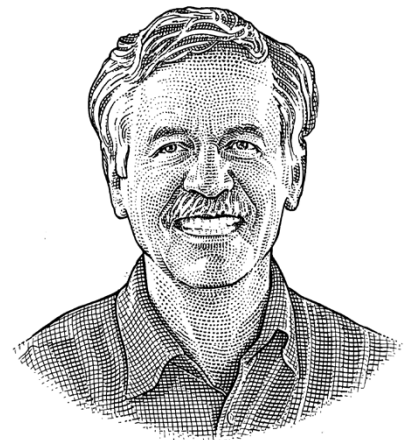
Both embryonic stem (ES) cells and induced pluripotent stem (iPS) cells—adult cells that have been reprogrammed to an embryonic stem-cell-like state—have attracted much attention because of their potential to mature into virtually any cell type in the body. Because ethical and legal issues have hampered human ES cell research, mouse cells have provided a more viable platform for ES cell studies. However, mouse and human ES cells differ in a number of significant ways, raising the very real possibility that breakthroughs in mouse stem cell science simply won't be reproducible with human stem cells. Human ES and iPS cells have different sets of expressed genes and depend on different signaling pathways for growth and differentiation than do mouse ES and iPS cells, making genetic manipulation and the prevention of differentiation (maturation beyond the base pluripotent state) more difficult.

The Jaenisch lab has identified a method that pushes human ES and iPS cells back to a more stable, “naïve” state, which is similar to that found in mouse ES and iPS cells. After bathing established human ES and iPS cells in a cocktail of four molecules, the human cells become more like their mouse counterparts, both in appearance and biochemistry. Considering that the differences between human, naïve human, and mouse ES and iPS cells could affect how these cells are used for disease research and therapy, the Jaenisch lab is further analyzing these various cell states.

To study genetic diseases, researchers also need the ability to efficiently change specific genes in human ES and iPS cells. The Jaenisch lab continues to develop and refine tools for manipulating genes in precise fashion, which should help accelerate disease research.



iPS cells are quickly becoming invaluable tools for genetic disease research, especially for studying inaccessible diseased cells. Using iPS cells generated from Parkinson's disease (PD) patients' skin cells, the Jaenisch lab has created dopamine-producing neurons (yellow), the cells that die deep within the brain and cause PD. Surrounding neurons are stained red.



ON THE VERGE...

“Making good controls for studying genetic diseases in patient-derived iPS cells is a key issue. Right now the control is from a healthy individual, which is genetically very different from the patient. When you see a difference you don't know if it's due to the disease or some other issues. Our goal is to make pairs of ES or iPS cells that differ exclusively at maybe the one disease-causing nucleotide. This, I feel, will be the new standard of the field.”

Rudolf Jaenisch

Susan LINDQUIST

THE NERVE TO SIMPLIFY THE STUDY OF COMPLEX DISEASES



ON THE VERGE...

"With the A-beta model of Alzheimer's disease (which has been validated in mice, rats, and *C. elegans*), I think we're really on the verge of something quite extraordinary. The yeast cells are providing us with a high-throughput method to find compounds to reduce A-beta toxicity. It's incredibly exciting, and we're already beginning to see results."

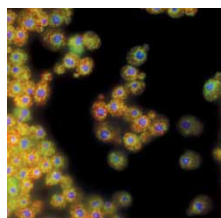
Susan Lindquist

Armed with simple baker's yeast, a lab full of brilliant young researchers, and the courage of her creative scientific convictions, Susan Lindquist is changing the way we look at and perhaps combat some of our most dreaded neurodegenerative diseases.

Disorders such as Huntington's disease, Parkinson's disease, multi-system atrophy, and dementia with Lewy bodies are characterized by protein-misfolding, resulting in toxic accumulation of proteins in the cells of the central nervous system. Lindquist has devised a platform using yeast cells as living test tubes in which to study protein folding, function, trafficking, and aggregation in models of these and other diseases.

Owing to its simplicity, genetic manipulability, and rapid growth, yeast, Lindquist says, is an "unrivaled toolkit" in this domain. And she's proven it. She has genetically modified yeast cells to over-produce the protein alpha-synuclein, whose aggregation plays a causative role in Parkinson's disease. This yeast platform not only allows the lab to study the cellular effects of high levels of alpha-synuclein, but, significantly, it also enables scientists to explore methods, including chemical intervention, to rescue cells from alpha-synuclein toxicity. The lab has been using the yeast model to conduct high-throughput screens for potentially beneficial compounds. In a screen of roughly 150,000 candidates, scientists identified four compounds capable of restoring normal cellular functions, not just in the yeast model of Parkinson's, but in rat and mouse models as well—an indication that these effects may be seen in human cells, too.

Lindquist is now setting her sights on Alzheimer's disease, deploying the yeast system to investigate aggregation and trafficking of the protein amyloid beta (A-beta). Plaques of A-beta in the brain are hallmarks of Alzheimer's disease. By inserting into yeast a gene coding for the A-beta peptide, the lab has been able to reproduce A-beta in yeast cells and has observed that its movement replicates that seen in human cells. The lab is now in the midst of screening 350,000 compounds for their effects on A-beta. Although the work is preliminary, at least one compound appears to rescue mouse neurons exposed to A-beta.



Using baker's yeast (*Saccharomyces cerevisiae*), Lindquist is investigating the aggregation and trafficking of the protein amyloid beta (A-beta), which is implicated in Alzheimer's disease. In these yeast cells, A-beta (purple) is expressed in the yeast secretory compartment.

Harvey LODISH

ADDRESSING A RATHER ANEMIC PERFORMANCE

ON THE VERGE...

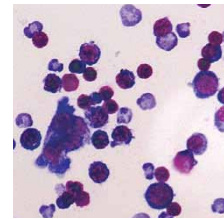
"We're on the verge of starting clinical trials in Singapore. This is based on the work that we published a few years ago, where we identified a cocktail of five growth factors that could stimulate human cord blood stem cells to divide in culture and make as many as 20-fold more stem cells. Now, our collaborators are scaling up from 15-microliter cultures to 150-milliliter cultures of cord blood. That's more than a thousand-fold difference. **Harvey Lodish**



By studying diseases of the blood, the Lodish lab is revealing the basic biology of red blood cell production and producing research that could lead to several potential new therapies. To this end, the lab recently investigated two blood diseases in two very different ways: by sequencing patients' DNA to identify the genes they have in common and by analyzing the mechanism of action of current drug therapies.

Sickle cell anemia patients fare better if their red blood cells contain elevated levels of fetal hemoglobin. To find the genetic cause of abnormal hemoglobin production in certain patients with an extra copy of part of chromosome 13 (known as partial trisomy 13) the Lodish lab analyzed the triplicated portions of these patients' genomes. The lab determined that the genes of two microRNAs, which are tiny snippets of RNA that fine-tune the activity of their target genes, were being overexpressed in the patients. These microRNAs, 15a and 16-1, target the gene for the protein MYB, which normally silences the production of fetal hemoglobin. In the partial trisomy 13 patients, the overexpression of microRNAs 15a and 16-1 suppress MYB expression too much, allowing continued production of fetal hemoglobin.

In the case of EPO-resistant anemias, the Lodish lab looked at the therapy currently used to treat these diseases. EPO, which is short for the drug erythropoietin, stimulates red blood cell production and is a highly effective therapy for many types of anemia. However, some anemias, including those caused by certain genetic diseases, trauma, sepsis, kidney dialysis, and chemotherapy, are not affected by EPO. Instead, corticosteroids are often prescribed for certain EPO-resistant patients. The Lodish lab identified the early red cell progenitors affected by the corticosteroids and screened successfully for small molecule drugs that interact similarly with these progenitors. Because these small molecule drugs are capable of increasing red blood cell production up to 100 times when used in conjunction with corticosteroids, they may represent promising therapies for EPO-resistant anemias.



In this slide of fetal mouse blood being studied in the Lodish lab, red blood cells (purple) are seen extruding their nuclei (magenta). Maturing mammalian red blood cells undergo this process to create more cellular space for the hemoglobin molecules they carry.

Terry ORR-WEAVER

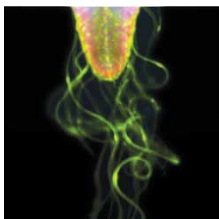
WHEN THE COPY MACHINE GOES HAYWIRE



ON THE VERGE...

“This work—which has really been made possible by the unique blend of collaboration and shared technology resources here at Whitehead—has put us on the verge of understanding how developmental signals control genome duplication. This opens the door to determining what’s different in the developmental regulatory steps that are causing the onset and progression of cancer”

Terry Orr-Weaver



Sub-perineurial glia nuclei (green) in the ventral nerve cord and peripheral nervous system appear to dangle from this larval fruit fly brain. These glia cells, which act as support cells for neurons (nuclei labeled pink), may have extra gene copies to meet high demand for protein production or to increase cell size.

Terry Orr-Weaver has long been determined to understand exactly what controls DNA replication in a developing organism. This is no trivial pursuit, as DNA replication during development can cause variations in gene copy number, and such copy number variations can be found in a number of cancers.

In a body of work more than two decades in the making, Orr-Weaver has made significant progress—much of it coming in the past few years as the introduction of novel genome sequencing technologies synergized powerfully with traditional genetic approaches. Working with the fruit fly *Drosophila*, the Orr-Weaver lab found regions of the genome with over-replicated genes, discovering at the same time multiple factors involved in controlling replication. In other words, loss of regulation could occur in many different ways. The finding suggested that a variety of defects can lead to increased gene copy number in human cells that become cancerous.

More recently, the lab has discovered what’s happening on the other side of the equation to suppress replication. In a series of experiments, researchers have found in developing flies regions of decreased DNA copy number—that is, regions of under-replication—that vary by tissue type. These examples have permitted Orr-Weaver and colleagues to define chromatin states that repress DNA replication and surprising cases in which gene expression occurs despite blocks to replication.

Members of the lab have also performed the first genome-wide mapping of binding sites for the origin recognition complex (ORC), a bundle of proteins that promotes the initiation of DNA replication in differentiated metazoan cells. By focusing on known regions of under-replication, the lab discovered a distinct absence of ORC binding, indicating that in such areas, replication never really gets started. Then the researchers found something else: a protein that acts to stop replication in its tracks.

“For the first time, we’ve defined what the origin of replication is in differentiated tissues, and what’s involved in activating and shutting off these origins,” says Orr-Weaver. “There’s tight developmental control over which parts of the genome get replicated. It matters to the genome to have regions not replicated in certain cell types, and to control the time at which distinct parts of the genome are duplicated in dividing cells.”

Orr-Weaver notes that over- or under-replication can create fragile genomic regions vulnerable to breaks. Such vulnerability has consequences for tissue and organismal function and, ultimately, viability.

David PAGE

EXPOSING THE CHROMOSOMAL BATTLE OF THE SEXES

ON THE VERGE...

"In mammalian reproductive biology, most labs study either the testis or the ovary, in either adult or fetus. We're foolish enough to try it all, but having adopted this strategy has put us on the verge of enormous insights and meaningful connections between fetal germ cell development and the factors involved in the processes of making eggs and sperm." **David Page**

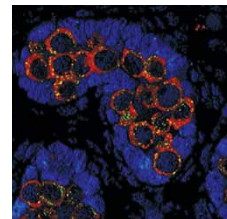


From tracing the evolution of sex chromosomes to revealing the intricacies of the origins of sex determination, David Page has spent nearly three decades exploring the myriad forces and defining moments that have shaped who we are and how we got here. Along the way, he's taken more than a little pleasure in overturning conventional wisdom.

Page discovered large, mirror-imaged genetic sequences on the human Y chromosome that enable the Y to maintain its genetic health—and ensure its own survival—by swapping genes with itself. The finding should have dispelled the then-popular notion that the Y was losing genes at a rate that would lead to its eventual extinction. Somewhat surprisingly, the “dying Y” theory persists, but Page’s ongoing work is making it increasingly uncomfortable for those who cling to it.

The lab has been conducting a series of cross-species comparisons of Y chromosomes that confirm that this oft-maligned chromosome is alive and well and here to stay. A recent examination of the human and chimpanzee Y chromosomes shows that both are evolving more quickly than the rest of their respective genomes. A comparison of the human Y chromosome and that of the Rhesus monkey now indicates that gene loss on the human Y actually ceased some 25 million years ago. And, the lab is planning soon to unveil the sequence of the mouse Y chromosome, a remarkably large chromosome so filled with surprises that Page expects it to “reframe the debate for the rotting Y crowd.”

Not to be overlooked is the lab’s ongoing study of germ cells, unique among all other cells in their ability to halve their chromosomes via meiosis. Page has known for several years that the gene *Stra8* is a key player in meiotic initiation, but he has often spoken about “expanding its job description.” The lab has recently done just that, finding that *Stra8* also promotes stem cell differentiation during the highly complex process of sperm production.



In addition to studying the Y chromosome, the Page lab investigates the production of sperm cells. This image of embryonic mouse testes highlights two proteins essential for spermatogenesis, MILI (green) and Mvh (red), specifically expressed in the cytoplasm of the germ cells, when the cord-forming Sertoli cells (blue) that support germ cell development enclose them inside the cord.

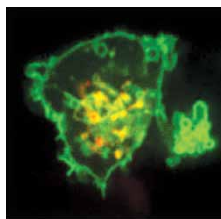
Hide PLOEGH

CREATING THE TOOLS TO TRACK INFECTIOUS PATHOGENS

ON THE VERGE...

"Synthetic methods are increasingly commonplace in biology, ranging from the generation of small molecule tool compounds to the synthesis of entire genomes. Clever exploitation of what nature has to offer and what we can make in the laboratory places us on the threshold of a new biology."

Hide Ploegh



To notify the immune system that they are under attack, cells present on their surfaces bits of their invaders using major histocompatibility complex (MHC) molecules. Usually, MHC II molecules present their invader cargo on the surface for a limited time and are recycled. But in this mouse cell, mutant forms of MHC II (green) remain at the cell surface, while wild type MHC II (red) are being recycled.

The Ploegh lab has seen exciting new developments in the areas of mouse models for infectious disease. Working with the Jaenisch lab to produce cloned mice from nuclei of antigen-specific lymphocytes has dramatically accelerated the production of transnuclear mice with properties suited for intense scientific exploration. Ploegh is now using these models to study T-cell development and to track tumor-specific T-cell responses in ways not previously possible.

The lab also borrows heavily from the world of chemistry to produce new affinity handles to facilitate isolation of scarce proteins under mild conditions, with one of the prime targets being the enzymes and substrates of the so-called ubiquitin-proteasome pathway. The Ploegh lab simultaneously examines this pathway through the use of engineered enzymes that act on ubiquitin-modified proteins. In so doing, the lab has been able to illuminate aspects of protein quality control in the endoplasmic reticulum at unprecedented resolution. Beyond using fluorescent proteins such as GFP (green fluorescent protein) to study cellular activity, the lab continues to develop alternative methods of protein labeling, notably through use of sortase-catalyzed reactions. Using the sortase reaction, the lab has achieved site-specific and quantitative labeling of a large variety of substrates with only minimal modification to a protein of interest. Ploegh and colleagues have applied these methods to the production of labeled bacterial toxins to determine how these invaders actually gain entry to the cells they target.

Ploegh's lab has also been applying a strategy developed by former Whitehead Fellow Thijn Brummelkamp to screen human haploid cells to identify host factors essential for bacterial toxin binding and trafficking. Ploegh maintains that his combination of chemistry-based approaches with more commonly used cell biological and biochemical techniques continues to be a fruitful strategy to explore host-pathogen interactions, which remains a core interest for him and the members of his lab.

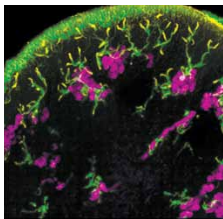
Peter REDDIEN

THE WHOLE FROM SOME OF THE PARTS

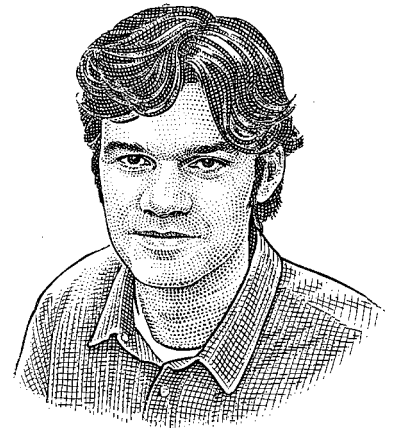
With its endearing, crossed-eyed appearance, the planarian (*Schmidtea mediterranea*) has been the darling of scientists studying regeneration for more than a century. These tiny flatworms can rebuild themselves from a sliver of tissue and regrow missing heads or tails, feats that humans and other advanced organisms cannot perform. By cracking the biochemical underpinnings of planarian regeneration, researchers hope to understand how similar systems in humans could be tapped for regrowing our own tissues.

The Reddien lab recently investigated one of the first steps in the regeneration process that occurs immediately after injury. According to their work, once the animal is wounded, stem cells throughout the planarian's body respond with a rapid burst of cell division. Then, those cells travel to the wound site, where they are triggered to mature into the missing tissue. The migration and maturation occur only when a piece of tissue is missing, and the Reddien lab is determining how the planaria distinguishes between—and responds appropriately to—a simple wound and the loss of tissue.

The lab has also identified a gene essential for planaria regeneration. This gene, called CHD4, is related to genes active in human embryonic stem cells and stem cells in other organisms. When CHD4 is turned down, regeneration stalls because the planarian's stem cells fail to mature into replacement tissue. The Reddien lab is now searching for additional genes that control the transition from the stem cell state to mature, specialized cells. As these genes are described, the Reddien lab will have a better understanding of the regeneration process in planaria and, perhaps by extension, in humans.



From a sliver of tissue, planarians can regenerate their entire bodies, including fairly complex organs. In the planarian excretory system, cilia in the flame cells (yellow) move fluids toward excretory pores on the skin by way of cilia-bearing tubules (green and yellow). A previously unknown accessory cell type has been identified (magenta).



ON THE VERGE...

“The number of potential physical insults to the animal that can occur is unlimited: a simple incision, regeneration of two-thirds of the body, elimination of a few neurons, etc. Regeneration requires tailoring the response to replacement of just the right missing things. It will be a long time before we understand this fully, but I think we'll begin to see some molecular insights into the decision-making processes happening at wound sites to elicit just the right regenerative response.” **Peter Reddien**

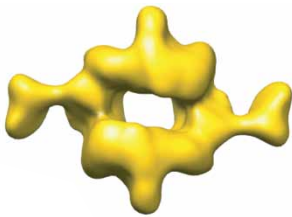
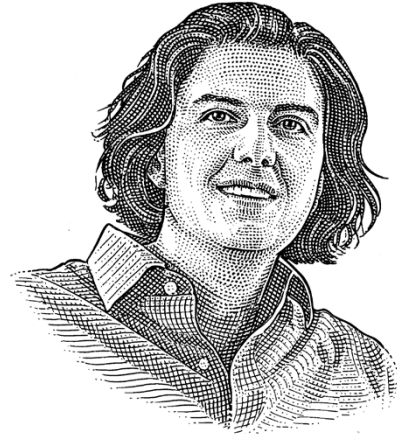
David SABATINI

THE METABOLICS OF AGING AND CANCER

ON THE VERGE...

"A significant portion of our genome, probably about 1,000 or 1,500 genes, represents metabolic enzymes. We've been trying to find if there are metabolic processes that are unique to cancer cells. If so, can those be targeted in a way that will be therapeutically beneficial? We have several very interesting findings that indicate that targeting cancer metabolism may harbor possible treatments."

David Sabatini



The mTORC1 protein complex is under intense study in the Sabatini lab. This computer-generated model of mTORC1 is based on almost 30,000 cryo-electron microscopy images of the molecule. mTORC1's overall dimensions are about 290 Å wide by 210 Å high by 135 Å deep. One angstrom (Å) is 1×10^{-10} meters.

As baby boomers reach retirement age, the media have been buzzing with news about our aging population. Wrinkles, gray hair, and forgetfulness are all considered inevitable consequences of growing older, but little is known about the aging process at the cellular level. Previous research has shown that when the cellular pathway known as mTOR (for mammalian target of rapamycin) is inhibited, a variety of animals, including worms, flies, and mice, tend to live longer. However, increased lifespan is considered a poor proxy for studying aging, as it is not always a cause of death.

One well-defined trait of aging is a decrease in ketogenesis—the conversion of fatty acids to vital sources of energy, called ketones, during sleep or other times of low carbohydrate intake. As animals age, their ability to produce ketones as a response to fasting declines. The cause of this phenomenon remains unknown. However, the Sabatini lab has found a connection between ketogenesis and the mTOR pathway. In mice, activating the mTOR pathway reduces ketogenesis, while inhibiting it maintains high ketone production, even as the mice age. However, inhibiting mTOR simply to slow age-related reductions in ketogenesis can have deleterious consequences, as mTOR is known to coordinate cell growth with nutrient availability and other growth factors, and its deregulation is often linked to diseases, including cancer.

In its role as an important sensor of amino acids and other nutrients, the mTOR pathway must interact in some way with nutrients at the molecular level. Finding that interaction point has been a “holy grail” for scientists studying mTOR. Recently, the Sabatini lab identified the “Ragulator” protein complex as interacting with mTOR and being vital for mTOR's registering and responding to amino acids. When the link between Ragulator and mTOR is partially lost, mice experience stunted growth, immunosuppression, and longer lifespans, all demonstrations of mTOR's activity in each of these functions.

Hazel SIVE

LIVING TEST TUBES AND THE ORIGINS OF AUTISM

What can developing zebrafish embryos teach us about the roots of autism? Far more than most would ever imagine, and Hazel Sive's lab is at the forefront of efforts to use the zebrafish as a living test tube in which to study the mechanisms underlying autism spectrum disorders.

Sive's research in this domain rests on the understanding that zebrafish have genes that correspond (that is, are homologous) to mental health disorder risk genes in humans.

The Sive lab is now focused on a region of the human genome identified by former Whitehead Fellow Mark Daly, now with the Center for Human Genetic Research at Massachusetts General Hospital. This region on chromosome 16 is susceptible to spontaneous deletions known as copy number variations, which greatly increase the risk for development of autism.

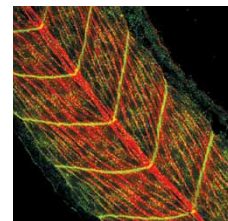
The region on chromosome 16 includes 25 genes. The Sive lab has identified 21 homologous zebrafish genes and is systematically evaluating their role during development of zebrafish embryos. The results have been remarkable. In complete loss-of-function studies, Sive has found that 20 of 21 gene "knockouts" affect brain development, causing abnormalities related to nerve growth, neuromuscular connections, and the shape of the brain itself. Strikingly, the abnormal fish can be repaired by introducing the human gene homolog, showing that the fish and human genes have similar functions. "Genes in this region are incredibly active during brain development, which may be why this is a target for development of mental health disorders," Sive says.

Because many autism patients are hemizygous in this susceptibility region—having only one genetic copy—Sive hypothesized that the region may contain "dosage sensor" genes, which must be present in the correct amount for normal brain development. "We developed an assay to find such genes, monitoring whether we see an abnormal fish embryo when 50 percent of the normal RNA is removed, the equivalent of losing one of the chromosomal copies," Sive says. "When 50 percent of the RNA is removed, only two genes give a phenotype, suggesting that they are the all-important dosage sensor genes."

Sive suggests that the genes involved may be exerting their harmful effects in something of a dose-dependent manner—the result of reduced protein production that is a consequence of copy-number variation. "Through our research in this area, we should be able to tell a human geneticist which genes to investigate further, as most pivotal in autism etiology."

ON THE VERGE...

"The synergy between human studies and fish is fantastic, and it puts us on the verge of making real and useful connections between animal tool systems and human clinical studies. There is a sense that translational research (that is, developing information or therapeutics directly relevant to patients) is often bad science. I realize now that the best translational research has at its core top-notch basic research whose fundamental observations can be applied to patient studies. We are learning from this approach in ways one never could through clinical studies alone." Hazel Sive



Within 24 hours after fertilization, this zebrafish embryo already has defined strands of the protein actin (red) and a well-organized pattern of focal adhesion kinase (green), an enzyme associated with cellular adhesion.

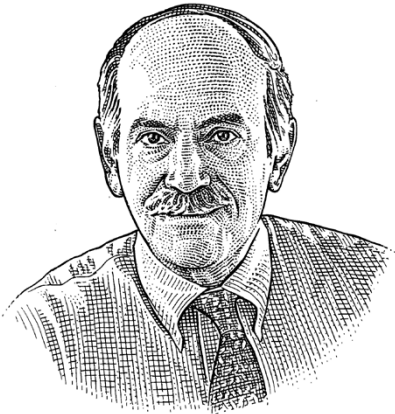
Robert WEINBERG

THE ONGOING WAR BETWEEN THE STATES

ON THE VERGE...

"We can now enumerate the signaling pathways that are required, in aggregate, to enable the cancer stem cells to maintain themselves. We might one day be able to make these cells differentiate, thereby eradicating the subpopulation of cancer stem cells. What we still don't know, however, is how to get drugs that cause this differentiation into a tumor.

Robert Weinberg

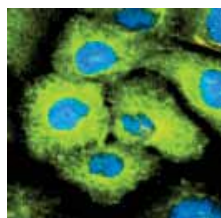


In its ongoing exploration of tumor invasion and metastasis, the Weinberg lab has turned its focus toward the mechanisms that control cell state and the surprising relationships between epithelial cells and stem cells—both normal and cancerous.

A few years ago, the lab found that some carcinoma cells can undergo a change that allows them to separate from the primary tumor and form a new tumor at a distant site in the body. They then made the surprising discovery that this change, known as an epithelial-mesenchymal transition (EMT), also confers a key property of stem cells: the ability to self-renew; this trait, in turn, enables a single cancer cell, to form an entire tumor. Having confirmed that the product of an EMT in a tumor cell is a cancer stem cell, researchers also found that the product of an EMT in normal epithelial cells is a healthy adult stem cell.

Since then, the forces that drive this shift between the differentiated, epithelial state and the undifferentiated, stem-like state have been under investigation. Researchers in the lab recently discovered that a subpopulation of cells in human breast tissue can spontaneously convert from the mature, differentiated state into stem cell-like cells. The discovery flies in the face of scientific dogma that states that differentiation is exclusively a one-way process—once cells achieve their end state, they cannot return to the flexible, stem-like state on their own. The researchers also observed that this spontaneous conversion can occur in malignant cells, creating new cancer stem cells. This unanticipated result suggests that therapies targeted at eliminating cancer stem cells may not suffice, as remaining tumor cells could “de-differentiate” to form more cancer stem cells.

In related work, the lab has identified cell signaling pathways that can induce an EMT and then maintain the resulting cells in their stem-cell state. The implications are many. Activating these pathways in normal epithelial cells may allow for the efficient production of large numbers of epithelial cells for use in regenerative medicine. Conversely, disrupting these pathways in tumors could result in the differentiation of cancer stem cells, removing their tumor-initiating capacity.



Cells that undergo an epithelial-mesenchymal transition (EMT) are capable of moving out of a tightly packed formation. Once these human mammary cells are pushed through an EMT, they no longer have the cytokeratins (green) typical of epithelial cells, but exhibit another marker found on mesenchymal cells.

Richard YOUNG

FINDING NEW FORMS OF EXPRESSION

ON THE VERGE...

"More and more members of the lab have come to realize that their research has implications for translational medicine. As we gain new insights into how the embryonic gene expression program is controlled, it's leading us to ever more insights into the mechanisms that underlie a variety of diseases, diseases that are a consequence of mutation. That in turn motivates us to think about new ways of developing therapies."

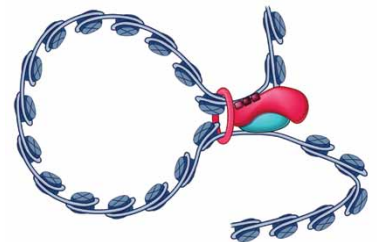
Richard Young



Packed in each human cell's tiny nucleus is two meters of DNA encoding the instructions for every cell in the body. But not all genes are expressed in all cell types—liver cells, for example, have different gene expression profiles than do brain cells or embryonic stem cells. Although scientists know what genes are expressed in most cell types, they do not understand how cellular operating systems function to express specific subsets of all genes in each cell type. However, the Young lab recently identified two key mechanisms by which cellular operating systems control gene expression.

For gene activation, regulatory factors and gene expression machinery, which are bound to two different parts of the DNA called the promoter and the enhancer, must come in contact. However, the promoter and enhancer may be located far away from each other, which had left scientists puzzled about how this machinery achieves the necessary proximity. Young's lab found that the DNA becomes looped, pulling those parts of the DNA together. To anchor the loop, a band of protein wraps around it. The process, though, is not perfect, and errors can have dramatic effects. Mutations in the band or the proteins that load it onto the DNA can cause multiple cancers and developmental diseases, including Cornelia de Lange syndrome, Opitz-Kaveggia (FG) syndrome, and Lujan syndrome.

The lab also pinpointed the important role that the transcription factor c-Myc plays in controlling gene expression in normal and in cancer cells. To initiate gene expression, a group of proteins attaches to the gene and begins transcribing it into RNA. The Young lab found that the process stalls until c-Myc kickstarts transcription again. Because c-Myc is very active in rapidly expanding cell populations, like those found in cancer, defining c-Myc's role in transcription is providing new insights into how normal cells transform into cancer cells and should help identify novel therapeutic targets.



For gene activation, transcription factors and gene expression machinery (RNA polymerase), bound to two different parts of the DNA called the promoter and the enhancer, must come in contact. A band of protein, called cohesin, holds the complex together, forming a loop in the DNA. Each cell has its own DNA loop profile dependent on which genes are active.

The Whitehead Fellows program offers a handful of the world's most promising young scientists a unique launching pad. With Institute support and freedom from teaching and other faculty responsibilities, Fellows pursue independent research programs with all the passion and creativity they can muster. Since inception, success has been a virtual certainty.

Whitehead FELLOWS

Yaniv Erlich



As the Andria and Paul Heafy Fellow of Whitehead Institute, Yaniv Erlich is bringing new efficiencies to the use of high-throughput genome sequencing in a search for rare genetic variants. Technically known as compressed genotyping, the approach—which Erlich has dubbed “DNA Sudoku”—combines sophisticated mathematical and statistical modeling with the latest technologies to identify rare genetic mutations in large cohorts.

Erlich’s method is born of the growing realization that large-scale genome sequencing projects (so-called genome-wide associated studies, or GWAS) are revealing little about the genetic causes of common diseases. Instead, it seems, rare variants are behind many diseases, fostering what’s known as the common disease-rare variant hypothesis. As the name implies, rare variants are extremely difficult to detect and require costly, large-scale sequencing of large numbers of genetic samples. Erlich is now validating DNA Sudoku as a practical alternative to GWAS for specific applications.

In other work, the Erlich lab is taking a multi-pronged approach to identifying the genetic causes of rare Mendelian disorders. By combining whole exome sequencing (which selectively sequences only the protein-coding regions of the genome) with established comparative techniques, Erlich has identified genetic mutations causing Joubert syndrome in Ashkenazi Jews and hereditary spastic paraparesis in a single Palestinian family.

Andreas Hochwagen

Gametes, including eggs, sperm, and yeast spores, are created during meiosis—which commences with a single cell containing two copies of each chromosome and concludes with gamete cells harboring a single copy of each chromosome. When the gametes fuse during fertilization, the two cells contribute their DNA to the offspring’s genome. Errors in meiosis can result in gametes with the wrong number of chromosomes and grave outcomes. Down syndrome, for example, is caused by an extra copy of chromosome 21, and an estimated one in six pregnancies is spontaneously aborted because of improper chromosome allotment.

Studying meiosis in yeast, Hochwagen’s lab has identified a network of checkpoints that pairs chromosome copies, helping to ensure that the resulting spores have the correct number of chromosomes. At the start of meiosis, the yeast cell’s 16 chromosome pairs align randomly and stick together. The lab recently found two enzymes, Mec1 and PP4, with opposing effects on a protein, Zip1, which controls chromosome stickiness. When Mec1 activates Zip1, formerly sticky chromosomes fall apart. PP4 suppresses Zip1, allowing the chromosomes to stick again. As the chromosomes toggle between states of stickiness, they jostle around, adhering to different partners until they eventually find their match. Then, Mec1 shuts down, leaving proper pairings intact. Later in meiosis, these pairs are pulled apart, sending one copy of every chromosome to each spore.



The Institute's formula for success has its share of constants and variables. From comings and goings to engaging and educating the public, the mission never changes, even if the methods and the players often do.

COMMUNITY EVOLUTION

Institute News

The Institute bid a fond farewell to three Whitehead Fellows during 2010. Special Fellow **Defne Yarar** accepted the position of Senior Scientist at Merrimack Pharmaceuticals, a privately held, Cambridge-based biopharmaceutical company developing therapeutics for the treatment of autoimmune disorders and cancer.

Yarar arrived at Whitehead in 2007, having earned her PhD at University of California, Berkeley, and having completed a stint as a postdoctoral fellow at The Scripps Research Institute in La Jolla, California. Her research here focused on the role the protein actin plays in maintaining the structure of cells. Actin is also an integral player in endocytosis, a process during which a cell's outer membrane folds inward on itself, engulfing external matter in a membrane-enclosed pouch. Endocytosis is the primary mechanism by which cells ingest nutrients and other macromolecules. Although she hadn't necessarily been contemplating a move to industry, she found Merrimack's academically oriented approach to drug development particularly appealing.

Whitehead Fellow **Thijn Brummelkamp**, who arrived in Cambridge in 2004 upon completion of his PhD at the Netherlands Cancer Institute (NKI), is now a group leader there. In early 2011, Brummelkamp returned to Amsterdam—with family and friends nearby—to run his own lab at NKI.

Brummelkamp's six years at Whitehead were both formative and productive. His studies of cancer genetics generally, and the role of RNA interference (RNAi) specifically, earned him a spot in 2005 on *Technology Review* magazine's closely watched "TR35", an annual roster of 35 individuals under 35 years of age whose innovative work in business and technology is having a profound impact on the world. Less than one year later, he was one of 15 young scientists in the country receiving the Kimmel Scholar Award from the Sidney Kimmel Foundation for Cancer Research. The award provided Brum-

During 2010, Whitehead Fellows (left to right) Defne Yarar, Thijn Brummelkamp, and Paul Wiggins left the Institute to take the next step in their respective scientific careers.



melkamp with \$200,000 in research support over a two-year period. Brummelkamp was tempted to stay in the MIT community but ultimately could not resist the chance to go home, at least for a few years.

In the fall of 2010, Whitehead Fellow **Paul Wiggins** received an appointment as Assistant Professor of Biophysics and Physics at the University of Washington in Seattle. A physicist by training, Wiggins came to Whitehead in 2005 and found himself alone in a population of biologists.

During his time here, he embraced both scientific disciplines in focusing on the physical structure of cells and tapping into the biology expertise around him to try to determine how the organization of chromosomes and the compacting of chromatin affect gene expression and cellular function. In Seattle, Wiggins is continuing to straddle both worlds and has established a lab with a 50-50 split between physics and bioengineering.

Public Outreach

Whitehead Institute's commitment to engaging and educating the public dates almost to its inception. Sensing a responsibility to inform on science policy when necessary and to connect with teachers and students regularly, Whitehead faculty are willing participants in ongoing outreach programs and one-off events that present unique opportunities to contribute to public discourse.

In March, the Institute, in conjunction with Biogen Idec and MIT, organized and hosted Johns Hopkins University's Center for Talented Youth Traveling Science and Technology series, "Biotechnology and Bioengineering." The program brought together 150 high school students and their parents from across the Northeast for a one-day examination of how scientists in top academic, research, and pharmaceutical settings are employing state-of-the-art biotechnology to tackle human disease.

Whitehead's core outreach programs—the spring lecture series for high school students and the seminar series for high school teachers—continued successfully in 2010. Approximately 80 teachers from high schools throughout Massachusetts attended monthly lectures as part of a series entitled *The Genetics of Human Disease*, which wrapped up in June. They returned in the fall for a new series, *Reassessing the Threat: Infectious Diseases in the 21st Century*, which explores the re-emergence of diseases once thought eradicated, the development of drug resistance, and the public health and policy implications associated with both phenomena.

Massachusetts public schools' spring vacation week saw more than 100 students from 30 high schools converge on the Institute for *The ABCs of Childhood Disease*. This three-day program featured lab tours, field trips to neighboring biotechnology companies and research facilities, and lectures from leading scientists on the development of novel approaches for diagnosing and treating a host of prevalent pediatric disorders, including childhood cancers, asthma, cystic fibrosis, and autism.



More than 100 scientifically inclined young men and women gathered at the Institute for the annual Whitehead Spring Lecture Series for High School Students. The 2010 program was entitled *The ABCs of Childhood Disease*.

Whitehead Institute recognizes with deepest gratitude those individuals, organizations, foundations, and corporations who lent their support so generously in fiscal year 2010, between July 1, 2009 and June 30, 2010.

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Sometimes beautiful scientific moments happen by accident. In this case, a bottle of 5 molar sodium chloride solution with a slightly loose cap resulted in evaporation and the formation of these intricate crystals.

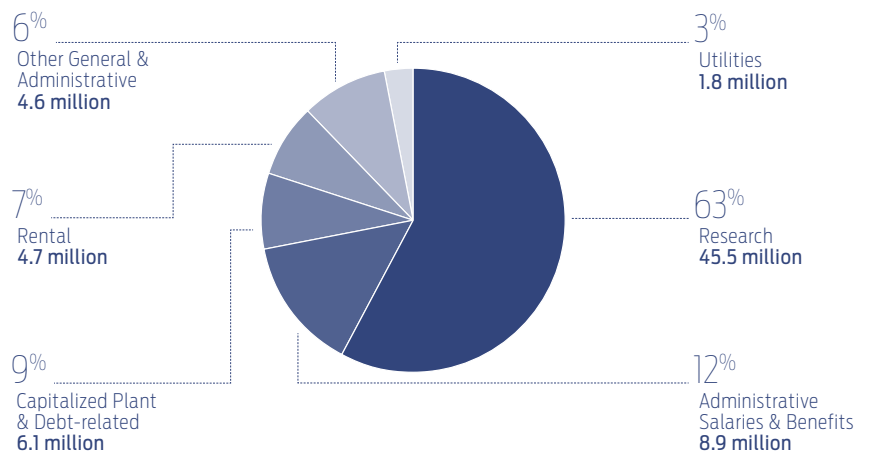


FINANCIAL SUMMARY

2009

Research
 41.5 million (58%)
 Administrative Salaries and Benefits
 9.8 million (14%)
 Capitalized Plant and Debt-related
 5.8 million (8%)
 Rental
 6.1 million (8%)
 Other General and Administrative
 6.3 million (9%)
 Utilities
 2.4 million (3%)
TOTAL
 71.9 million

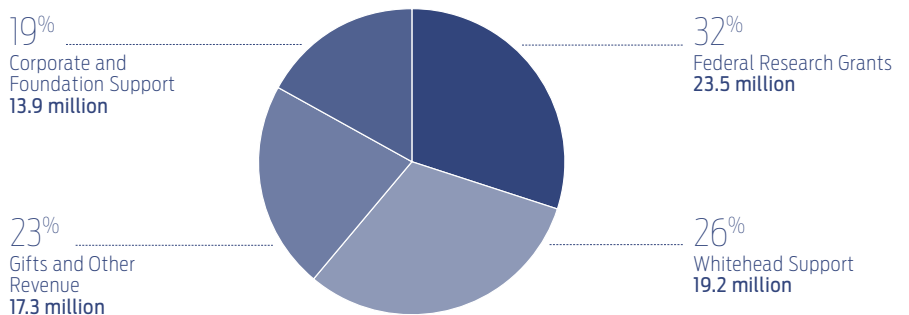
2010 EXPENDITURES & DISBURSEMENTS 2010 total \$71.6 million



2009

Corporate and Foundation Support
 12.4 million (17%)
 Gifts and Other Revenue
 16.5 million (22%)
 Federal Research Grants
 23.4 million (31%)
 Whitehead Support
 22.0 million (30%)
TOTAL
 74.3 million

2010 REVENUES & SUPPORT 2010 total \$73.9 million



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 2010 National Medal of Science (Lindquist), the 1997 National Medal of Science (Weinberg), eight members of the National Academy of Sciences (Bartel, Fink, Jaenisch, Lindquist, Lodish, Orr-Weaver, Page, and Weinberg), seven fellows of the American Academy of Arts and Sciences (Fink, Jaenisch, Lindquist, Lodish, Page, Ploegh, and Weinberg), five members of the Institute of Medicine (Fink, Jaenisch, Lindquist, Page, and Weinberg), four Howard Hughes Medical Institute investigators (Bartel, Lindquist, Page, and Sabatini), and one Howard Hughes Medical Institute early career scientist (Reddien).

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A researcher in Robert Weinberg's lab is studying skeletal muscle cells in order to investigate the role of different tissues in cancer progression. As the mouse muscle cells shown here differentiate, the skeletal muscle progenitors change color, transitioning from green to red to light pink. Resulting mature muscle cells fuse, creating long, tubular cells with multiple nuclei.

