THEN

Whitehead Institute

2009 ANNUAL REPORT

NOW

" I'm constantly amazed now at how much of development seems to be about nuance...We have made enormous progress in describing many of the genes required, but the magnitude of the challenge to get the real picture of what's actually occurring, and the subtleties involved, is something I didn't appreciate 20 years ago. "

CONTENTS

cover quote

Commentary from Whitehead Institute Member Hazel Sive contemplating the 2009 Annual Report theme, "What I thought then...What I know now." Her colleagues' perspectives on the same subject may be found beginning on page 11 of this report.

background image

During endocytosis, clathrin-lined pockets of a cell's membrane engulf exterior molecules, creating membrane-bound bubbles that shuttle the molecules into the cell's interior. Whitehead Special Fellow Defne Yarar is studying the activity of a clathrin protein shown here (stained green in this monkey kidney cell) and other molecules that associate with it, including one known as SH3D19 (stained blue).

credits

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Our Future Is Now

Breaking news on the opening page of a document as traditionally retrospective as an annual report may seem a tad unorthodox. However, shortly before this publication reached the presses, I was able to conclude a process whose outcome is so fundamental to the continued success of Whitehead Institute that I can think of no medium more appropriate for its announcement.

As supporters and friends of the Institute well know, my top priority as Director has been faculty recruitment. Last year in this space, I described a Board-approved plan for new faculty hires. Now, after an exhaustive search and thorough vetting of a remarkably deep pool of candidates, I'm delighted to inform you that two exceptionally creative young scientists will soon join our ranks. You'll learn much more about these talented individuals in the months and years to come, but allow me to introduce them briefly.

Plant biologist Mary Gehring comes here after completing her postdoc at Fred Hutchinson Cancer Center in Seattle. Mary earned her PhD at the University of California, Berkeley after receiving a BA in biology with highest honors from Williams College. Mary's arrival heralds a welcome return to our roots in plant biology. She'll fill our seventh-floor greenhouse with *Arabidopsis thaliana*, which she'll use as a model in which to study epigenetic reprogramming. Her work will provide valuable insights into this and other developmental processes not only in plants but in mammals as well, and will complement research occurring in several other Whitehead labs.

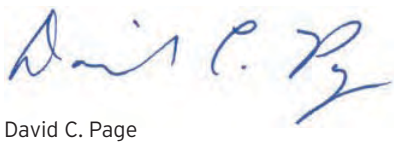
Mary's cross-country journey to Cambridge is considerably longer than that taken by cancer researcher Piyush Gupta. An honors graduate of the University of Chicago, Piyush earned his PhD under the tutelage of our own Bob Weinberg and became a postdoctoral research associate with our neighbor and former Whitehead Member Eric Lander at Broad Institute. Piyush is studying the genes and signaling networks that control both normal epithelial stem cells and cancer stem cells. His research will add to Whitehead's already considerable contributions in this arena.

In addition to these faculty hires, our Whitehead Fellows program, which allows a handful of particularly promising, newly minted scientists to establish labs and pursue their own research agendas over a four- or five-year period, has attracted a new recruit. Yaniv Erlich, who graduated from Tel-Aviv University with honors degrees in biology and psychology, recently completed his doctorate at Watson School of Biological Sciences at Cold Spring Harbor Laboratory. Yaniv will focus on high-throughput personal genomics during his time here.

The excitement generated by the launching of these three careers aligns perfectly with a theme of this report: "What I thought then...What I know now." Within these pages, our Members recount conceptual shifts and occasional surprises that can alter a continuum of research. We can't predict what those might be for Mary, Piyush, and Yaniv, but it's thrilling to know they're about to find out for themselves.

In closing, I should note that all three newcomers had multiple suitors vying for their services. That they have chosen Whitehead Institute is a tribute to our faculty, staff, friends, and supporters, whose passion and dedication make ours such a uniquely appealing culture. And for that, I am extraordinarily grateful.

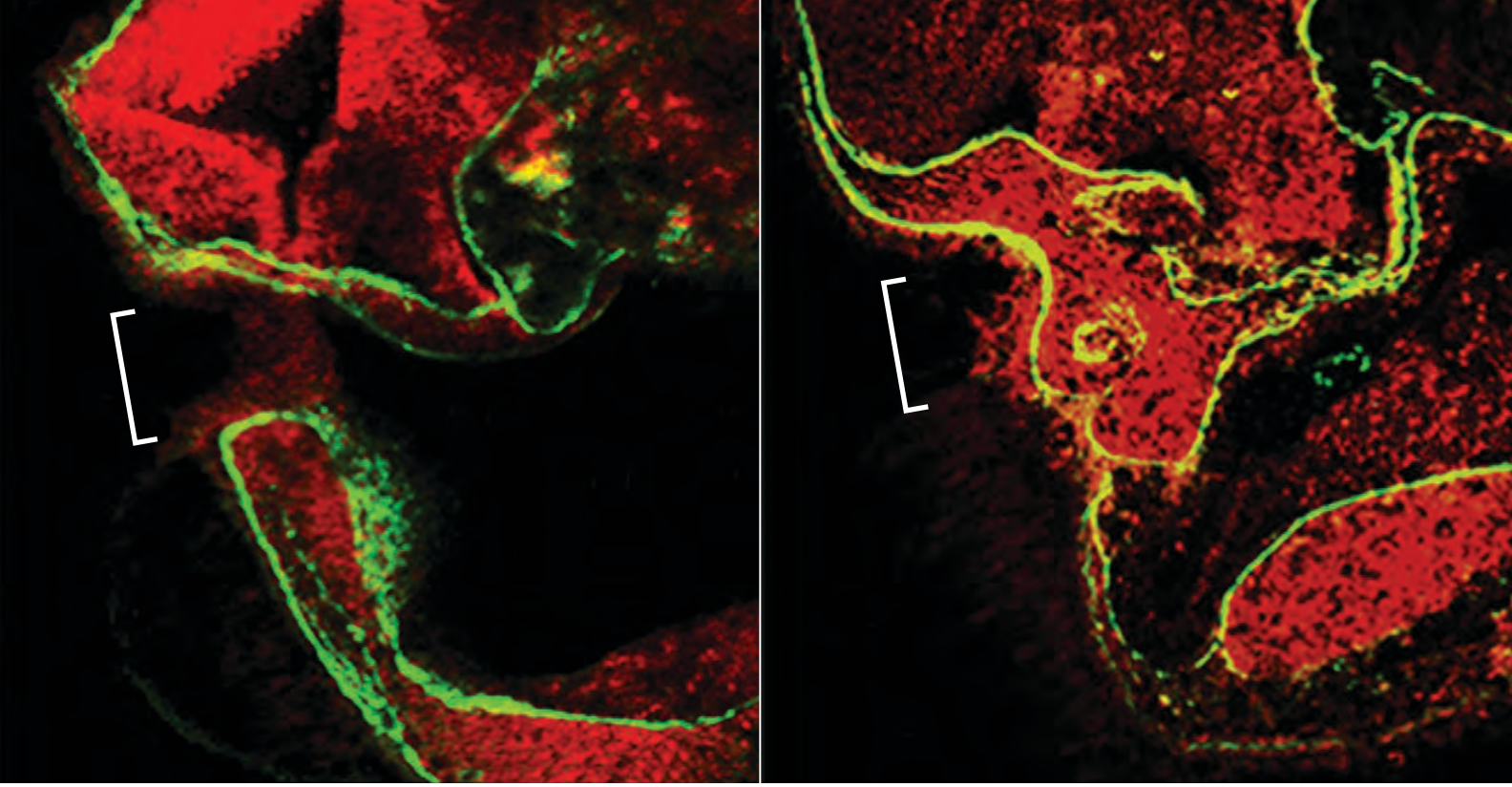
Sincerely,



David C. Page

Scientific Achievement

The productivity of Whitehead laboratories continued apace in 2009. High-impact research findings were published throughout the year, adding to a burgeoning base of knowledge in such areas as genetics, genomics, molecular biology, developmental biology, immunology, cancer research, and stem cell science. Accordingly, many of those behind work of this significance were honored for their contributions.



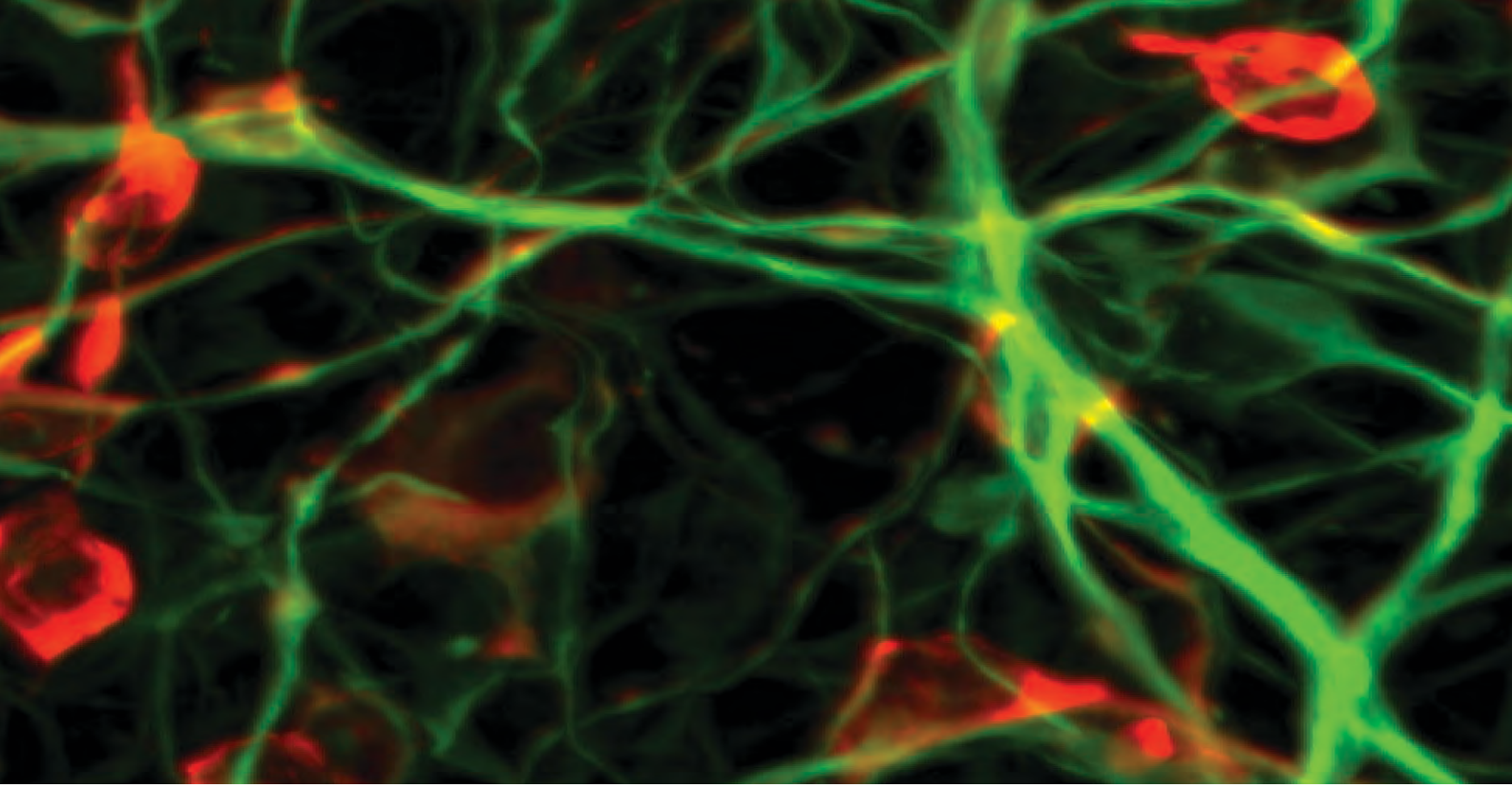
In the Xenopus frog embryo, opening the primary mouth (bracketed in the image at left) depends on the dissolution of the basement membrane (stained green). If the Wnt signaling pathway is interrupted, the basement membrane remains intact (right image).

Organisms develop—as they're 'Wnt' to do

The Wnt signaling pathway is a workhorse in nearly all multi-cellular organisms. This potent network of genes and related proteins mediates multiple patterns of cell-to-cell communication, thereby regulating a host of core biological processes, ranging from embryogenesis, to morphological development, to carcinogenesis. As fundamental as the pathway is, a comprehensive accounting of its components, their functions, and subsequent effects remains a work in progress. Research in Whitehead labs continues to add to the Wnt story, recently implicating the pathway in two more pivotal developmental events.

Scientists in the lab of Member **Hazel Sive** found Wnt signaling at work in forming the so-called primary mouth in embryos of the frog Xenopus. Formation of the primary mouth—the first opening between the outside of the embryo and the intestine—is a critical developmental step requiring the dissolution of a protein sheet known as the basement membrane. Researchers identified two genes that become highly expressed in the region during the formation of the primary mouth, noting that the proteins these genes code for are known to interrupt Wnt signaling. Blocking the expression of these genes (*frzb-1* and *crescent*) and their subsequent protein production (which then allows Wnt signaling to occur) leaves the basement membrane intact and prevents the formation of the primary mouth. The researchers thus concluded that Wnt inhibition is essential in forming the mouth opening and may play a role in other developmental processes involving basement membrane remodeling.

Meanwhile, in the lab of Member **Peter Reddien**, scientists intent on understanding what's known as the head-to-tail polarity decision were discovering that Wnt signaling is pivotal in determining whether a planarian flat worm regenerates the proper body part in its proper place. Researchers found that blocking the expression of a Wnt-related gene *(wntP-1)* in an animal whose tail had been removed prompted growth of a head in place of a tail—that is, a two-headed planarian. During their work, the scientists noted that increased Wnt signaling triggers tail regeneration. From this research, Reddien and his colleagues have concluded that low levels of Wnt signaling, which are normally observed at the anterior pole of the animal, promote head growth, while higher levels of Wnt signaling are typically a posterior event, leading to tail growth. It now appears this signaling pattern guides development of the head-to-tail axis across a vast number of species.



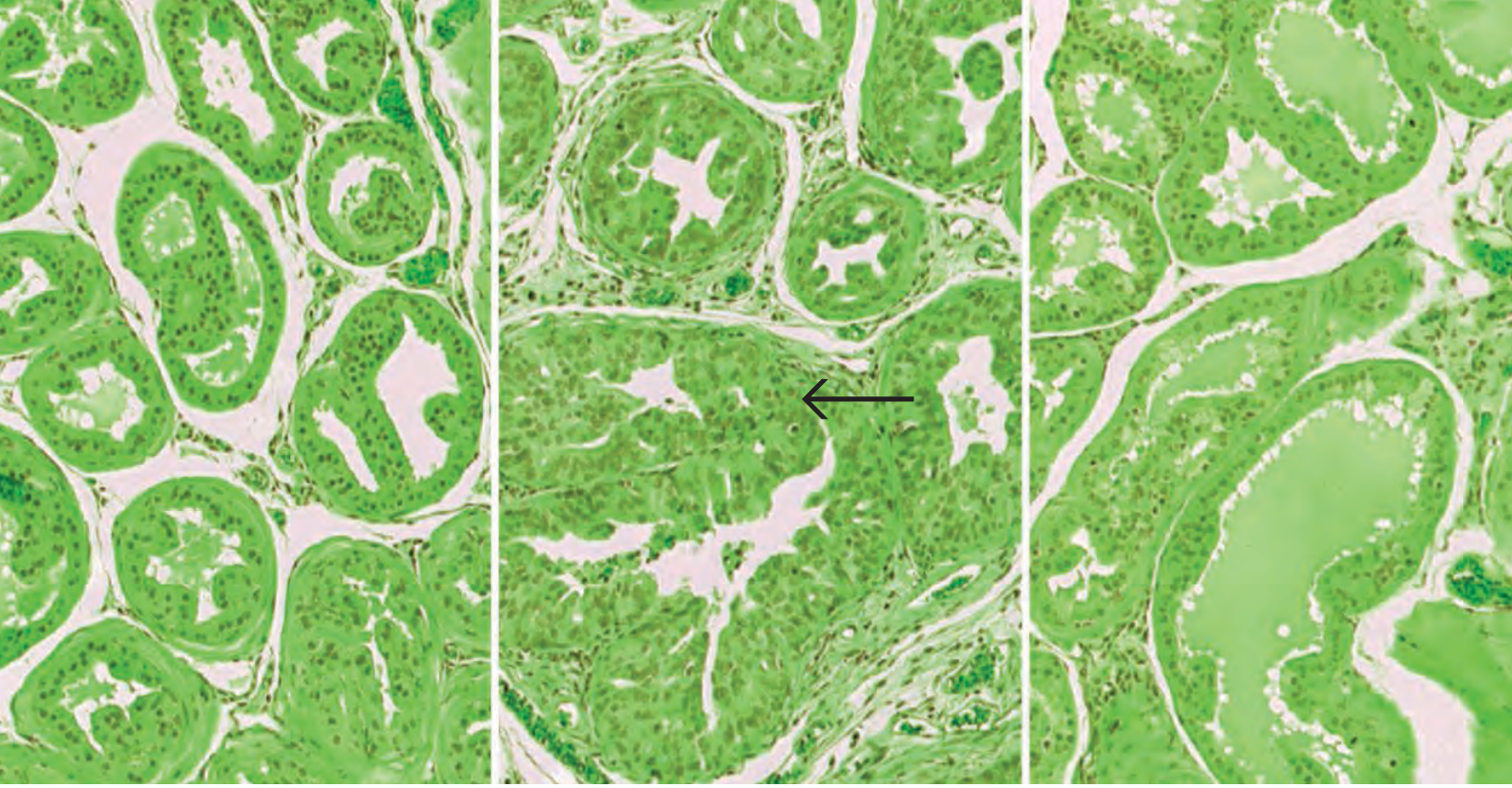
Parkinson's disease (PD) causes neurodegeneration, leading to insufficient levels of the neurotransmitter dopamine. Via cellular reprogramming, the Jaenisch lab derived from the skin cells of PD patients neurons capable of producing dopamine (stained green in the image above) and an enzyme found only in dopaminergic neurons (stained red).

When the program needs editing

The discovery of cellular reprogramming brought with it enough hope to obscure the fact that, though extraordinary, the process was far from perfect. The successful reversion of fully matured cells to an embryonic stem cell-like state—from which they could have the potential to become any cell type in the body—was practically the stuff of science fiction. But the earliest reprogramming efforts relied on the use of viruses to deliver four genes into the DNA of adult cells. The approach is problematic, in part because one of the inserted genes *(c-Myc)* is known to cause cancer, and in part because all of the genes introduced may interact with as many 3,000 existing genes, resulting in unintended and undesired changes in overall gene expression. In 2009, researchers in the lab of Member **Rudolf Jaenisch** advanced the field with a ground-breaking, two-part experiment with both methodological and clinical implications.

In the first portion of the experiment, scientists reprogrammed skin cells from Parkinson's disease (PD) patients to an induced pluripotent state. They achieved this by inserting the four known reprogramming genes along with another gene coding for the enzyme Cre. The scientists also bracketed the reprogramming genes with short DNA sequences called loxP, which respond to the Cre enzyme. Post-insertion, the team introduced Cre into the cells, triggering a reaction at the loxP sites that caused a deletion of all four of the target genes. Beyond successful removal of the genes, expression analysis of these induced pluripotent stem cells revealed their genomes to be virtually identical to those of the PD patients from whom the original skin cells came. Notes Jaenisch: "Other labs have reprogrammed mouse cells and removed the reprogramming genes, but it was incredibly inefficient, and they couldn't get it to work in human cells. We have done it much more efficiently, in human cells, and made reprogrammed, gene-free cells."

In the second part of the experiment, the researchers used the new pluripotent cells to derive patient-specific, dopamine-producing neurons. Destruction of these cells is a hallmark of PD, but the study of their degeneration is hampered because of their inaccessible location in the brain. The creation of these cells from individual patients is a critical step in attaining what's known as the disease-in-a-dish paradigm; that is, the establishment of patient-derived models to enhance our understanding of heretofore inscrutable disease processes.

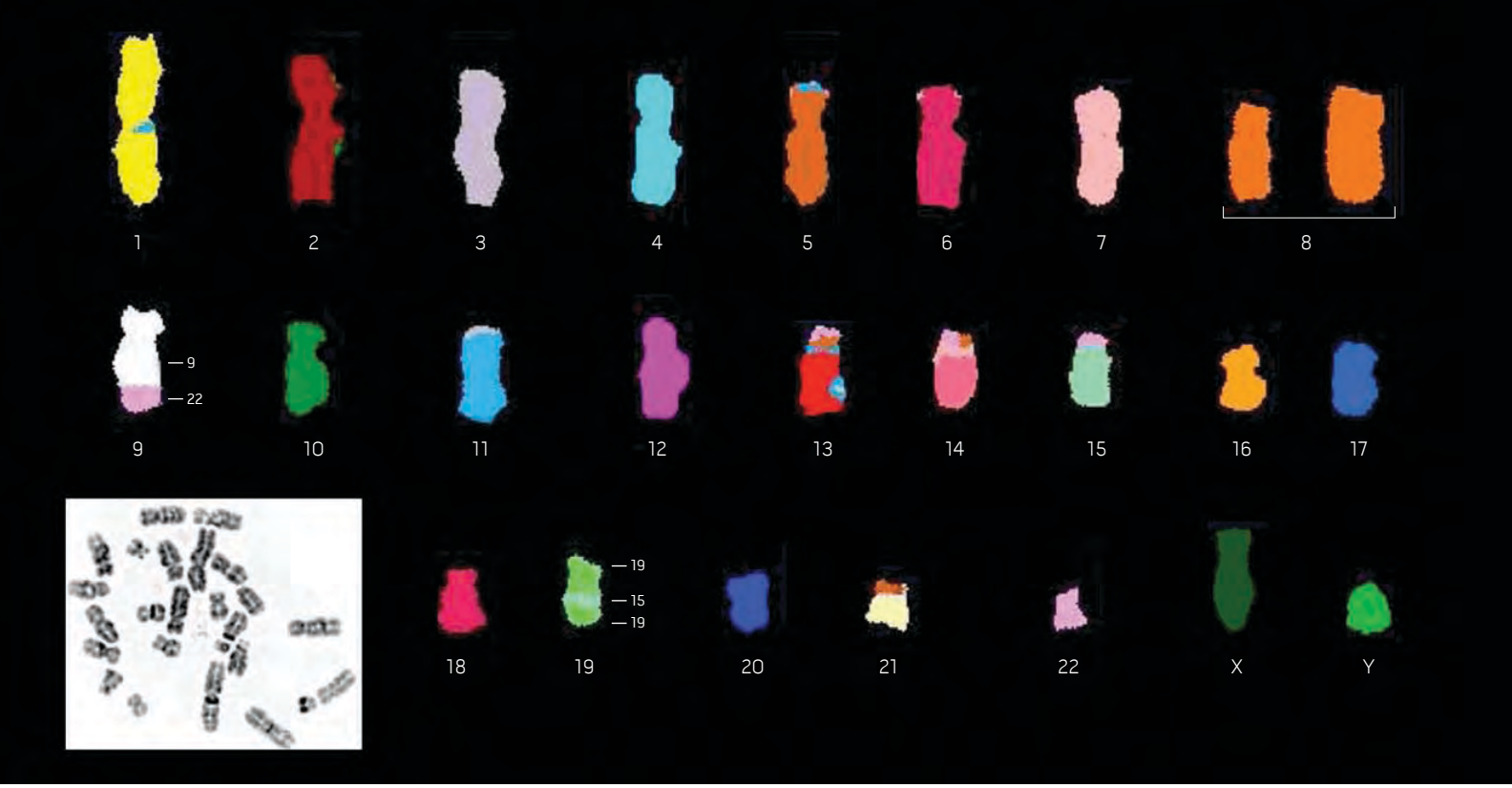


Mice lacking the tumor suppressor gene *PTEN* develop prostate tumors (see arrow, above center). Inhibiting the mTORC2 protein complex in these mice prevents tumor formation (above right), lending prostate tissue an appearance similar to that of mice with functional *PTEN* (above left).

Targeting tumor growth

In the therapeutic battle against malignant tumors, cancer stem cells (CSCs) are formidable adversaries. Although few in number, these cells have the ability to seed new tumors—not only at the primary site but also at remote sites in the body. Moreover, they are resistant to standard chemotherapies. Their existence explains why many solid tumors shrink dramatically after treatment, only to reform later. Attempting to find drugs that target CSCs has been an appealing proposition, but such efforts have been hampered by the cells' scarcity. There simply aren't enough of them in tumor samples to allow for large-scale compound screenings. However, a discovery in the lab of Member **Robert Weinberg** is changing that. By inducing in certain tumor cells a change known as an EMT (or epithelial-mesenchymal transition), scientists in the Weinberg lab are able to produce large, stable populations of CSCs. Weinberg lab members and collaborators recently employed this technique to enable a screen of roughly 16,000 compounds for anti-CSC activity in breast cancer tumors. During the screen, scientists found that a drug called salinomycin was 100-times more effective than the anti-cancer agent paclitaxel at reducing the number of CSCs in breast tumors. It's too early to know whether salinomycin could be used to treat cancer in humans, but the research that unearthed its potential suggests a fundamental approach for finding novel drugs.

Underlying the development of many cancerous tumors is abnormal cell growth. Such aberrant growth is often caused by a mutation in or deletion of tumor suppressor genes, which, as the name implies, serve to constrain improper cell division. An estimated 70 percent of men with prostate cancer, for example, have a deletion of the known tumor suppressor gene *PTEN*. In mouse models of human prostate cancer, as one might expect, tumors form in the absence of *PTEN*. However, researchers in the lab of Member **David Sabatini** recently discovered that tumor growth also requires the presence of a protein complex known as mTORC2, part of a pathway that plays a critical role in regulating cell growth. As it turns out, mTORC2 is so integral to tumor formation, that inhibiting its activity halts the development of tumors—even in cells lacking *PTEN*. Interestingly, mTORC2 inhibition in normal cells appears to have little or no impact, which may make mTORC2 a potential therapeutic target.



A human cell line with a single copy of each gene, except the genes on chromosome 8 (shown above), forms the basis of a new genetic screen. By "knocking out" individual genes in this cell line, Whitehead scientists can now identify genes that are hijacked by invading pathogens.

Resistance may be futile

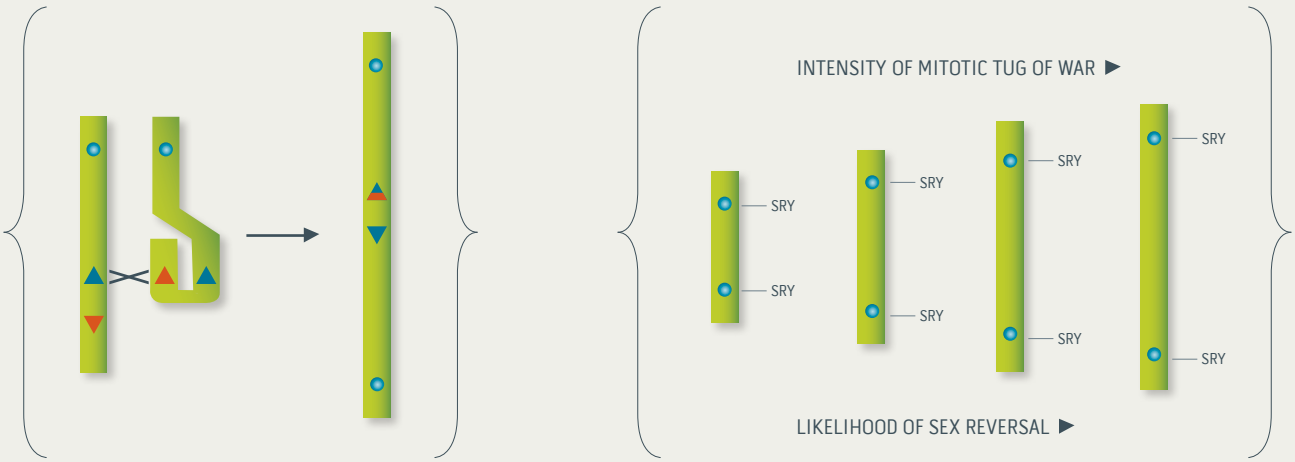
Drug-resistant fungal infections in immunocompromised patients can have deadly consequences. Such infections in these patients—including those undergoing chemotherapy, receiving organ transplants, or battling HIV—are associated with mortality rates ranging from 50 to 90 percent. At issue are fungi's ability to evolve resistance to antifungal drugs in rapid fashion, thanks in part to the activity of a heat-shock protein known as Hsp90. Hsp90 appears to trigger a stress response in fungi, prompting adaptations rendering the fungi impervious to therapeutic intervention. Impeding Hsp90, researchers in the lab of Member **Susan Lindquist** surmised, might offer an approach to overcoming drug resistance. Blocking Hsp90 on its own proved ineffective, but combining Hsp90 inhibitors with common antifungal drugs delivered a deadly blow to the fungi *Candida albicans* and *Aspergillus fumigatus,* two of the most prevalent sources of human fungal infections. "This is an entirely new strategy for making fungi susceptible to preexisting drugs and for preventing fungi from deploying the resistance mechanisms they have evolved against those compounds," Lindquist says. "It could make the difference between life and death."

As they initiate infection, pathogens (i.e., viruses, bacteria, bacterial toxins) cleverly target specific genes and proteins in their hosts. The infectious agents interact with these targets to exert their toxic effects. Identifying these host factors could provide clues to disease prevention and treatment, but pinpointing pathogens' genetic points of entry in human cells has been exceedingly difficult. Large-scale loss-of-function genetic screens in model organisms such as haploid yeast can yield this sort of information because only one copy of each gene exists. Most human cell lines, however, are diploid. With two copies of each gene present, the effects of inactivating a gene via mutation are neutralized when the second copy takes over. Whitehead Fellow **Thijn Brummelkamp** and colleagues have cleared this hurdle by developing a genetic screen that relies on a rare, near-haploid human cell line. Using these cells, the Brummelkamp lab has "knocked out" nearly every gene, allowing for systematic study of gene-pathogen interactions. Thus far, the work has exposed a gene used by diphtheria toxin and an enzyme influenza virus hijacks during cellular invasion. Says Brummelkamp: "In addition to many aspects of cell biology that can be studied, knockout screens could also be used to unravel molecular networks that are exploited by a battery of different viruses and bacteria."

Formation of an isodicentric Y chromosome is depicted in the drawing below left. Crossing over between arms at a palindrome (denoted by the X in the graphic) results in an isodicentric Y chromosome (right of the arrow) with two centromeres (blue dots) and two copies of the masculinizing *SRY* gene. The image below right depicts four isodicentric Y chromosomes. The Page lab discovered that instability of the chromosome increases with the distance between the centromeres—and, that the more unstable the chromosome, the more likely the loss of genetic material during mitosis. Such loss increases the likelihood of sex reversal.

EXPLAINING THE 'Y'

BEHIND SEX DISORDERS



The discovery was a blow to the group of scientists convinced that the human Y chromosome is moving inexorably toward extinction. Those heralding the Y's demise noted that the chromosome had steadily been losing genes throughout evolution. Further, these fatalists argued, without a partner with which to swap genes to maintain genetic quality and diversity, the Y would continue to shed genes until its decay was complete. But from the Whitehead lab of Member (now Director) **David Page** came a defiant "Not so fast!" (or the academic equivalent thereof).

Some six years ago, with the help of collaborators at Washington University in St. Louis, Page completed the sequencing of the Y and, along the way, discovered eight large regions of mirror-imaged genetic sequences, or palindromes. It turns out that in the absence of another chromosome with which to pair and exchange genes, the Y, by folding at its palindromic regions, actually trades genes with itself. It's an elegant mechanism that has ensured the Y's evolutionary survival.

Now, however, it appears the Y's process of self-preservation may also be responsible for a range of sex disorders, from failed sperm production to sex reversal to Turner syndrome. The Page lab recently found that the process may randomly go awry, turning the entire chromosome into a palindrome. The result is a so-called isodicentric Y chromosome (idicY)—an abnormal structure with two centromeres. In a comprehensive review of DNA samples from nearly 2,400 sex disorders patients who had been studied over many years, idicYs were found in 51 patients. Page et al determined that these idicYs were associated with spermatogenic failure in a number of male patients. But then they discovered something else: 18 of those 51 patients were anatomically female, despite carrying two copies of the sex-determining *SRY* gene on their idicY chromosomes. Suspecting that this feminization was related to instability inherent to idicYs, and subsequently finding that the instability increases with the size of the chromosome, Page arrived at the seemingly paradoxical conclusion that the larger the Y chromosome, the greater the likelihood of sex reversal.

This new model for the formation of idicY chromosomes, along with the size-instability correlation, may explain a possible cause of Turner syndrome, an abnormality in girls or women characterized by the lack of one sex chromosome. Page now believes a sizeable percentage of the disorder could be caused by this palindrome-to-palindrome recombination.

YEAST RISING

After centuries of study, the utility of this humble organism continues to expand.

Long a staple in bakeries, breweries, distilleries, and wineries, yeast's role as a model organism in which to study cell biology and genetics began to emerge in the mid-1930s with the first genetic analysis of yeast. Since then, yeast research has yielded a staggering number of insights into gene function.

"It turned out that yeasts have some remarkable characteristics that made them an absolute dream organism for understanding the basic principles of heredity," says Whitehead Member **Susan Lindquist**. More recently, however, Whitehead Institute researchers, including Lindquist, are changing the way we think about yeast with a dramatic expansion of its job description.

Although the general term "yeast" typically refers to the organism *Saccharomyces cerevisiae*, which ferments beer and leavens bread, it more accurately describes thousands of single-celled members of the fungal kingdom. In many important ways yeast cells are very similar to human cells: they have a nucleus and other organelles that fulfill specific cellular functions, resulting in behavior more akin to their counterparts in humans than in bacteria. Importantly, yeast can live in a haploid state, with only one copy of each gene. Plants and animals are diploid: one gene copy comes from the mother and one from the father. Diploid organisms have a backup system; if one gene is faulty, the other copy could take over and mask the effects of the faulty gene. In haploid yeast, there is no genetic backup. So, if a gene is defective, its effects cannot be masked. The ability of yeast to grow as a haploid allows researchers to document the effect a specific gene has on the cell's processes.

Moreover, yeast offers predictable genetic inheritance patterns, easy and inexpensive maintenance, and a rapid life cycle. These attributes enable efficient genetic experiments on successive generations in short order. In the 1970s and 80s, yeast genetics focused on understanding the life cycle and manipulation of yeast strains. During that time, Whitehead Founding Member **Gerald Fink** developed a revolutionary technique, transformation, that permitted a gene from any organism to be inserted into a yeast cell, triggering the yeast cell to produce the protein coded by that gene. In 1996 yeast was the first

Used for thousands of years in baking bread and brewing beer, the yeast *Saccharomyces* cerevisiae, shown in colony form at left, has been a focus of biological study since the late 19th Century. In Whitehead Institute laboratories, *S. cerevisiae* and other yeasts are integral to genetic, human disease, and cell biology research.

nucleated organism to have its genome sequenced. The genome sequence together with transformation enabled researchers to associate genes with their protein products and produce even human proteins in quantities sufficient for pharmaceutical use. Today many human vaccines and therapeutic proteins such as insulin are produced in yeast using these technologies.

While Fink was studying genetics and physiology in yeast, other researchers were using it to study cancer.

"Do these cells get cancer? The answer is no," says Fink. "But once you find a pathway that is important for cancer, you can use yeast to study it."

Lindquist later took the notion of studying human diseases in yeast in an entirely different direction when she began working on models for the neurological disorders Huntington's disease (HD) and Parkinson's disease (PD). Leveraging techniques from Fink's work, Lindquist was able to genetically modify yeast cells to overproduce key proteins linked to both diseases: huntingtin in HD and alpha-synuclein in PD. This approach enables the Lindquist lab to study the effects of these potentially harmful proteins and to devise ways to disrupt their overproduction and aggregation.

More recently, Lindquist used yeast to create a platform with which to conduct rapid, cost-effective screens for potential PD drugs. This year, her lab identified four compounds capable of restoring normal cellular functions in yeast PD models. Significantly, these compounds also rescue neurons in rat models of PD. Lindquist also employed yeast to uncover the first definitive causal link between genetics and the environment in PD, finding that the gene *PARK9* protects cells from alpha-synuclein overexpression and exposure to manganese toxicity.

Working with MIT scientists, Lindquist has gone on to create a computational tool to analyze vast amounts of data from PD yeast studies worldwide. The system algorithmically depicts how the cells respond to stimuli and identifies genes and pathways that affect cell survival.

Meanwhile, in a lab across the hallway from Lindquist's, Whitehead Member **David Bartel** is exploiting yet another of yeast's capabilities—one scientists never knew it had. Part of Bartel's focus is in RNA interference (RNAi), an elegant system that protects cells from viruses and genomic parasites, and is often used to study a gene's function. Although RNAi is found in plants and animals, including humans, it does not exist in brewer's yeast. This notable absence fueled a widely held, long-standing assumption that RNAi is missing in other yeasts related to brewer's yeast.

Enter Bartel, who recently collaborated with Fink to discover that yeasts related to brewer's yeast, including *Saccharomyces castellii* and the human pathogen *Candida albicans*, have retained some or all of their RNAi systems. Based on this remarkable finding, Bartel is using knowledge about other organisms to help him better understand RNAi in yeast systems. It's something of an inversion of the traditional approach of yeast-as-model-organism, but Bartel expects RNAi research in yeast will quickly catch up to that in other organisms.

"Then the new things we learn about RNAi in yeast can inform us and inspire experiments in other systems," says Bartel. "Based on all of the other fundamental processes that have been studied in yeast, I'd be very surprised if we don't learn something in yeast that teaches us about RNAi and other gene-silencing pathways in mammals, including humans."

Clearly, what we thought about yeast then is not what we think now. But does the advent of these novel approaches refined in Whitehead laboratories mean we've finally discovered all that yeast has to offer? Not if history is any indicator.

"It's just an amazing organism," says Lindquist. "And there's been a legion of brilliant investigators over the last century who have created one important tool after another. And each time something new happens, everybody else gets to stand on their shoulders and get something even better."

Honors and Awards

Iain Cheeseman Whitehead Member Iain Cheeseman was selected a 2009 Searle Scholar. Cheeseman was one of 15 award recipients chosen from 178 recently appointed assistant professors in the chemical and biological sciences. The award provides $300,000 in research support for Cheeseman's lab, distributed over three years. Cheeseman is the sixth Whitehead Member to have been named a Searle Scholar. Others include Peter Reddien (2006), Terry Orr-Weaver (1988), David Page (1989), Hazel Sive (1992), and David Bartel (1997).

Rudolf Jaenisch In May 2009, Whitehead Member Rudolf Jaenisch received the prestigious James R. Killian Jr. Faculty Achievement Award from MIT for 2009-2010. Established in 1971 in honor of MIT's 10th president, the Killian Award recognizes extraordinary professional accomplishment by an MIT faculty member. Upon announcing the award, MIT Professor and Killian Award selection committee chair Terry Knight said Jaenisch "has made landmark contributions to his field year after year, decade after decade, throughout his 40-year career."

In June, Jaenisch received word that he would be inducted into Germany's prestigious Order Pour le Mérite for Sciences and Arts. Nomination to the Order, whose members have included Max Planck, Albert Einstein, and Albert Schweitzer, is conveyed by the president of Germany. Formal induction for Jaenisch was to take place at a ceremony in June 2010.

Jaenisch learned in September that he had been awarded the 2009 Ernst Schering Prize, one of the most prestigious German awards for scientists. According to the Ernst Schering Foundation, which confers the prize, Jaenisch was honored for his "groundbreaking work in the field of transgenic animal models and therapeutic cloning." As part of the prize, Jaenisch received a 50,000 Euro honorarium from the Ernst Schering Foundation.

Peter Reddien The Howard Hughes Medical Institute (HHMI) awarded Whitehead Member Peter Reddien an Early Career Scientist appointment, a six-year funded position that allows him to pursue his innovative biomedical research. Reddien was selected from a pool of more than 2,000 applicants to become one of HHMI's first 50 Early Career Scientists. The prestigious appointment provides Reddien with full salary, benefits, and a research budget of a total of $1.5 million over six years. Other expenses, such as research space and the purchase of critical equipment, will also be funded by HHMI. "We saw a tremendous opportunity for HHMI to impact the research community by freeing promising scientists to pursue their best ideas during this early stage of their careers," said former HHMI President Thomas Cech. "At the same time, we hope that our investment in these 50 faculty will free the resources of other agencies to support the work of other outstanding early career scientists." In addition to Reddien, three Whitehead alumni also received HHMI Early Career Scientist awards. They are Kevin Eggan (Jaenisch postdoctoral researcher), Harvard University; Konrad Hochedlinger (Jaenisch postdoctoral researcher), Massachusetts General Hospital; and Brent Stockwell (Whitehead Fellow), Columbia University.

Kate Rubins *Popular Science* magazine named former Whitehead Fellow Kate Rubins to its annual "Brilliant 10" list for 2009. The "Brilliant 10" program recognizes outstanding creativity, risk-taking, and scientific achievements among young researchers. Rubins left the Institute in August 2009 to join NASA's astronaut training program in Houston.

David Sabatini Whitehead Member David Sabatini received the Paul Marks Prize for Cancer Research in recognition of his discovery of a key pathway regulating cell growth and survival. Sabatini was one of three recipients of the prize, which has been awarded biennially since 2001 by Memorial Sloan-Kettering Cancer Center to young scientists (those under age 46) whose work is significantly advancing cancer research. Winners were selected by a committee of prominent members of the cancer research community, chaired by Titia de Lange, a professor at The Rockefeller University and a former Marks Prize winner. "Although all three winners are focused primarily on working in the laboratory, the translational aspect of their discoveries has already begun to influence the treatments that cancer patients receive," Dr. de Lange said. The prize is named for Paul A. Marks, President Emeritus of Memorial Sloan-Kettering, who led the Center from 1980 to 1999. This year's winners received an award of $50,000 and an opportunity to speak about their work at a public symposium held at Memorial Sloan-Kettering.

Robert Weinberg The French Academy of Sciences (Institut de France Académie des Sciences) bestowed upon Whitehead Member Robert Weinberg its highest honor, the Grand Medal (Grande Médaille), in June 2009. Weinberg was awarded the medal for his work "that has revolutionized the understanding of the molecular basis of cancer." At the close of 2009, the French Academy then elected Weinberg a Foreign Associate of its Section of Molecular and Cellular Biology and Genomics. Weinberg was one of 18 scientists worldwide elected for 2010.

Principal Investigators

Whitehead Faculty comprises 14 scientists, each among the world's best in his or her chosen field. Collectively, it is a formidable group of unparalleled caliber whose work has had an indelible impact on the landscape of biomedical research.

What I **thought then...**

"According to the classic view that started in 1993 and persisted for over a decade, microRNAs act as on/off switches to repress a few key messenger RNA targets, thereby initiating a developmental transition."

What I **know now...**

"...Pretty much all of the elements of the classical view have been revised since we and others have learned more about microRNAs in animals. Although microRNAs occasionally do act in accordance with the classical view, we now know that each microRNA usually acts more as a rheostat to optimize the output of hundreds of messenger RNA targets, which can reinforce cell identity and sometimes sharpen developmental transitions."

David **Bartel**

RNAs, so vital to myriad cell functions, are primarily involved in protein production and gene expression. This class of molecule includes many types, but David Bartel's lab focuses most of its research on two of them: messenger RNAs (mRNAs), which act as templates for proteins, and microRNAs (miRNAs), tiny RNA snippets that adjust how much protein is produced from the mRNAs.

In animals and plants, miRNAs can regulate gene expression and protein production through the so-called RNA interference (RNAi) pathway. Scientists had long thought that budding yeasts, however, lack RNAi because earlier research had failed to find it in the most commonly studied yeast species, *Saccharomyces cerevisiae*. In a collaboration with Gerry Fink, the Bartel lab recently dispelled that notion by discovering RNAi in two other budding yeasts: *Saccharomyces castellii* and *Candida albicans*. This surprising finding adds to yeast's value as a model organism. Having served as a fundamental tool for the study of genetics and a multitude of biological processes, yeast can now help further expand our knowledge of RNAi.

In other work, the Bartel lab has identified a link between truncated forms of mRNAs and cancer. Structurally, mRNAs consist of three sections. The first section initiates protein production, the middle section codes for the actual protein, and the tail section is where miRNAs and other types of regulatory molecules usually interact with the mRNA to help determine how much protein is made. The Bartel lab found that for many mRNAs the tail section tends to be shorter in cancer cells and that when the tail section is shortened, the mRNA produces about ten times more protein than when the tail section is longer. Moreover, they found that trimming the tail ends of certain mRNAs in healthy cells can convert them into cancer-like cells. One of the goals now is to decipher how cancer cells shorten their own mRNAs en route to protein overproduction.

Iain **Cheeseman**

Research in the Cheeseman lab revolves around the kinetochore, a protein complex essential to cell division. The kinetochore has the large and difficult job of connecting two vastly different types of biological molecules: DNA, which is made of nucleotides, and proteins, which are made of amino acids. The connection provided by the kinetochore must be able to withstand substantial physical force, especially during cell division, when it tows bulky chromosomes through highly viscous fluid filling the nucleus.

In preparation for cell division, the nucleus duplicates its genome and consolidates the DNA into tightly packed chromosomes. Each chromosome comprises two identical sister chromatids that are generally joined together in an X shape. At the intersection of that X is the centromere, where a kinetochore is rooted in each sister chromatid.

During cell division, protein filaments reach out from two anchor points on opposite sides of the cell, called spindle poles. These protein filaments, called microtubules, extend and retract until each hooks onto a kinetochore. Once all kinetochores are hooked to a microtubule and the chromosomes are properly aligned along the cell's middle, the bond that holds the sister chromatids together breaks. The kinetochore then harnesses the energy from the retracting microtubules to pull the sister chromatids apart—one to each spindle pole—thereby dividing the duplicated DNA equally.

The Cheeseman lab recently identified a human kinetochore protein that holds onto a shrinking microtubule. A microtubule shortens by peeling back narrow molecular strands from its chromosomal end, creating a large amount of force. The identified protein, called Ska1, is tethered to the chromosome and has the ability to be pulled along a microtubule by its fraying end.

THEN

What I **thought then...**

"When I started working on the kinetochore in graduate school, everyone assumed that it was a very simple structure, with just a handful of proteins involved in binding to the DNA and binding to the microtubule ..."

NOW

What I **know now...**

"...I think it was a huge surprise to people that the kinetochore is really made up of about 90 to 100 proteins. So instead of this very simple interface, it's this complex molecular machine. And that intricacy challenged the way people look at the molecular complexity of cell division's basic machinery."

THEN

What I **thought then...**

“I used to think that once we had the genome sequenced, we would be able to make accurate predictions about phenotypes and gene expression. We thought a gene was turned on and off by the proteins that bound to the switches in front of the gene...”

NOW

What I **know now...**

“...However, it’s more complicated than I thought. Now we know that many proteins are controlled by non-coding RNAs. So now the question is, ‘What is controlling the non-coding RNAs, and how do they work?’ We don’t know how they switch genes on and off.”

Gerald **Fink**

The invention of rapid DNA sequencing methods has created the expectation that the resulting genomic data may enable us to understand how changes in the genome affect health and disease; that is, to predict phenotype from genotype. The challenge is that, despite the fact that individuals within a species have most of their DNA in common, there exist many small differences that could make individuals quite distinct from each other.

To assess whether these small differences affect the expression of our genes, Gerald Fink recently compared what happens when exactly the same gene is defective in two yeast strains. In sequencing the DNA of both strains, Fink found on average only about 2 differences per 1,000 base pairs, making them as close as any two humans. Given this small difference, one would expect the two strains to have the same physiology and behavior. Surprisingly, Fink discovered that the two strains differed markedly. In some cases, a mutation that in one strain had no effect was enough to kill the other. The reason for this startling difference is that variations between the two strains in other genes suppressed the lethal effects of the mutation in question. Fink believes that modification of the effects of mutations by other so-called suppressor mutations may explain the enormous variation in the outcome of genetic diseases in humans.

The Fink lab recently found in a fungal study that two long, non-coding RNAs (ncRNAs, which do not code for proteins) have a profound effect on the expression of an adjacent gene, *FLO11*. These two non-coding RNAs, whose detection is made possible by recent technological advances, control *FLO11*, which itself determines whether this fungus switches morphology from a yeast form to a thread-like, filamentous form. When ncRNA1 is active, the *FLO11* gene is inactive; when ncRNA2 is active, the *FLO11* gene is, too. The two ncRNAs are thought to act like toggle switches, allowing the cells to alternate between the yeast and filamentous forms. This remarkable change occurs in spite of identical genotypes.

Fink argues that both of these intricate mechanisms are proof that we have much to learn about interpreting genomic information before reaching the ultimate goal of predicting phenotype from genotype.

Rudolf **Jaenisch**

The Jaenisch lab continues to advance the state of the art in the areas of cellular reprogramming and the cultivation of novel human embryonic stem cell (ESC) lines. Since the discovery several years ago that mature, fully differentiated cells could be turned back to an ESC-like state through the viral insertion of four reprogramming genes, researchers under Rudolf Jaenisch's guidance have been refining the methods that produce these so-called induced pluripotent stem (iPS) cells. Achievements to date include successful removal of reprogramming genes (which, if left in the cellular genome can cause malignancy) from human iPS cells in an experiment that marked the first time such cells maintained their pluripotency in the absence of the original reprogramming factors. The lab has also developed a novel technique employing proteins called zinc finger nucleases to insert genes into human ESCs and iPS cells with unprecedented precision. Heretofore, targeted gene insertion in human ESCs (a relatively straightforward process in mouse cells) had been extraordinarily difficult; this discovery should help accelerate creation of cell types specific for modeling multiple human diseases.

The lab also focuses on epigenetics, the study of changes in gene expression caused by mechanisms other than alterations in underlying DNA sequence. Jaenisch and his researchers recently determined that the levels of oxygen present during the culturing of human ESCs can have an enormous impact on the epigenomes and, subsequently, on the fates of such cells. In a groundbreaking experiment, scientists found that culturing human ESCs in an oxygen concentration of 5% (which approximates naturally occurring, *in vivo* oxygen levels) maintains the activity of two X chromosomes in the cells. However, ESCs cultured in a typical atmospheric oxygen concentration of 20% manifest X-chromosome inactivation. The presence of two active X chromosomes in an ESC is a hallmark of what is thought to be the "purest," most fundamental state of pluripotency—a state not previously attained with any consistency. Jaenisch believes that deriving human ESCs under physiologic oxygen concentrations represents the new gold standard.

THEN

What I **thought then...**

"For years we've been able to work with mouse embryonic stem cells with two active X chromosomes, but we were never sure we could do this with human cells. Could we derive embryonic stem cells before they underwent X-chromosome inactivation? This had bothered us for a long time..."

NOW

What I **know now...**

"...We took a big gamble four or five years ago to study the effects of oxygen levels, and none of this was eligible for federal funding. Thanks to generous private support, we pursued it. And I think now people will have to adopt this approach. We will also now want to see if X-chromosome inactivation is reversible."

Susan **Lindquist**

Proteins are the workhorses of a cell, but before they get down to business, they begin rather inauspiciously as shapeless chains of amino acids. To work properly, most proteins need to fold into proper conformation. If a protein folds incorrectly, it won't function as it should, and, in some cases, may cause considerable damage. Misfolded proteins can accumulate in clumps that ultimately kill the cell. Susan Lindquist's lab studies a variety of proteins, including heat shock proteins that are co-opted by cancer cells to spur their survival. The lab also investigates prion proteins that produce a revolutionary mode of protein-only inheritance in yeast and the alpha-synuclein protein, creating a new model for Parkinson's disease (PD).

PD is caused by multiple genetic and environmental factors. One genetic factor is the overexpression of alpha-synuclein. Another is mutations in a gene of previously unknown function (*PARK9*). An environmental factor once thought to be unrelated to all of these is exposure to the metal manganese. In a recent breakthrough, the Lindquist lab has found that all three factors are intertwined. In a yeast model of PD, normal expression of *PARK9* suppresses alpha-synuclein toxicity and increases resistance to damage from manganese exposure. However, in the same model, extra *PARK9* expression renders cells resistant to toxicity from both alpha-synuclein and manganese. This finding formally establishes one of the first links between genetics and environment in PD.

The Lindquist lab and collaborators at MIT have also established a new computational technique, called ResponseNet, to extract information from existing datasets developed during the study of yeast models of PD. The ResponseNet algorithm analyzes data from screens of 5,500 yeast strains based on a model that creates large amounts of alpha-synuclein, thereby mimicking some of the toxic effects of alpha-synuclein accumulation in PD patients' brain cells. Using these data, ResponseNet identifies relationships between alpha-synuclein toxicity and basic cell processes. The algorithm recently identified a highly conserved pathway targeted by the statin class of cholesterol-lowering drugs and another pathway targeted by the immunosuppressant rapamycin.

What I **thought then...**

"When I started my work in grad school on the heat shock response, it was an obscure response only characterized in fruit flies. At the time, I was interested in changes in protein expression and couldn't care less what the proteins themselves were doing."

What I **know now...**

"...Then it became apparent that this response and these same proteins are conserved in every organism on the planet. And they're making these proteins not only in response to heat, but in response to oxidative damage, metal ions, radiation, just about any stress you could imagine...So all of a sudden I thought, 'I've got to figure out what these proteins are doing.' And that opened up whole new realms of biological investigation for us and completely changed the course of what we do."

What I **thought then...**

“I’ve been studying red cells since 1958. About 25 years ago, we were the first to isolate genes for key mammalian red cell proteins, including the first protein that facilitated glucose uptake. In the late 1980s, we cloned the Epo receptor and spent 20-odd years studying how Epo stimulates red cell production, and then 10 years ago, we began studying stem cells. What ties all of these projects together is their focus on the basic cell and molecular biology of genes and proteins important for human physiology and disease.”

What I **know now...**

“...The underlying points for us over the long term have been the same—the synergism between a basic understanding of cell function and the questions that arise from an understanding of specific human diseases.”

Harvey **Lodish**

Harvey Lodish’s study of red blood cells, and hematopoiesis more generally, is now in its sixth decade. Needless to say, he and his lab aren’t about to stop any time soon. In the last decade one focus has been on hematopoietic stem cells (HSCs)—characterized by the ability to both self-renew and differentiate into all blood cell types. The lab has been trying to determine what regulates the number of HSCs *in vivo* and *in vitro*, and in 2009 reported on the discovery of a cocktail of growth factors capable of expanding the number of human HSCs in culture by a factor of 20. Recently, the lab has identified a small population of stromal cells in the fetal liver that express a set of at least seven growth factors needed to support maximum expansion of HSCs within the liver, which is a key site of hematopoiesis during development. Now the lab will try to tease out the specific roles of each these growth factors and the impact their signaling has on the behavior of HSCs. With colleagues in Singapore Lodish hopes to start clinical trials using their technique for expanding cord blood HSCs for bone marrow transplantations.

The lab is also working to overcome a condition known as Epo-resistant anemia, wherein even high levels of the hormone erythropoietin (Epo), which typically regulates much of red blood-cell production, are insufficient to generate necessary numbers of red cells. The condition occurs in certain pediatric disorders and among adults with severely impaired kidney function. For insight into the problem, Lodish and his lab studied the physiological process known as stress erythropoiesis (SE), a mammalian and avian response to severe, traumatic blood loss. It had been known that SE is regulated not only by Epo, but by circulating glucocorticoids (GCs) as well. What was unclear, however, was how GCs were actually working to stimulate red-cell production during SE. By replicating the conditions of SE in culture, the lab determined that GCs trigger self-renewal in the early progenitor cells known as burst-forming unit-erythroids (BFU-Es), which, through a series of downstream events, promotes rapid, sustained production of red blood cells. The identification of the role of BFU-Es in SE suggests a potential target for therapeutic intervention.

Terry **Orr-Weaver**

For Terry Orr-Weaver, it's all about control; more specifically, the control of fundamental cellular processes and their relationship to developmental events. Among the processes under intense scrutiny in the Orr-Weaver lab are DNA replication and the mechanisms that regulate activation or repression of replication origins. Modification of DNA replication during development can cause an increase in the copy number of certain genes. While it's long been known that changes in gene copy number are highly prevalent in tumors, an explanation for this phenomenon has been elusive. Using the fruit fly *Drosophila* as a model for study, the lab has identified multiple genomic regions where genes are over-replicated and has found, quite unexpectedly, that multiple factors influence replication in these regions. "The big surprise is that there are myriad ways to control whether a site gets replicated," Orr-Weaver says. "Thus, it's likely that in human cells, there are multiple ways the cells can lose their regulation. We believe that those regions of the genome in *Drosophila* mutants where we find copy number is increased mimics what's seen in cancer cells." The task at hand now is to determine what actually promotes this loss of regulation and what makes these regions vulnerable to it.

The lab is also unraveling the mechanisms that control meiosis and embryogenesis, and both are as complicated as they are essential. Driving this endeavor is a set of core questions, such as: How are sperm and egg able to halve their number of chromosomes (meiosis)? What controls the specific progenitors of sperm and egg that is necessary for them to become functional gametes? What stops meiosis in a developing female egg and then restarts it as the organism enters puberty? How is the transition from egg to activated, fertilized embryo triggered? Research in the lab to date has identified a protein kinase complex that triggers the transition from egg to embryo by activating the first mitotic divisions within the embryo. This protein kinase later facilitates activation of expression of the embryonic genes. Ultimately, Orr-Weaver and her lab are bent on elucidating fully the controls that ensure proper cell division, embryonic development, and the potential glitches that can knock these processes off track—often with dire consequences.

What I **thought then...**

"Although I thought that the machinery controlling cell metabolism would be conserved between divergent organisms, I assumed that in the regulation of cell division and development there would be more species-specific features than common regulators. Meiosis, in particular, was thought by researchers to be controlled uniquely in each eukaryote and even to have evolved multiple times independently!"

What I **know now...**

"...The conservation of regulators from simple, single-cell eukaryotes to humans is remarkable. Two of the genes we discovered, because they are essential for DNA replication and meiotic chromosome segregation in *Drosophila*, play crucial roles in ensuring accurate human cell division. Paradoxically perhaps, while this conservation of crucial control genes is so striking, we are finding exceptional developmental situations in which regulatory proteins are used in distinct ways. These provide powerful models to uncover new functions for these proteins."

What I **thought then...**

"When I started studying the X and Y chromosomes in the early 1980s, everyone had accepted the standard textbook stories about them. The X was all about X-linked recessive disorders, like color blindness. We were all taught to recognize this pattern of inheritance. And the Y was seen as the partner for the X, with very few genes and a primary role in sex determination.

In 1990, when the *SRY* gene (the sex-determining gene on the Y chromosome) was discovered, a lot of folks jumped ship. I was wondering whether the Y had a future intellectually or whether it was time to move on. It looked like a pretty tenuous topic upon which to base a career."

What I **know now...**

"...Today the Y looks better than ever, and taken together with the X, we see that what were once a pair of ordinary autosomes have, in a grand experiment of nature over hundreds of millions of years, become extraordinary. There's no hint of the richness of this grand experiment in biology textbooks. Where once it seemed this topic might be exhausted, I'm now convinced my career will be too short to explore its breadth and depth."

David **Page**

Devotees of David Page's research know that the Whitehead Director is obsessed with the fundamentals of developmental and reproductive biology. The origins of life and the evolution of mammalian sexual reproduction are under intense scrutiny in the lab because, as Page puts it, "The defining feature of life is absolutely to reproduce."

Answers to fundamental questions are pursued in what Page refers to as "two sides of the house." On one side are scientists determining why germ cells enter meiosis (the process that halves their chromosomes), what commits a germ cell to become an egg or sperm in the process, and what relationships exist between these two occurrences. Current research implicates a rather complex signaling pathway in which retinoic acid plays a prominent inductive role in the expression of specific genes. Page hopes this work will one day resolve a core question of gender identity: how a mammalian embryo decides whether it will be a maker of eggs (female) or a maker of sperm (male).

On the other side of the house, studies of the human Y and mammalian Y chromosomes continue to bear fruit. The lab has discovered that the very mechanism that has assured the human Y's evolutionary survival (that is, its ability to swap genes with itself via mirror-image genetic sequences known as palindromes) may also inadvertently be responsible for a range of sex disorders. More recently, Page's lab completed the sequence of the chimpanzee Y chromosome and, through comparisons with the human Y, discovered that both Ys are evolving more quickly than the rest of their respective genomes via continual genetic "renovation."

Hidde **Ploegh**

Research in Hidde Ploegh's lab, though varied, is united by a common approach: take advantage of naturally occurring processes to learn more about the immune system and infectious diseases. In doing so, the lab has managed to produce a number of elegant, highly effective tools for studying cell and organismal biology.

One of the latest of these tools is a mouse model that represents how the T cells of the immune system respond to infection. In a collaborating effort with the lab of Rudolf Jaenisch, the Ploegh lab used nuclear transfer to make mice from T cells. T cells can rearrange their genetic material to produce a specific receptor that can identify an antigen. In this work, the T cells were engaged in an immune response to the parasitic infection toxoplasmosis. These animals provide an altogether new window on host-pathogen interactions.

Another tool exploited by the Ploegh lab uses the bacterial enzyme sortase to attach a tag to specific sites on a protein. These tags are used to track a molecule's movement in a cell or tissue to learn more about how it is made and how it works. The lab is using this method to track how flu particles are formed and released from a living cell. Another potential use is to attach tags in a site-specific fashion onto proteins that are therapeutically useful, to slow down their metabolism without changing their efficacy. This technique could extend the effectiveness (and reduce the number of administrations) of cytokine treatments for a variety of indications.

THEN

What I **thought then...**

"The advances in DNA sequencing would have been difficult to foresee even five years ago."

NOW

What I **know now...**

"...All of a sudden, you can now sequence entire genomes or entire sets of RNA molecules. And that is clearly a tool we need to learn how to play with. We don't think we've seen the full range of possibilities of that methodology."

Peter **Reddien**

Peter Reddien is captivated by regeneration—of tissues, organs, and even entire body parts. Reddien's lab is working toward uncovering some of the secrets behind the process by studying the planarian flatworm, an animal whose legendary regenerative powers enable it to re-grow a severed head, tail, or virtually any other part of its body.

Reddien has systematically examined the functions of more than 1,000 genes in planaria, cataloging the roles each plays in regeneration. Notably, a relatively large percentage of these genes have closely corresponding genes in other organisms. The lab recently identified two genes along a key signaling pathway, known as Wnt signaling, that are integral in the so-called head-or-tail polarity decision. This discovery represents an important advance in the quest to understand how the wounded animal "decides" what tissues to make at wounds. In simplest terms, when Wnt signaling activity is increased, the animal is instructed molecularly to re-grow a tail. Inhibition of Wnt signaling triggers head regeneration. Reddien now believes that this pattern of Wnt signaling guides formation of the head-to-tail axis not just in planaria but in most animals, meaning it could well prove to be an evolutionarily fundamental mechanism of developmental biology. Says Reddien, "There's a code of information for regeneration... spatial cues that cells interpret and that specify the identity of tissues to be regenerated. We want to decode it."

Also vital to planarian regeneration is a population of cells known as neoblasts, which are adult stem cells capable of differentiating into any cell type in the body. The lab is currently exploring the various factors that regulate neoblast activity.

What I **thought then...**

Before settling on the planarian as an ideal platform for the study of regeneration, Reddien conducted gene function experiments with another model organism: the roundworm C. elegans.

"I was used to creating mutants (in *C. elegans*) and then studying phenotypes emerging at the end of a developmental process to determine the function of genes. But it's not an approach that could really work well in planarians..."

What I **know now...**

"...I really had to learn how to study gene function in an adult animal, which is quite different. Here, we start with a normal animal and pull the plug on individual genes to see what happens. It can be like dominoes falling, where one defect causes another, which causes another. It took a while to learn how to study gene function with this approach."

The development of RNA interference approaches and strategies for studying gene function is now enabling the lab to exploit the full potential of the planarian model.

David **Sabatini**

The Sabatini lab is dedicated to understanding the intricate interplay among nutrients, cell growth, and metabolism and their relationships to aging and such human diseases as cancer and diabetes. At the heart of much of the lab's research is the so-called TOR (target of rapamycin) pathway, which plays a critical role in controlling cell growth. Several years ago, David Sabatini discovered that the mammalian version of TOR, known as mTOR, includes two major protein complexes—mTORC1 and mTORC2—that exert effects on cell growth, division, and ultimately, survival.

Recent research in the lab implicates mTORC2 in prostate cancer. Scientists discovered that in a mouse model of the disease, blocking mTORC2's activity prevents the formation of prostate tumors—even in cells genetically modified to be predisposed to tumor development. Intriguingly, mTORC2 may be inhibited in normal cells with little effect, suggesting that mTORC2 may represent a promising therapeutic target.

Additional work in the lab focuses on the correlation between food consumption, cancer, and aging. In the early 20th Century, scientists had noted an association in animals between a restricted diet and tumor incidence and size: in general, the lower the food intake, the fewer and smaller the tumors. However, it had also been observed that certain tumors are unaffected by caloric restriction in a mystery that the Sabatini lab is beginning to unravel. Researchers recently identified a cell-signaling pathway, PI3K, whose activity determines whether certain cancers respond to dietary restriction. It seems that a genetic mutation in some tumors leaves this pathway in a perpetually active state, rendering cancerous cells unaffected by a low-calorie diet. The finding opens the door to the possibility of developing therapies that mimic dietary restriction for use in patients whose tumors lack the aforementioned mutation.

What I **thought then...**

"I came of age at a time when conducting loss-of-function (gene function) studies in mammalian systems was very, very hard to do and basically relied on genetically engineering mice..."

"In studying signal transduction, the goal had been to find a single, straightforward pathway. We always drew arrows where 'A' talks to 'B', 'B' talks to 'C' and so on..."

What I **know now...**

"...The advent of RNAi (RNA interference) completely changed how we tackle loss-of-function studies. This is a methodological approach that has dramatically increased the number of hypotheses we can test per unit time."

"...We never anticipated the complexity of these pathways and the multiple loops and levels of feedback. This knowledge is increasingly important in the cancer world. Perturbing a single system is quite a bit harder than we first thought."

THEN

What I **thought then...**

"I thought it would be relatively simple to understand many aspects of development..."

NOW

What I **know now...**

"...but I'm constantly amazed now at how much of development seems to be about nuance. It's not just about which gene is necessary, but the amount of gene product involved, as well as timing of when that product is made. We have made enormous progress in describing many of the genes required, but the magnitude of the challenge to get the real picture of what's actually occurring, and the subtleties involved, is something I didn't appreciate 20 years ago."

Hazel **Sive**

In Hazel Sive's lab, frog and zebrafish embryos are revealing much about processes critical for proper vertebrate development. The lab is particularly interested in understanding mechanisms that shape the embryo's craniofacial region, including those that help form the primary mouth (the important first opening between gut and the embryo's exterior) and those that ensure the developing brain assumes the conformation necessary to fit and function within the skull.

Researchers recently discovered that a signaling pathway known as Wnt plays a key role in forming the primary mouth in frogs. For this opening to develop, a protein sheet known as the basement membrane must dissolve. Sive lab scientists identified two genes whose regional expression disrupts Wnt signaling, thereby promoting basement membrane degradation. In follow-on work, Sive says the lab has found that primary mouth formation depends on virtually simultaneous "making and breaking" of the basement membrane in what she calls "a very fine balance." This balance is likely needed throughout the embryo during tissue and organ development.

The lab has also recently described a phenomenon it calls "epithelial relaxation," which is essential for proper expansion and formation of the embryonic brain. Vertebrate brains, including those in humans and in zebrafish, are formed from a tube known as the neural tube. During development, the neural tube fills with embryonic cerebrospinal fluid (eCSF), which causes expansion and formation of cavities called brain ventricles. The lab discovered that expansion occurs correctly only if the walls of the tube become less rigid as expansion normally begins. Using zebrafish mutants, they determined that the activity of the motor protein myosin must be suppressed for the tube walls to "relax" sufficiently for normal ventricle formation.

Beyond using zebrafish as models for brain development, Sive employs the animals as a tool to study genes associated with the mental health disorders autism and schizophrenia. Mental health risk genes in humans have homologs in zebrafish and, significantly, these genes are active during brain development. Because of this, Sive says screens in the fish for chemicals that alter the genes' activity can be conducted and their effects analyzed.

Robert **Weinberg**

Much of the work in Robert Weinberg's lab is propelled by the lab's own recent paradigm-shifting discovery that certain tumor cells undergo a profound change in their behavior that enables them to leave the primary tumor and form new tumors in remote locations—the process of metastasis. This change, known as the epithelial-mesenchymal transition or EMT, confers on these tumor cells the key properties of cancer stem cells; specifically, the ability to self-renew and to seed new malignancies. By inducing EMT in cancer cells, scientists can now create cancer stem cells—which are naturally quite rare—in quantities sufficient for large-scale screening of compounds able to kill these cancer stem cells preferentially. (This work is ongoing, and collaborators outside the lab have already identified a handful of potential drug candidates.) Remarkably, researchers in the lab have also discovered that induction of EMT in normal epithelial cells appears to create normal adult stem cells. This is a finding with potentially important implications for regenerative medicine.

The lab is currently exploring a host of EMT-related issues, including the role of the cellular environment around a tumor and the pathways of signaling cues that induce the EMT. Researchers are also attempting to elucidate patterns of gene expression that likely underlie not just EMT induction, but other critical steps in the invasion-metastasis cascade as well. Such work led to the recent finding that low cellular levels of a microRNA known as miR-31 are associated with increased metastatic activity in a model of human breast cancer. This particular research also suggests that measuring miR-31 levels might have a role in predicting the likelihood that an already-diagnosed primary tumor will eventually metastasize.

What I **thought then...**

"I used to think that all the cancer cells in a tumor were identical..."

"I used to think that metastasis was impossibly complex..."

What I **know now...**

"...it's clear now that there are several kinds of cancer cells in a tumor, with cancer stem cells being the most important of them. This is a wrenching new reality requiring a recalibration of our thinking about how tumors grow and spread. Moreover, the fact that we could produce epithelial stem cells from normal epithelial cells also suggests a way to make epithelial stem cells that could not have been anticipated several years ago."

"...I now believe that we are within reach of some important concepts indicating that metastasis is much simpler and experimentally more accessible than we once thought it would be. This is a major conceptual shift. It's also far more satisfying to study metastasis with the realization that it's likely driven by a relatively small set of identifiable master regulators."

Richard **Young**

Embryonic stem (ES) cells hold the key to improved understanding of human development and disease. These cells have the unique ability to perpetuate themselves and, when they receive the appropriate signals, to become almost any cell type in the body. The embryonic state and the process of maturation into adult cells is controlled by a number of poorly understood "switches", including transcription factors, which sit on the DNA and promote or prevent gene translation; signaling pathways, which bring messages from outside the cell to the nucleus; and chromatin regulators, which modify how DNA is bound for storage. To better understand these control processes the Young lab is running large-scale genetic screens to identify the switches that maintain ES cell state.

This year, a Young lab screen revealed that a chromatin regulator known as SetDB1 plays an important role in ES cell maintenance. Chromatin regulators wrap the DNA around protein spools called histones for longer-term storage and to control gene expression. The tighter a gene is wound around histones, the less likely the cell's transcription machinery will access the gene and express it. SetDB1 works with a partner to silence a specific set of genes in ES cells by winding the genes very tightly around histones. When SetDB1 or its partner is switched off, the DNA loosens around the histones, allowing for gene expression that triggers cell maturation.

Many human diseases are thought to involve defects in the switches that normally control embryonic cells. According to Young, as we learn more about chromatin regulators and the other switches that control ES cells, we should be able to therapeutically target these switches in cancer cells and other cells with defects in gene expression. For now, drugs that target gene expression are frustratingly elusive.

THEN

What I **thought then...**

" There are about 2,000 genes that regulate gene control, and I used to think that in any one cell type, there were hundreds of these regulators, all working together in some really complex way..."

NOW

What I **know now...**

" ...It's become clear that in many cells, only a few key regulators can in fact program an entire cell state. The implication of that discovery is that a deep understanding of a few key regulators should lead us more rapidly to understand human development and how to control many diseases."

Whitehead Fellows

Thijn **Brummelkamp**

Thijn Brummelkamp focuses on cancer research and uses genetic screens to identify genes that play a role in human disease. His lab recently developed a novel screening approach that is having significant impact in the field of infectious disease. The basis of this new technique is a human cell line that is predominantly haploid—that is, each cell has only a single copy of each chromosome and, therefore, only a single copy of each gene. Using this cell line, the Brummelkamp lab is able to systematically, consistently, and reliably knock out the function of each non-essential gene and observe the result(s). Armed with these knockouts, the lab can pinpoint which genes and proteins these pathogens utilize when causing infection. In more than 20 independent screens, the lab has identified multiple host factors used by a variety of different bacterial toxins and viruses, including diphtheria toxin and influenza. And this is only the beginning. Having knockout cells for nearly all human genes "in the freezer," as Brummelkamp puts it, should enable the generation of a comprehensive overview of cellular factors directly implicated in infectious disease.

Andreas **Hochwagen**

Cell division is an intricate process. If anything goes awry, the resulting daughter cells can be plagued by genetic errors that can cause birth defects or cancer. Fortunately, our cells have built-in surveillance mechanisms, known as checkpoints, to prevent catastrophe. In the lab of Whitehead Fellow Andreas Hochwagen the role of these checkpoints during meiosis, the complex and error-prone cell division that gives rise to sperm and eggs, is under intense study. When cells undergo meiosis, they enter a stage of chromosome fragmentation and reshuffling that dramatically increases the risk for genetic mistakes. Scientists have long suspected that checkpoint surveillance is essential to ensuring that our genome emerges unscathed from this process. It had been thought, however, that checkpoints come into play only when chromosome repair fails. Now, research in the Hochwagen lab indicates that the checkpoint system is actually an integral part of normal meiosis. By studying the sexually reproducing baker's yeast, the Hochwagen lab has found that the checkpoint machinery acts much like a molecular master of ceremonies for meiosis. When breaks are detected, the checkpoint system coordinates break repair with chromosome movements and remodeling. The lab recently discovered the first molecular toggle that enables this coordination by triggering significant alterations in chromosome movement.

The success of the Whitehead Fellows program borders on legendary. The program frees a handful of blossoming researchers from teaching responsibilities and dares them to follow their dreams in the lab. Seldom do the results disappoint.

Defne **Yarar**

The inside of a cell is a bustling place, with bubble-like vesicles zooming along protein cables, organelles churning out and modifying proteins, and mitochondria tearing molecules apart for energy.

None of this activity occurs in a vacuum. Events outside the cell can significantly affect what's happening inside. Defne Yarar explores one of these interactions: how the stickiness of a surface that a cell contacts can affect the cell's uptake of large molecules through endocytosis.

During endocytosis, a section of cell membrane traps exterior molecules as it bends into the cell and then pinches off from the rest of the membrane. Because this is the only way a cell can absorb certain molecules, including nutrients, hormones, and drugs, endocytosis is vital for both normal and diseased cells. However, when a cell adheres to a surface, as most cells do when they form tissues and organs, Yarar has found that endocytosis slows considerably. She's also found that proper dynamics of the actin cytoskeleton, which helps maintain cell shape, are necessary for endocytosis at these sticky sites. Altering the actin cytoskeleton can be perilous, and Yarar is currently investigating how cells successfully organize and regulate actin assembly and disassembly at these adhesion sites.

Paul **Wiggins**

Despite the central importance of DNA to molecular biology and genetics, remarkably little is known about the way the chromosomes are folded inside the cell. Paul Wiggins is working to change that.

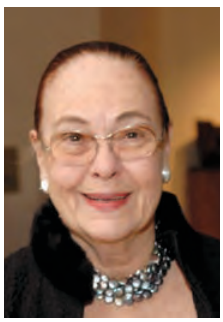
The Wiggins lab recently mapped the physical conformation of the *E. coli* chromosome. Surprisingly, the majority of genes were found to inhabit precise locations in the cell. Wiggins and coworkers demonstrated that this precise organization was the result of the chromosome's being folded into a precisely ordered chromosome filament. This highly ordered chromosome structure appears to be essential for efficient segregation of sister chromosomes into the daughter cells during cell division, although the biological consequences of chromosome structure remain poorly understood. The lab is now working to uncover the mechanism of the chromosome folding and segregation processes in bacteria.

Community Evolution

Never at rest, the Institute is constantly evolving and advancing in myriad ways. Some changes are subtle, others profound. In 2009, the Whitehead community saw its share of transitions. Simply put, stasis doesn't happen here.

Board and Philanthropy News

MIT economics professor **Nancy Lin Rose** was elected to the Institute's Board of Directors in December 2009. Nancy, who serves as Director of the National Bureau of Economic Research program in Industrial Organization, analyzes firm behavior and the economics of regulation. She received her A.B. magna cum laude in Economics and Government from Harvard University and her PhD in Economics from MIT. She was a member of the faculty of MIT's Sloan School of Management from 1985-1997, and joined MIT's Economics faculty in 1994. In 2000 and again in 2004, she received the MIT Undergraduate Economics Association Teaching Award. Nancy now fills the Board seat formerly held by MIT chemistry and biology professor Barbara Imperiali, who had served since 2006.



Board member and longtime Institute supporter **Brit d'Arbeloff** generously contributed $100,000 to help support a new childcare assistance program. In June 2009, the Institute announced a partnership with daycare provider Bright Horizons Family Solutions to provide discounted positions for children of Whitehead scientific and administrative staff at its nearby facility. In thanking Brit—long an advocate of initiatives helping women in science balance career and family challenges—Director David Page noted that her gift not only bolsters Whitehead's commitment to families but also its ability to attract and retain the best people for the Institute.

Just before 2009 expired, Board of Associates members **Andria and Paul Heafy** performed two remarkable acts of generosity to help launch the careers of young scientists. Motivated by word of a budgetary constraint that would delay the hire of a promising postdoctoral researcher in the lab of Member Robert Weinberg, the Heafys donated $100,000 specifically to expedite that process. At the same time, they pledged $750,000 in support of the Andria and Paul Heafy Fellow of Whitehead Institute. This extraordinary contribution, to be matched by the Institute, will underwrite a Whitehead Fellow during his or her four or five years in an Institute laboratory. In acknowledging their exceptional gifts, David Page lauded the Heafys' "bold decision to advance biomedical research" and praised their outstanding philanthropic leadership.



Institute News

In the spring of 2009, **Fernando Camargo** wrapped up a four-year stint as a Whitehead Fellow to accept a joint appointment in the Stem Cell Program at Children's Hospital in Boston and the Department of Stem Cell and Regenerative Biology at Harvard University. The Children's and Harvard programs emphasize exploring the potential of stem cells in treating human diseases.

Camargo's time at Whitehead was highlighted by interactions with other labs, including those of Members Harvey Lodish, David Bartel, and Rudolf Jaenisch, enabling him to learn from their respective expertise in blood-forming stem cells, microRNAs, and cellular reprogramming.

Kate Rubins shortened her term as Whitehead Fellow to join eight other men and women selected by NASA for its astronaut candidate class. NASA announced its selections after a months-long screening of more than 3,500 applications. Rubins left for Houston in August 2009 to begin a training program that, among other things, requires her to pilot supersonic jet aircraft and speak Russian fluently. Her time at Whitehead, however, was not without its adventures. She routinely visited the Democratic Republic of Congo, where she established a lab to study human outbreaks of monkey pox, and gained experience handling samples of lethal Ebola and smallpox viruses in collaborations with the U.S. Army and U.S. Centers for Disease Control.

Public Outreach

Nineteen years ago, Whitehead faculty solidified a commitment to outreach with the Whitehead Partnership for Science Education, which exposes area teachers and students to cutting-edge research. Each program aims to enhance science teaching and learning for communities. The two longest-running programs are Whitehead's Seminar Series for High School Teachers and the Spring Lecture Series for High School Students.

During 2009, the high school teachers' series concluded the program *Pursuing the Promise: Advances in Stem Cell Science*, which addressed not only the vast potential of stem cell research, but also misconceptions and hurdles to be overcome. At the start of the academic year, the Institute welcomed back more than 80 participating teachers to kick off the 2010-2011 series, *The Genetics of Human Disease*, offering a look at possible genetic links to illness and an introduction to the burgeoning field of epigenetics.

The April school vacation week brought more than 100 scientifically inclined high school students to the Institute for a three-day program, *Deconstructing Evolution*. Coinciding with the 200th anniversary of the birth of Charles Darwin and the 150th anniversary of the publication of Darwin's *On the Origin of Species*, the program reminded students how scientists still study evolutionary mechanisms to decipher human diseases.

Honor Roll of Donors

Whitehead Institute recognizes with deepest gratitude those individuals, organizations, foundations, and corporations who lent their support so generously in fiscal year 2009, between July 1, 2008 and June 30, 2009.

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In honor of Matthew and Katrina Nichols, Eve and Nick Nichols

In honor of Arthur Brill and Carol Tobin, Robert Parnes and Gwenn Mussman-Parnes

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In memory of Joseph Purcell III, Deborah and David Gallin

In memory of Henry Allen, Ruth Sandak

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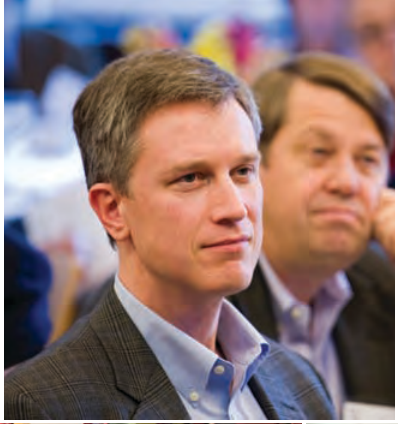




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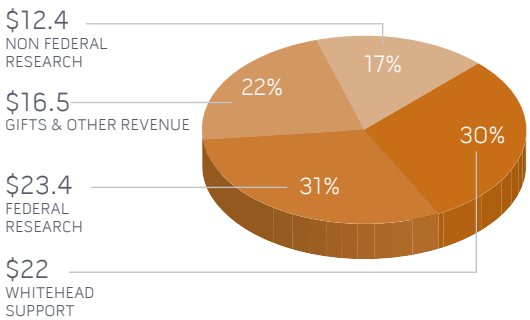
Financial Summary

Owing to its financial strength, Whitehead Institute has been able to weather this period of global economic uncertainty and maintain its commitment to best-in-class science. The quality of Whitehead research allows the Institute's faculty and associated scientists to compete successfully for federal and non-federal funding, while the generosity of individuals, corporations, and foundations provides critical support where funding gaps might otherwise appear. Contributing to the Institute's fiscal stability, the administration continues to reduce operating expenses in a concerted effort to maximize research-specific spending.

Revenues & Support

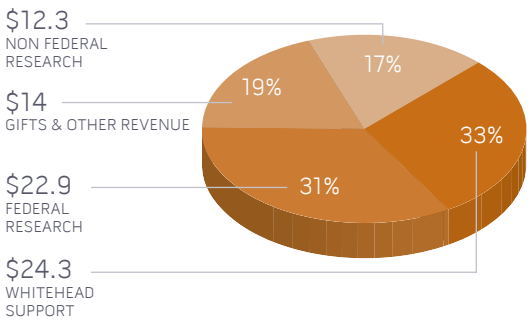
IN MILLIONS

2009



2009 TOTAL
$74.3

2008

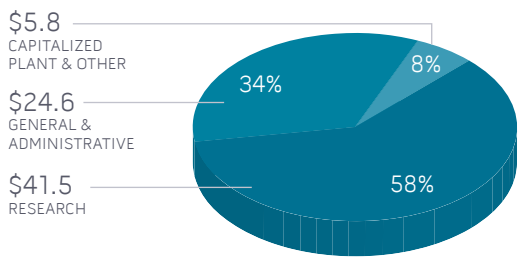


2008 TOTAL
$73.5

Expenditures & Disbursements

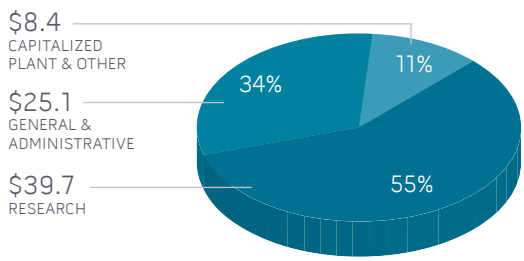
IN MILLIONS

2009



2009 TOTAL
$71.9

2008



2008 TOTAL
$73.2

Leadership

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

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

FACULTY ACHIEVEMENTS Whitehead faculty includes the recipient of the 1997 National Medal of Science (Weinberg), seven members of the National Academy of Sciences (Fink, Jaenisch, Lindquist, Lodish, Orr-Weaver, Page, and Weinberg), six fellows of the American Academy of Arts and Sciences (Fink, Jaenisch, Lindquist, Lodish, Ploegh, and Weinberg), five members of the Institute of Medicine (Fink, Jaenisch, Lindquist, Page, and Weinberg), 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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