Whitehead Institute
2011 Annual Report

Why not?

In the face of uncertainty, the safe play often feels like the best choice. Conventional wisdom abounds: Minimize risk. Invest conservatively. Hunker down. Stick with what works. Don't be a hero. Live to fight another day…

At Whitehead Institute, conventional wisdom rarely has a seat at the table. Here, the world's most talented scientists embrace risk. They are empowered to think creatively, to act boldly. They are not reckless, to be sure, but when confronting challenges that would freeze the timid, they move forward asking defiantly, "Why not?"

COVER/INSIDE *Cells shown in this fruit fly gut image copy their DNA (blue) hundreds or thousands of times. A cell signaling protein (green) is thought to influence this abundant DNA replication.*

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COVER/INSIDE FRONT COVER Jessica Von Stetina/Whitehead Institute **PAGES 4–5** Dan Wagner/Whitehead Institute **PAGE 6** Reprinted with permission from *PNAS*. "High levels of nuclear heat-shock factor 1 (HSF1) are associated with poor prognosis in breast cancer." Santagata S, Hu R, Lin NU, Mendillo ML, Collins LC, Hankinson SE, Schnitt SJ, Whitesell L, Tamimi RM, Lindquist S, Ince TA. **PAGE 7** Reprinted from *Cell*, 147(7), Ulitsky I, Shkumatava A, Jan CH, Sive H, Bartel DP. "Conserved function of lincRNAs in vertebrate embryonic development despite rapid sequence evolution," p.1537–50, Copyright 2011, with permission from Elsevier. **PAGE 8** Reprinted by permission from Macmillan Publishers Ltd: *Nature Biotechnology,* Aug 24; 477(7364):340–3, copyright 2011. **PAGE 9** Reprinted from *Cell*, 146(4), Soldner F, Laganière J, Cheng AW, Hockemeyer D, Gao Q, Alagappan R, Khurana V, Golbe LI, Myers RH, Lindquist S, Zhang L, Guschin D, Fong LK, Vu BJ, Meng X, Urnov FD, Rebar EJ, Gregory PD, Zhang HS, Jaenisch R. "Generation of isogenic pluripotent stem cells differing exclusively at two early onset Parkinson point mutations", p. 659, Copyright 2011, with permission from Elsevier. **PAGE 11** Christina Scheel/Whitehead Institute **PAGE 13** Top: Jessica Von Stetina/Whitehead Institute Bottom: Allyson Whittaker/Whitehead Institute **PAGE 16** Zuzana Keckesova/Whitehead Institute **PAGES 18–49** Kathleen Dooher **PAGE 50** Yueh-Chiang Hu/Whitehead Institute **PAGES 52–53** Kathleen Dooher **PAGES 55, 56, 59** Justin Knight **PAGE 61** Robert Mathis/Whitehead Institute **PAGE 62** Chris Sanchez **PAGE 63** (inside back cover) From *Science Signaling* online cover, Vol. 5, Issue 224, 15 May 2012. [Image: Kris C. Wood, Whitehead Institute for Biomedical Research, Broad Institute of Harvard and Massachusetts Institute of Technology] Reprinted with permission from AAAS.

Contents

Why not be extraordinarily basic?

"We don't know what we don't know." This truism-cum-cliché reminds us how far we have to go.

Yet, outside the realms of science and medicine, there is a growing sense that scientists and physicians collectively know, or imminently will learn, everything about the physical world and the human body; that the era of discovery is ending and the time has come to focus on practical application of basic knowledge. It's a falsehood, of course, but such thinking has surfaced throughout history—following the charting of new territories by the great explorers in the 15th and 16th centuries, Jenner's experiments with smallpox vaccination in the 18th century, or Roentgen's discovery of the X-ray in the 19th century. Fortunately for humanity, these great investigators and those who have followed never stopped seeking fundamental scientific truths in the wake of successes.

Today, we avail ourselves of extraordinary technologies that allow us to probe and expand our base of biological knowledge in ways once unimaginable. Our grasp of biology has never been stronger, our technical capacity never deeper. Thus, in our impatience for medical progress, it is tempting to hit the fast-forward button, not knowing what we're sacrificing by perhaps skipping a basic step or two. But shortcuts often lead to dead ends.

Whitehead Institute was founded on the belief that basic biomedical research offers our best hope for improving human health. While on occasion we may have been poorly served by unfortunate semantics—as our research is anything *but* basic—our faculty, their laboratories, and the scientists expertly trained in them have contributed some of the most important advances in their fields. That's why we're here: to deliver fundamental understandings that eventually lead to the therapeutic breakthroughs and cures society so desperately needs.

Because our commitment to basic science remains firm, I am heartened by this report's thematic query: "Why not?" It is an exhortation to our scientists, a rejoinder to skeptics, and a reminder of the risk-taking approach that has made Whitehead Institute so successful. It's truly gratifying that our faculty, staff, friends, and supporters join me so enthusiastically in calling the question.

David C. Page

Scientific Achievement

The research conducted in thes e laboratories has distinguished Whitehead Institute from incep tion. Despite another year of impactful, award-winning disco veries, Whitehead scientists are far from satisfied. For a world awaiting more breakthroughs, that is very good news indeed.

In this image of an adult planarian, a single stem cell, called a cNeoblast, has given rise to a colony containing multiple cell types, including proliferating (green) and differentiating (yellow and magenta) populations.

Cancer: *Ups and downs for negatives and positives*

Of the many pathology screens performed on a breast cancer biopsy, the test for estrogen receptor (ER) status is among the most telling. ER-positive tumors tend to respond to hormone-suppression therapy and are generally associated with more favorable outcomes, while patients with ER-negative tumors are notoriously difficult to treat and have low five-year survival rates.

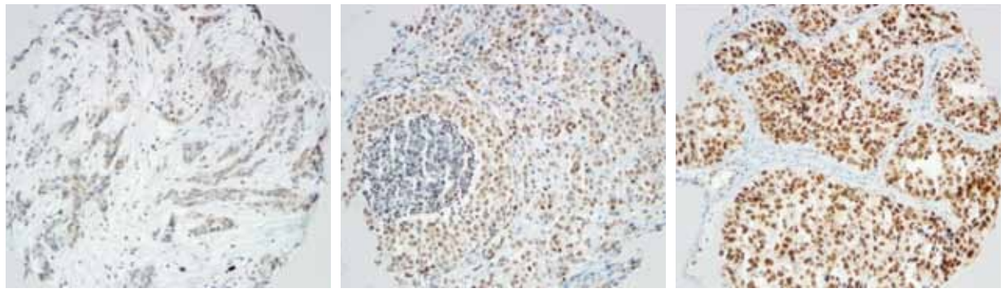
In a finding that may one day help overcome treatment resistance, researchers in the lab of Whitehead Member **David Sabatini** recently identified a protein in a key metabolic pathway that plays a prominent role in the growth of ER-negative breast tumors. The lab developed a novel *in vivo* system to screen a set of 133 genes that have been linked to aggressive breast cancer, finding that a gene known as *PHGDH* codes for a protein that is elevated in 70% of ER-negative breast cancers. Working with human breast cancer cell lines grown in mice, researchers found that suppressing production of the protein (which is one of three enzymes in the serine biosynthesis pathway) in cells in which it is overexpressed led to a dramatic reduction in tumor cell growth.

"We do think this has some therapeutic relevance, where an inhibitor of this enzyme would have effects on the cells we identified that overexpress this enzyme," says Sabatini. "We've provided proof of principle. Whether a drug against this protein would be valuable remains to be determined."

Meanwhile, scientists in the lab of Whitehead Member **Susan Lindquist** have found that ER-positive breast cancer patients whose tumors have high levels of a cellular survival protein known as heat shock factor 1 (HSF1) experience increased mortality.

The heat shock response, which is controlled by transcription factors like HSF1, enables cells to withstand temperature spikes and other stressors. To survive within the stressed environment of a tumor, cancer cells often hijack the normally beneficial heat shock response to support their existence. By examining HSF1 levels in tissue samples from more than 1,800 patients in a large epidemiological study, Lindquist lab researchers discovered that patients whose ER-positive tumors have high levels of HSF1 had poorer outcomes, with tumors that tended to be larger and more aggressive.

"HSF1's relationship to prognosis raises possibilities for diagnostic applications," says Sandro Santagata, a postdoctoral researcher in the Lindquist lab. "HSF1 levels could help determine who will fare better and possibly who will have a poorer response to certain drugs."



After analyzing data and tissue from over 1,800 patients, including the tumor samples above, researchers determined that in patients with ER+ breast cancer, tumors with high levels of heat shock factor 1 (HSF1) expression (right; HSF1 stained brown) are associated with poorer patient outcomes than those with low (middle) or no HSF1 expression (left).

Long non-coding RNAs: *These 'lncs' aren't missing at all*

The human genome has a dirty, not-so-little secret: a huge portion of it is essentially unaccounted for, comprising dark matter of unknown function. In fact, according to estimates from a massive project funded by the National Human Genome Research Institute, only 10% of RNAs transcribed in a human cell go on to template functional proteins. The remainder of RNAs is lumped under the umbrella term "non-coding RNAs (ncRNAs)."

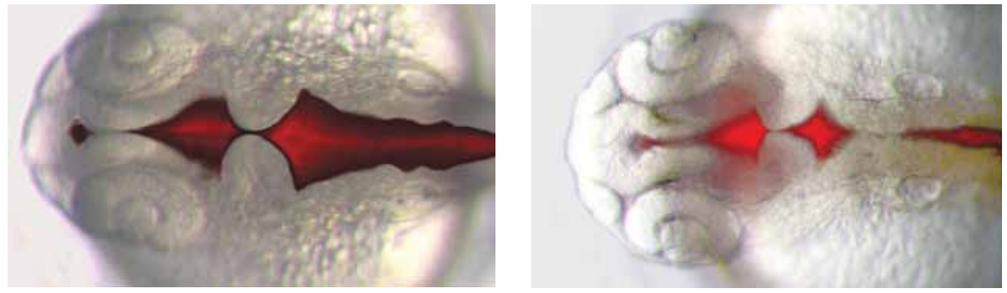
Among the varieties of ncRNAs are tiny microRNAs, which have been relatively well explored, and a group of larger ncRNAs (those longer than 200 base pairs) known as long intervening non-coding RNAs (lincRNAs). Located between protein-coding genes, lincRNAs, though abundant, have only recently come under systematic scrutiny—with surprising findings.

Researchers in the lab of Whitehead Founding Member **Harvey Lodish** recently identified a lincRNA that plays a pivotal role in the production of red blood cells by preventing programmed cell death, or apoptosis, in red blood cell progenitors.

"Apoptosis, is very important, particularly in the hematopoietic (blood-forming) system, where inhibition of cell death leads to leukemias," says Lodish. "We know a lot about the genes and proteins that regulate apoptosis, but this is the first example of a non-coding RNA that plays a role in blood cells. We would not be surprised to find this lincRNA or others like it upregulated in cancers."

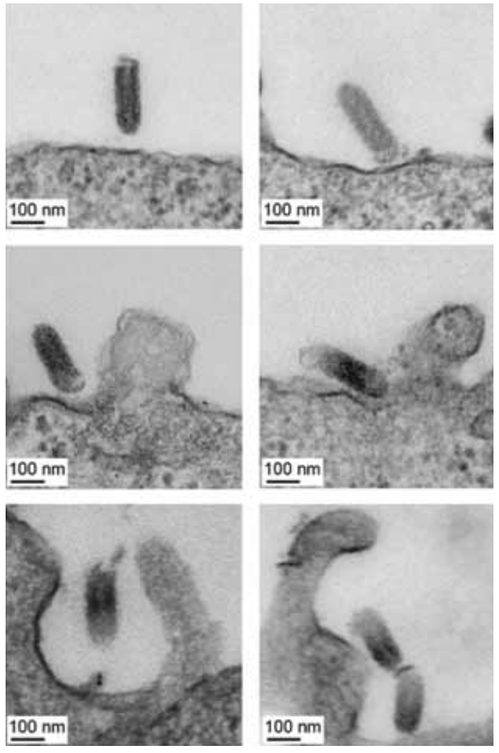
Meanwhile, a recent collaboration between the labs of Whitehead Members **David Bartel** and **Hazel Sive** revealed fascinating functional equivalence for lincRNAs found in humans and zebrafish. Researchers began by identifying more than 500 lincRNAs in zebrafish, 29 of which proved to have homologs in mammals. Perturbing expression of two of the 29 caused dramatic physical effects in developing zebrafish embryos. Suppression of one resulted in abnormally large nasal regions and extremely small heads and eyes, while knockdown of the other produced embryos with malformed heads and enlarged brain ventricles. Intriguingly, injection of the human homologs of the lincRNAs led to normal cranial formation in the developing embryos.

"These studies show that zebrafish, which are frequently used to study the genetics of animal development, can also serve as a tool to uncover in systematic fashion the functions of lincRNAs," says Bartel. "This is another case in which a phenomenon in zebrafish provides insight into what's probably happening in humans, as has been established in many studies of protein-coding genes."



Long intervening non-coding RNAs (lincRNAs) are crucial for certain organismal functions. As shown in the image above right, suppressing just one lincRNA in developing zebrafish embryos has startling effects—in this case, the head and eyes are shrunken and brain development is defective. A zebrafish with proper expression of the lincRNA in question (left) develops normally.

Immune Response: *Thwarting unauthorized entry*



Electron micrographs show membranes of normal human cells engulfing the black, capsule-like Ebola virus (left), unlike the cells on the right, which carry a genetic mutation that foils the virus's entry.

A healthy immune system's first step in mounting a defense against attacking invaders is to recognize the enemy. In the case of certain fungi, however, the hostile cells may be so cleverly disguised that they're able to slip past our cellular guardians undetected and wreak havoc through infection. Such infections are a rising source of morbidity and mortality in healthy individuals, and can be utterly devastating in the immunocompromised.

Whitehead Members **Hidde Ploegh** and **Gerald Fink** have long been focused on such evasion, and researchers in their labs recently identified a novel mechanism by which immune cells can distinguish between pathogenic and non-pathogenic fungi and modulate the immune response accordingly.

Earlier work had found that dectin-1, a protein found in the macrophages of the immune system, reacts to the presence of beta-glucan, a sugar molecule that supports fungal cell walls, triggering an immune response. However, over millennia of human-fungal interactions, pathogenic fungi have acquired the ability to mask their beta-glucan beneath a blanket of proteins and other sugar molecules on their cell surfaces. With the help of live-cell imaging, researchers discovered that dectin-1 gets an assist from another protein, galectin-3, which recognizes and binds to disguising molecules that are only present on pathogens such as *Candida albicans*. This recognition flags the fungal cells as hostile and modulates the dectin-1-mediated immune response.

In other studies of infectious processes, researchers in the lab of former Whitehead Fellow **Thijn Brummelkamp** used an unusual human cell line to conduct genetic screens that identified a protein the deadly Ebola virus exploits to gain entry into the cells of its host. The discovery may offer a new and better approach for the development of antiviral therapies, as it would target a structure in the host cell rather than a viral component.

"Right now, people make therapeutics to inactivate the pathogen itself. But the problem is that pathogens can quickly change and escape detection and elimination by the immune system," says Brummelkamp, now a group leader at the Netherlands Cancer Institute. "Here we get a good idea of the host genes that are needed for the pathogen to enter the cell for replication. Perhaps by generating therapeutics against those host factors, we would have a more stable target for antiviral drugs."

Stem Cells: *Target acquired, with unprecedented precision*

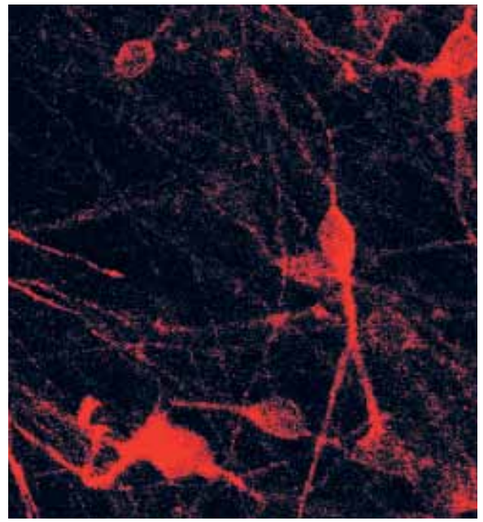
Despite the enormous potential implicit in research with embryonic stem (ES) cells and reprogrammed, induced pluripotent stem (iPS) cells, progress has been slowed by a number of hurdles. One of the more significant obstacles in the path to clinical advances has been scientists' inability to manipulate targeted genes in both human ES and iPS cells in a consistent, reliable manner.

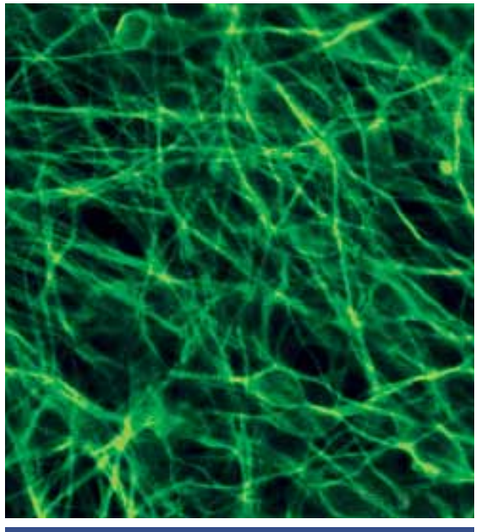
During 2011, researchers in the lab of Whitehead Member **Rudolf Jaenisch** employed two methods to overcome this challenge. In one case, lab members used proteins known as zinc finger nucleases (ZFNs) to change a single base pair in the genome, allowing them either to insert or remove mutations known to cause early-onset Parkinson's disease (PD). The second method relies on proteins called transcription activator like effector nucleases (TALENs) capable of altering specific genes with the efficiency and precision found with ZFNs.

This targeted genetic manipulation brings the field closer to realizing the therapeutic promise of these cells, which depends on such changes to fix disease-causing mutations before the cells could be transplanted into patients or to create cell lines that researchers can use to study genetic diseases. Such disease studies—the much-heralded "disease in a dish" approach—and the search for disease-modifying therapies also require the use of cells and controls that are genetically identical, except for a specific alteration whose impact can then be observed.

"This is very relevant for diseases like Parkinson's, which likely will display only subtle phenotypes in the Petri dish," says Jaenisch. "It is very important that the cells be genetically identical, have the same history, and differ only by a single mutation that is either introduced or eliminated. If you use control cells from one person and a diseased cell from another person, it's really just like comparing apples and oranges."

In Jaenisch's research, scientists were able to create from normal and PD patients' cells, sets of mutated and control cell lines. By either removing or adding a mutation to the alpha-synuclein gene, which is associated with PD, the scientists generated lines of cells whose genomes differ only by a single base pair. Subsequent differences seen in comparative studies of the cells can therefore be attributed directly to the mutation in question.





Using a precise method, researchers removed disease-causing mutations while reprograming skin cells from Parkinson's disease (PD) patients. Once corrected, the cells were cultured into neurons (green), including dopamine-producing neurons (red) wiped out by the disease.

Highs and Lows in the Study of Cancer Stem Cells

Cancer biologists focused on demystifying the strange ways of cancer stem cells—with an eye toward ultimately developing related therapeutic strategies—have been on a bit of a roller coaster ride of late. The highs from discoveries pointing to potential vulnerabilities have been accompanied by lows from revelations that these opponents are craftier and more resilient than previously imagined.

Such has been the case in Whitehead Founding Member **Robert Weinberg's** lab, which has long been at the forefront of cancer stem cell research. It was the Weinberg lab that made the seminal discovery back in 2008 that certain cancer cells undergo what's known as an epithelial-mesenchymal transition (EMT), which confers on them the properties of cancer stem cells; specifically, the ability to self-renew and seed new tumors. The EMT also enables cells to migrate from the primary tumor and form new malignancies at distant sites.

The research, a major advance in our understanding of metastasis, also enabled development of a novel method for producing large numbers of cancer stem cells, which are naturally quite rare. By inducing an EMT in cells in culture, scientists can generate enough of these cells to screen for compounds that might selectively kill them. Taken together, this work fueled excitement that cancers could be treated successfully with traditional chemotherapies that kill the bulk of tumor cells *and* targeted agents that eradicate the small population of cancer stem cells, which are resistant to standard therapy and are thought to be responsible for recurrence.

Fast forward to 2011, when new research emerging from the Weinberg lab put a damper on that proposition. The picture became more complicated with the discovery that fully differentiated cells in breast tissue can *spontaneously* convert to a stem-cell-like state. This surprising finding marked the first time such behavior had been observed in mammalian cells. It also flew in the face of longstanding scientific dogma that differentiation is a one-way path; once cells specialize, they cannot return to the flexible stem-cell state on their own. The implications are powerful.

Notes Weinberg: "It may be that if one eliminates the cancer stem cells within a tumor through some targeted agent, some of the surviving non-stem tumor cells will generate new cancer stem cells through spontaneous de-differentiation."

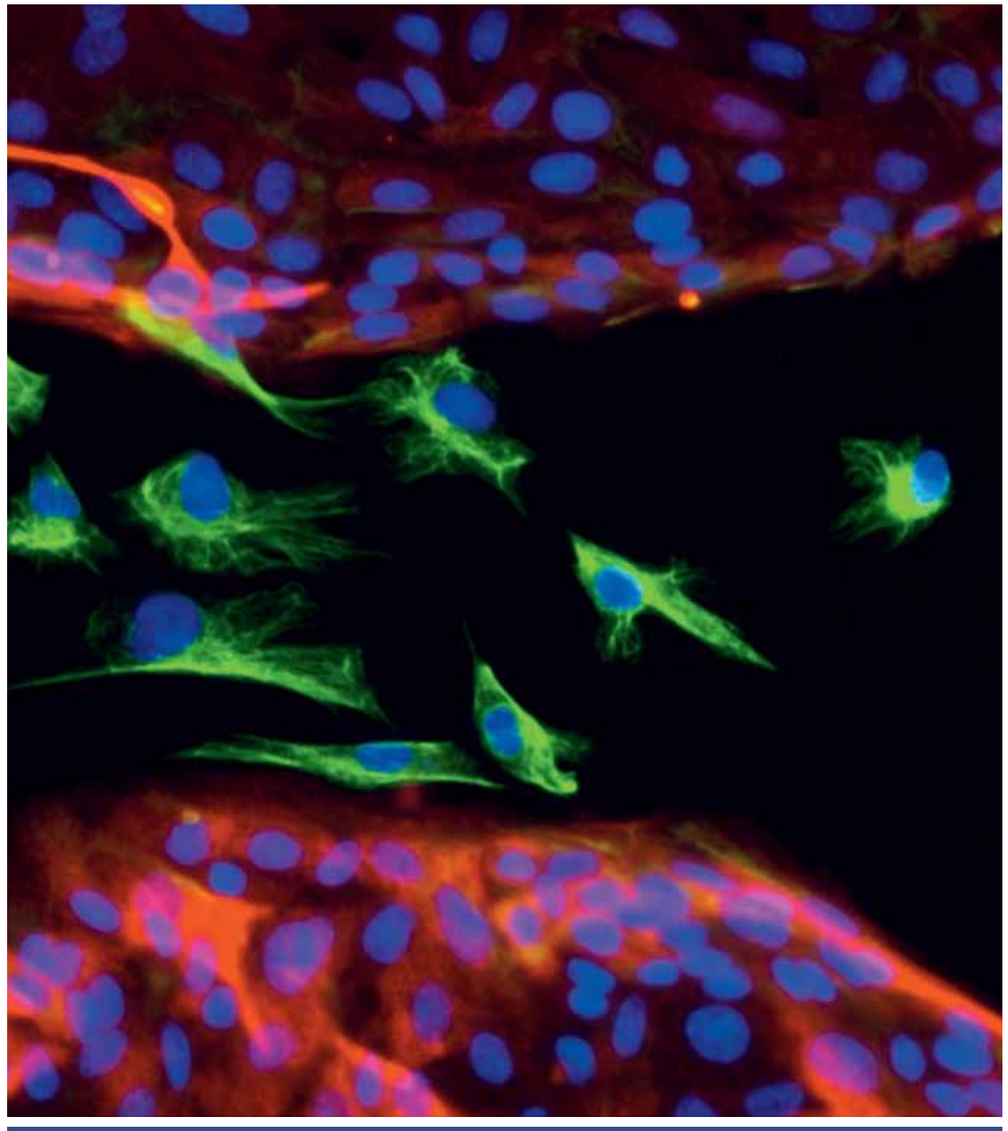
From another corner of the lab, however, where scientists were trying to determine what environmental cues send cells through an EMT, came findings that may eventually restore a little optimism. By studying human breast epithelial cells, researchers identified three cell-signaling pathways (TGF-beta, non-canonical Wnts, and canonical Wnts) that together maintain the migratory and self-renewing traits of both normal breast epithelial stem cells and breast cancer stem cells. These pathways are kept active in the stem cells by autocrine signals; that is, signals produced by the cells themselves.

Further exploration revealed that normal epithelial cells are kept in their differentiated state via inhibition of the three signaling pathways. Researchers found that these cells naturally produce proteins that block the signaling, and, as expected, removal of these inhibitors *in vitro* via chemical manipulation induces an EMT that pushes the cells into a mesenchymal and stem-like state.

These findings suggested that blockade of autocrine signaling could prevent cancer cells from morphing into their aggressive, stem-like state, but would it work *in vivo*? As a test, researchers implanted into mice human breast cancer epithelial cells that had passed through an EMT. They then injected the implantation site with proteins that block the three pathways. The injected mice had one-tenth the number of tumors found in mice that did not receive the inhibitory proteins. In addition, breast cancer cells that were pre-treated *in vitro* with these proteins displayed a greatly reduced ability to metastasize when subsequently implanted into mice.

Beyond delivering important insights into transitions between, and maintenance of, cell states, the work provides a rationale for the development of therapies capable of preventing an EMT—and therefore, the generation of cancer stem cells. But, and because this is cancer research, there's always a but, could this approach be applicable beyond breast cancer?

Says Weinberg: "Are the same agents signaling the EMT in non-mammary tissues—the skin, liver, the gut, pancreas and so forth? Whether these signaling pathways turn out to have a degree of universality, we just don't know yet."



During an epithelial-to-mesenchymal transition (EMT), epithelial cells acquire the traits of mesenchymal cells. Unlike these tightly-packed epithelial cells (red with blue nuclei) that adhere to one another, loose mesenchymal cells (green with blue nuclei) can move freely within and among tissues.

Runaway replication

The genome encodes all of life's instructions, which are passed elegantly from mother cell to daughter cell during mitotic cell division. During this familiar process, the genome's double-stranded DNA helix is split and duplicated, forming two complete copies—one for each resulting cell.

It's simple, clean, and neat. However, there are times in an organism's life when such straightforward doubling and dividing just won't suffice; times when cells in various tissues require multiple copies of the genome or an increase or decrease in the copy number of specific genes. Ever resourceful, nature has found ways to oblige.

Consider the fruit fly salivary gland, whose cells' nuclei are crammed with more than 2,000 copies of the genome, thanks to a precise mechanism for over-replication. Other cell types may resort to over-replication in response to developmental cues to expand their overall size. Of course, hyperactive genomic copying is not always intended or beneficial, as in the case of cancer cells in which replication rages out of control.

"It's remarkable how a very basic process like DNA replication can be so dramatically changed from one cell type to another," says Jared Nordman, a postdoctoral researcher in the lab of Whitehead Member **Terry Orr-Weaver.**

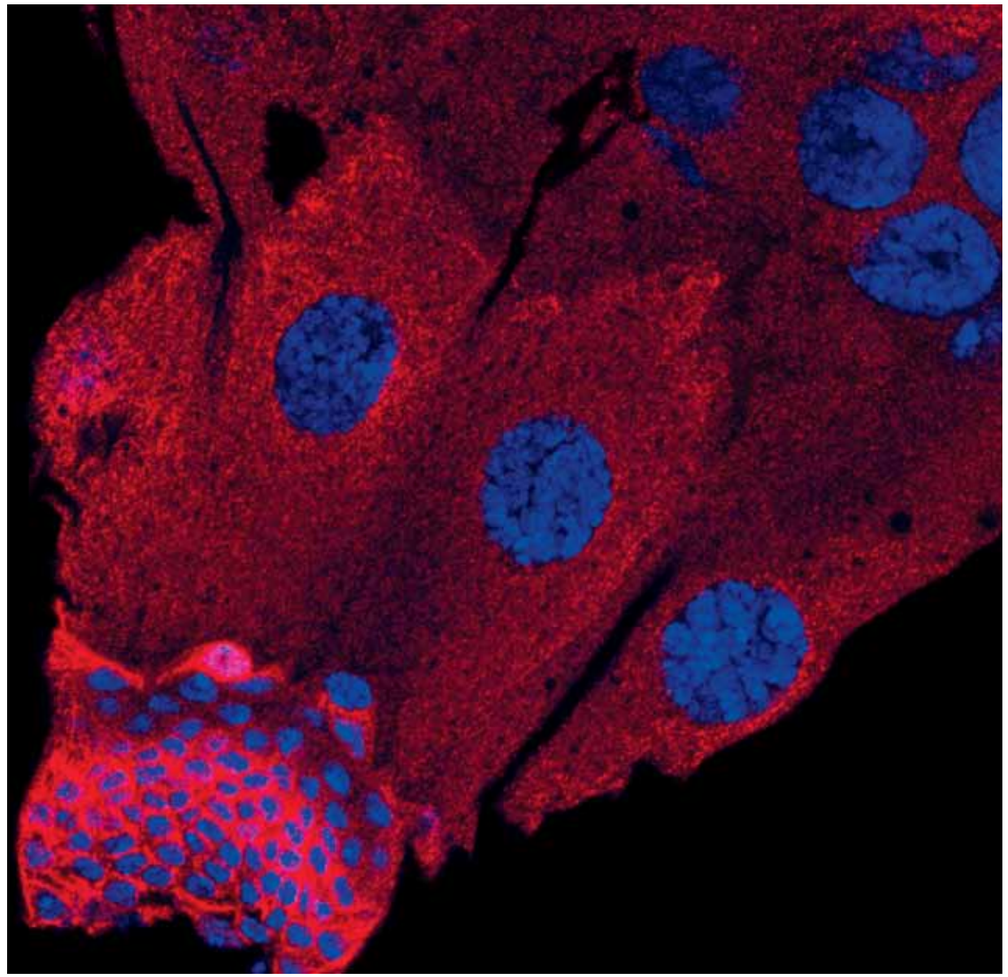
By studying various fruit fly tissues, Nordman and others in the Orr-Weaver lab are studying how these cells tap into DNA replication machinery and what goes awry in cancer cells. Until now, little was known about how DNA replication initiates in animals, in part because researchers had difficulty pinpointing the specific DNA sites where replication starts. These sites, known as origins of replication, require binding with the Origin Recognition Complex (ORC), a protein bundle that prompts replication. By identifying the DNA regions that are bound by ORC, the lab has located the few thousand potential origins of replication in the fruit fly genome and discovered that the positioning of origins differs between cell types. This impressive feat has yet to be accomplished in human cells.

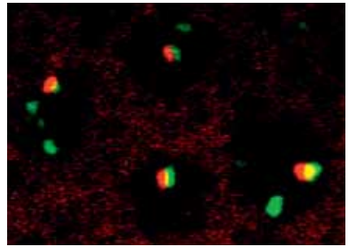
Fruit fly ovarian follicle cells, which secrete components of the eggshell, take DNA replication to a whole new level. The Orr-Weaver lab found that to increase copy number substantially at six specific DNA regions, the origins at these sites initiate replications in rapid succession. The original DNA strands are copied to become four strands as the replication machinery chugs along the DNA. A short time later, the origin kicks off another round of replication, and the four strands copy to form eight strands. Eight strands become sixteen, and so on, until the surrounding region looks like the many layers of an onion. To confine active DNA replication machinery to the proper area, chromatin sets up blockades along the perimeter of the region being copied.

While developmental signals can trigger over-replication, the process in some tissues may be blocked in specific genomic regions. In areas where DNA replication is repressed, the Orr-Weaver lab identified a protein called suppressor of under-replication (SuUR), which prevents copying of these regions. Additionally, origins of replication are sparse in these regions. Under-replicated domains can become fragile and prone to breakage, which can lead to genomic rearrangements that are frequently evident in cancer cells.

Cancer cell genomes typically harbor such rearrangements, along with a host of genetic deletions, additions, and multiple stretches of over-amplified DNA. Work in the Orr-Weaver lab has shown that many mechanisms may be commandeered to promote the over-replication of DNA. Because cancer cells have over-amplified DNA domains and deleterious genes that are over-expressed, some scientists have presumed that amplified sections of DNA are responsible for heightened gene expression. However, Orr-Weaver finds this is not necessarily the case. In fact, genes in amplified regions are often not robustly expressed.

"DNA replication is not a mechanism to regulate transcription," says Orr-Weaver, who is also an American Cancer Society professor of biology at MIT. "Instead, it's probably more fundamentally about a cell wanting to time exactly when different parts of the genome get duplicated."





This developing fruit fly's salivary gland (above) contains multiple, large cells with thousands of copies of DNA (blue) crowded into each nucleus. Cells achieve such high DNA content by repeatedly initiating DNA replication at origins of replication distributed throughout their genome. In fruit fly ovarian follicle cells (left), scientists in Whitehead Member Terry Orr-Weaver's lab located DNA replication sites (green) and origins of replication by tagging a protein complex (red) that attaches to the origins. According to Orr-Weaver, over-replication does not always lead to gene over-expression, but may be a mechanism for timing the duplication of certain segments of the genome.

Honors and Awards

DAVID BARTEL

Whitehead Member David Bartel was elected on May 1 to membership in the National Academy of Sciences in recognition of distinguished and continuing achievements in original research. Election to membership in the National Academy is considered one of the highest honors that can be accorded a U.S. scientist or engineer. A recognized leader in the study of microRNAs and their effects on gene expression, Bartel joined Whitehead Institute in 1994 as a Whitehead Fellow. With his election, he became the eighth Whitehead Member to hold membership in the National Academy of Sciences. The others are Gerald Fink, Rudolf Jaenisch, Susan Lindquist, Harvey Lodish, Terry Orr-Weaver, David Page, and Robert Weinberg.

MARY GEHRING

In June, The Pew Charitable Trusts named Whitehead Member Mary Gehring a 2011 Pew Scholar in the Biomedical Sciences. Gehring, who joined the Whitehead faculty in September 2010, was one of 22 promising young scientists selected for the honor from a field of 136 nominees. The Pew scholarship provides Gehring with $60,000 in research support annually over a four-year period. Gehring is the second Whitehead Member to be named a Pew Scholar. David Sabatini earned the same honor in 2003.

RUDOLF JAENISCH

In February, Israel's Wolf Foundation, whose stated mission is "to promote science and art for the benefit of mankind," named Whitehead Founding Member Rudolf Jaenisch a recipient of the prestigious 2011 Wolf Prize in Medicine. Jaenisch shared the prize with Kyoto University's Shinya Yamanaka for what the Wolf Foundation described as "their groundbreaking contribution to stem cell research." In announcing the award, the Wolf Prize Committee stated: "Collectively, the groundbreaking contributions by Dr. Yamanaka and Dr. Jaenisch form the basis for work on regenerative medicine currently performed in hundreds of laboratories around the world." Jaenisch and Yamanaka shared the $100,000 prize, which was awarded at a special ceremony at the Knesset at the end of May. Jaenisch is the second Whitehead Member to receive the Wolf Prize in Medicine. Founding Member Robert Weinberg was so honored in 2004 for his work in tumor genetics.

Four months later, Jaenisch was named the recipient of the 2011 J. Allyn Taylor International Prize in Medicine. The prize, awarded annually since 1985 by Canada's Robarts Research Institute, honors an individual or individuals who have made "significant contributions to a field of basic or clinical research in one of the Institute's principal areas of research." The 2011 topic was stem cell research.

In October, President Barack Obama presented Jaenisch with the National Medal of Science. In receiving our nation's highest scientific honor, Jaenisch was cited "for improving our understanding of epigenetic regulation of gene expression: the biological mechanisms that affect how genetic information is variably expressed. His work has led to major advances in our understanding of mammalian cloning and embryonic stem cells." Jaenisch is the third Whitehead Member to receive the National Medal of Science. Founding Member Robert Weinberg received the Medal in 1997 and Member Susan Lindquist received it 2010.

In October 2011, Whitehead Founding Member Rudolf Jaenisch received the National Medal of Science from President Barack Obama at a special White House ceremony.

SUSAN LINDQUIST

The European Molecular Biology Organization (EMBO) announced in October that Whitehead Member Susan Lindquist had been awarded a life-long EMBO membership. The organization supports talented researchers, stimulates scientific exchange, and advances policies for a world-class European research environment. The EMBO roster also includes Whitehead Members Rudolf Jaenisch, Harvey Lodish, Hidde Ploegh, and Robert Weinberg.

TERRY ORR-WEAVER

In January, Whitehead Member Terry Orr-Weaver was named a Fellow of the American Association for the Advancement of Science (AAAS). AAAS members are awarded the honor for their scientifically or socially distinguished efforts to advance science or its applications. Orr-Weaver was specifically cited for her distinguished contributions to *Drosophila* cell cycle research.

DAVID PAGE

In April, Whitehead Director David Page was elected to the American Academy of Arts & Sciences. Upon announcing its 2011 class of members, Academy officials wrote that Page's "genome sequencing work has advanced the understanding of human reproduction." Page joined Whitehead Members Gerald Fink, Rudolf Jaenisch, Susan Lindquist, Harvey Lodish, Hidde Ploegh, and Robert Weinberg as a member of the Academy.

The following month, Page accepted the 2011 March of Dimes Prize in Developmental Biology. The prize honored Page's groundbreaking body of research on the human Y chromosome. He shared the honor with another expert on human sex chromosomes: Patricia Ann Jacobs, professor of human genetics and co-director of research at Wessex Regional Genetics Laboratory in Salisbury, England. In announcing the prize's recipients, Michael Katz, MD, senior vice president for Research and Global Programs at the March of Dimes stated: "Taken together, the research of Prof. Jacobs and Dr. Page has expanded medicine's ability to diagnose and understand the basis of infertility and many other diseases."

HIDDE PLOEGH

The American Association of Immunologists (AAI) in January named Whitehead Member Hidde Ploegh the recipient of its 2011 Meritorious Career Award. The award recognizes a mid-career scientist for outstanding research contributions to the field of immunology.

PETER REDDIEN

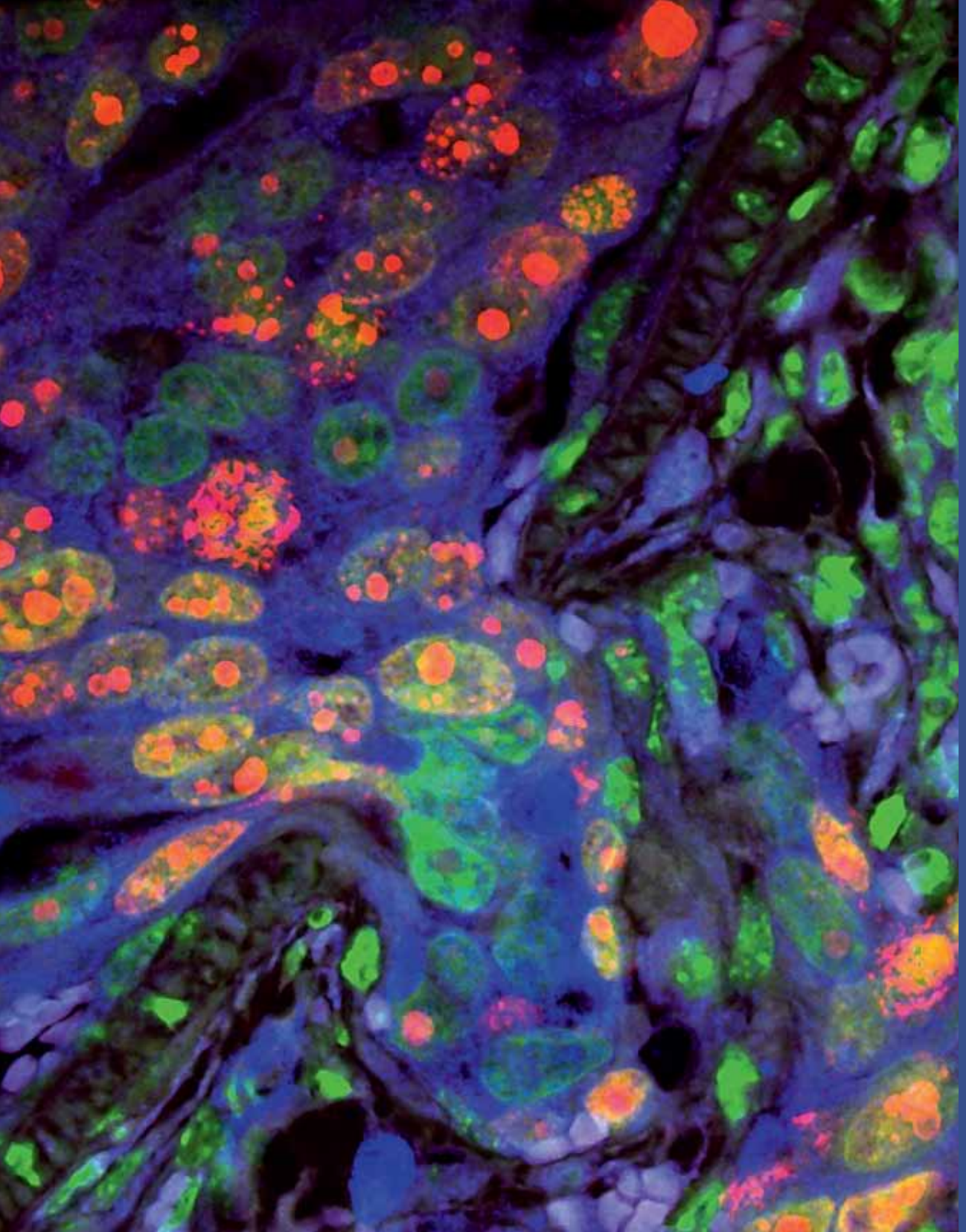
In December, the American Association of Anatomists named Whitehead Member Peter Reddien the recipient of its 2012 H. W. Mossman Award in Developmental Biology, one of four Young Investigator Awards the Association grants annually. Reddien is being honored for "his seminal contributions to the field of tissue regeneration by studying its underlying molecular and cellular mechanisms."

DAVID SABATINI

In July, the American Society for Biochemistry and Molecular Biology named Whitehead Member David Sabatini the first-ever recipient of the Earl and Thressa Stadtman Scholar Award, which is granted to a scientist with 10 or fewer years of post-post-doctoral experience, including medical residency and fellowship. The award will be given every other year, alternating with The Earl and Thressa Stadtman Distinguished Scientist Award.

WHITEHEAD INSTITUTE

For the second time in three years, Whitehead Institute was named the best place in the country for postdoctoral researchers to work. On March 1, *The Scientist* magazine released its closely followed annual rankings, which were based upon responses to a web-based survey of nearly 3,000 participants representing 93 research institutions. Whitehead Institute received high marks in such survey categories as facilities, infrastructure, and funding opportunities. Having slipped to third place in 2010 after landing the top spot in 2009, Whitehead Institute regained the number one ranking for 2011. Whitehead first cracked *The Scientist*'s annual Top 15 list in 2008, coming in at 14 that year.



Principal Investigators

Who are these 16 scientists? In simple terms, they are world-class researchers, teachers, and mentors whose contributions have forever altered the landscape of biomedical research, and whose passion and indefatigable dedication suggest their best may well be yet to come.

Whitehead Founding Member Robert Weinberg's lab is studying how metastasis occurs. Here, cancer cells (blue) and highly proliferative cancer cells (red) burst from a mouse's blood vessel into surrounding lung tissue, eventually leading to fatal metastasis.

"In a field whose dogma is that DNA codes for RNA, which codes for the proteins that ultimately perform key roles in an organism, **why not** explore the non-coding functions of RNAs?" David Bartel

In pursuing this very question, Bartel and his lab have assumed a prominent role in exposing just how abundant and biologically important these enigmatic RNAs actually are. Much of Bartel's work has focused on microRNAs—tiny segments of non-coding RNA that dampen expression of protein-coding genes. Once thought of as bit players in cellular and organismal function, microRNAs have been found, through research by Bartel and his colleagues, to target more than half of all protein-coding genes.

More recently, Bartel's lab turned an eye toward the functions of larger non-coding RNAs. Working with Whitehead Member Hazel Sive, they discovered that two particular lincRNAs (for long intervening non-coding RNAs) are essential for proper embryonic brain development in zebrafish. They first identified more than 500 lincRNAs in zebrafish, 29 of which turned out to have homologs in mammals. A series of experiments interfering with the expression of two of the 29 revealed striking effects on developing zebrafish embryos. Suppression of a lincRNA dubbed "cyrano" resulted in embryos with enlarged nasal regions and abnormally small heads and eyes, while knockdown of the lincRNA "megamind" caused the fish to have malformed heads and enlarged brain ventricles. Remarkably, injection of the human homologs of cyrano and megamind rescued the developing embryos, leading to normal cranial formation.

The significance of the research is three-fold: It introduces the zebrafish as a tool through which to study lincRNA function; it suggests the functional equivalence of lincRNAs in zebrafish and higher animals; and it establishes that certain lincRNAs have been highly conserved throughout evolution.

Adds Bartel: "Our work shows that these two lincRNAs have been playing important roles in embryonic development for at least the last 400 million years."

"Some of our most satisfying research has come from saying, '**Why not** pursue this line of research, even though it's outside our core area (the kinetochore)?' We have had some fun and unexpected recent projects, including exploring the role that dynein plays during spindle orientation." Iain Cheeseman

For nearly three decades, human geneticists have coveted a tool of yeast genetics—an artificial chromosome created from a DNA segment inserted into a cell's nucleus. Once inserted, the yeast cell's own DNA machinery replicates the artificial chromosome and passes it on to the next generation. Currently, scientists typically insert genes into human cells using viral vectors, which haphazardly inject the genes into the cells' DNA in a process that can corrupt surrounding genes.

Armed with an artificial chromosome, geneticists could analyze specific genes' functions in normal human cells and even study the downstream effects of chromosomal mis-segregation that often occurs in some cancer cells. The hurdle to producing an artificial human chromosome has been a protein complex known as the kinetochore. In vertebrates, cell division depends on the kinetochore, which assembles at a single site on each chromosome during early cell division. The kinetochore acts as an anchor for long, thin protein threads that pull the chromosome in half as the cell divides, ultimately ensuring one complete copy of the genome ends up in each resulting cell.

The Cheeseman lab recently identified two kinetochore components that are key to directing kinetochore assembly. When these two proteins, CENP-C and CENP-T, are targeted anywhere on a chromosome, they attract almost all of the remaining kinetochore proteins to form a complex sturdy enough to capture and withstand the forces of cell division. By manually attaching these two proteins anywhere along a piece of DNA, scientists are able to create an artificial chromosome that can be passed from one generation to the next.

"It's a very powerful system," says Cheeseman. "It's something that was elusive for so long for vertebrate and human cells, and it really is amazing how well it works."

In other research, the lab determined that an interaction between the protein dynein and signals from chromosomes and spindle poles works to align the mitotic spindle apparatus perfectly down the middle of a cell during cell division.

"**Why not** disinter a cryptic gene-silencing system to identify the function of genes involved in infection?"
Gerald Fink

For geneticist Gerald Fink, the budding yeast *Candida albicans* has long been an intriguing adversary. This human pathogen causes thrush and yeast infections in healthy individuals, but in the immunocompromised, a systemic *Candida* infection is devastating, with mortality rates of 40%. Such high mortality is a consequence of the dearth of drugs to treat fungal infections like those caused by *C. albicans*. Can one identify *Candida* genes that could be drug targets?

To answer this question, the Fink lab identified key aspects of the methods *C. albicans* uses to avoid detection by the immune system. In a seeming sleight of hand, *Candida* can alter its cell surface, cloaking the signature that alerts our immune system. The lab then found systems that enable the organism to switch from a yeast cell to an invasive, filamentous form. However, efforts to identify *C. albicans* genes controlling these processes, and representing potential therapeutic targets, have been impeded by the difficulty of correlating *Candida*'s genes with their functions in infection. This gene-function correlation, accomplished in other organisms by deleting a gene and determining whether its loss cripples the infection process, is extremely laborious in *Candida*.

Another method of gene silencing is RNA interference (RNAi), a naturally occurring system that shuts down genes, protecting them from viruses and other genome invaders. Scientists have re-engineered RNAi for silencing any gene in an organism, but because RNAi hadn't been found in the best-studied fungus (the common baker's yeast *Saccharomyces cerevisiae*), it had long been assumed it didn't exist in other budding yeasts like *Candida*. Recently, the Fink lab, working in concert with that of Whitehead Member David Bartel, dispelled that notion, finding that the key RNAi components (called Dicer and Argonaute) were present in some budding yeasts and have the same power to silence target genes.

Remarkably, Dicer and Argonaute are present in *C. albicans*, but they show eccentricities that suggest *Candida* has taken an evolutionary tributary. The *Candida* dicer gene, unlike those in its relatives, is required for viability. Tomorrow's challenge is to resurrect RNAi in *Candida* to silence each gene and determine its function. Fink is confident RNAi will eventually aid the analysis of fungal disease: "This will advance our understanding of *Candida* infections," he says.

"**Why not** try something really challenging, like mapping all of the methylation in single egg cells in order to understand epigenetic variation between individuals? That's never been done in any system before." Mary Gehring

A plant seed inherits one copy of its genes from its mother and another from its father. As if that weren't enough, its parents hand down one other gift: an owner's manual for how each of those genes should be expressed. The manual's instructions are imprinted on each gene copy, with mom's instructions attached to the set of genes she passed along and dad's affixed to the genes he contributed.

By studying the *Arabidopsis thaliana* plant, the Gehring lab is studying how one set of instructions, known as methylation, may affect not only the expression of the intended sequence, but also of other genes nearby. In pursuing this line of research, the lab is studying transposable elements—repeated DNA sequences that are frequently methylated and capable of inserting themselves randomly into the genome. By comparing strains with methylated transposable elements tucked next to a certain gene, say for seed size, to other strains whose seed-size gene lacks nearby transposable elements, the Gehring lab will determine if methylated transposable elements affect neighboring genes' expression or if their effects are due to another phenomenon.

To better understand the mechanisms and evolution of gene imprinting, the Gehring lab is also comparing the epigenetics of *A. thaliana* to two other plants: the closely related species *A. lyrata*, which diverged from *A. thaliana* about five million years ago; and maize, a grass that split from *A. thaliana* more than 100 million years ago. Despite their evolutionary distance, *A. thaliana* and maize have about 10 imprinted genes in common, including the gene for auxin biosynthesis. This plant hormone controls many facets of cell growth, and the Gehring lab is investigating imprinting's role in this vital hormone's biosynthesis.

"**Why not** systematically elucidate the cellular and signaling processes that control cellular differentiation decisions? Our strategy of using synergistic chemical, genetic, technological, and computational approaches is leading to unanticipated findings that are taking us in exciting new directions." Piyush Gupta

Cancer biologist Piyush Gupta describes tissue development as a "complex and beautiful process." But he knows the complexity of the process loses its beauty if any of the many cell types involved begin behaving badly.

At the heart of tissue development are stem cells, possessed of the ability to either differentiate into cells with specialized functions or renew themselves and remain poised for further tissue development and maintenance. Gupta is determined to understand what has been among biology's great mysteries: What controls these cell states, and cell-state decisions, within both normal and cancerous tissues?

Knowing that a range of factors—from cell-cell signaling to variations in gene expression—are combining in some fashion to influence cell states, Gupta and his lab are now deploying genetic, genomic, and biochemical technologies, along with computational models, to great effect in this endeavor. The lab has developed a method to find chemical compounds that selectively target the different cell states—including the highly aggressive, highly malignant stem-like state—that populate a cancerous tumor. Using RNA interference, scientists can then identify which genes influence the cellular response to exposure to such compounds. These studies have led to new insights into the biological processes active in stem-like cancer cells.

Complicating matters, however, is recent research from the Gupta and Weinberg labs finding that cancer cells can spontaneously move into and out of the stem-like state, suggesting that the eradication of an existing population of cancer stem cells, perhaps with a targeted compound, may not be enough to eliminate the threat of recurrence. Gupta has developed a quantitative model to predict the dynamics of how cancer cells transition between phenotypic states. Such models could prove useful in anticipating the effects of genetic manipulations and therapeutic interventions on cancer cell states, particularly in light of new research showing that tissues, including cancerous tumors, tend naturally to maintain a state of cellular diversity with consistent proportions of cell types. The Gupta laboratory is also developing new technologies that will provide insights into the behaviors of single cells within larger populations.

"**Why not** embrace risky and novel ideas? I switched the lab's entire direction after the first cloned animal, Dolly the sheep, was produced. We adapted nuclear transfer to mice and used for the first time this method as well as the iPS approach to cure diseases in mice." Rudolf Jaenisch

Owing to their ability to become almost any cell type in the body, so-called induced pluripotent stem (iPS) cells harbor vast potential for use in the study and eventual treatment of myriad diseases and medical conditions, including Parkinson's disease (PD), diabetes, and spinal cord injuries. Moreover, because they can be generated from fully differentiated cells from individual patients, iPS cells are also free from the controversies surrounding human embryonic stem (ES) cell research. Yet despite its obvious promise, iPS cell research has been hampered by a number of issues, including enormous variability in the reprogramming methods employed among laboratories, leading to marked differences in the quality and even the degree of pluripotency in resulting cells. Simply put, not all iPS cells are created equal.

An established leader in the iPS field, the Jaenisch lab has been tackling these issues in impressive fashion. Recent comparisons of the pluripotent states of mouse iPS and ES cells have revealed that iPS cells may be slightly more differentiated (and, by extension, "less pluripotent") than ES cells, leading some scientists to question the equivalence of iPS cells and "gold standard" ES cells. However, by tweaking the ratio of reprogramming factors, the Jaenisch lab has generated iPS cells with increased pluripotency, indicating that iPS cells' pluripotency can indeed approach that of ES cells.

The lab has also recently developed precision methods to correct disease-causing mutations in ES and iPS cells. Such targeted genetic manipulation addresses another problem that has been plaguing human stem cell research—the ability to cleanly and site-specifically modify the genomes of human ES and iPS cells. Realizing the therapeutic promise of these cells depends on such changes to fix pathogenic mutations before the cells can be transplanted into patients or used to create cell lines that researchers can use to study genetic diseases.

"**Why not** explore a novel mechanism of inheritance and prove that it is in fact biologically and evolutionarily important?" Susan Lindquist

Susan Lindquist can describe her lab's focus in a single sentence: "We study the fundamental ways in which protein folding determines the biological properties of an organism."

It sounds simple, but don't be deceived. This fixation on protein conformation is revealing an extraordinary breadth and depth of insights—from clues to the underlying pathologies of, and potential therapies for, Alzheimer's disease, Parkinson's disease, and cancer, to the manner in which both simple and complex organisms have over time developed strategies to adapt quickly to survive in hostile environments.

In a recent discovery that overturns conventional wisdom, the lab has shown that prions, the much-maligned proteins most commonly known for causing "mad cow" disease, can produce beneficial traits in yeast strains found in the wild. Such traits can also become "hard-wired" into the genome to be transmitted to subsequent generations.

Scientists had observed more than a decade ago that some proteins in simple baker's yeast grown in controlled laboratory conditions can spontaneously switch from a normal shape into a self-perpetuating prion conformation. The switch to the prion state alters protein function, resulting in the emergence of new traits, some helpful, some detrimental. Importantly, proteins were found to switch into and out of the prion state more rapidly in response to environmental stress, suggesting that they are part of an inherent survival mechanism that helps yeasts adapt to changes in their surroundings. Although these earlier findings made a compelling case for this protein-based mechanism of inheritance, its biological significance had been hotly debated for one key reason: Prions capable of modifying traits had never been found in nature.

Enter the Lindquist lab, which, in a massive undertaking, looked for prion elements in 700 wild yeast strains from diverse environments and found them in one-third of all the strains. All the prions were capable of creating diverse new traits, nearly half of which proved beneficial. These unexpected findings strongly counter the old argument that prions are merely yeast "diseases" or rare artifacts of laboratory culture.

"**Why not** explore long non-coding RNA copies of so-called junk DNA? This is how we've found lncRNAs involved in red blood cell production and fat cell formation." Harvey Lodish

Approximately 90% of the RNAs coded for in the human genome are not templates for proteins—molecules that perform most of the important functions in the body. Regions of DNA transcribing these non-coding RNAs were once referred to as "junk DNA." However, it has become clear that the "junk" is giving rise to some important players in the non-coding RNA field: microRNAs, which fine-tune the expression of more than half our protein-coding genes; piRNAs, which can act as gene silencers; and long non-coding RNAs (lncRNAs), many of whose specific functions have only begun to come to light recently.

Working with the progenitors of red blood cells, the Lodish lab recently discovered a lncRNA that plays an active role in red blood cell production and preventing cell death.

As red blood cell progenitors mature into red blood cells, they depend on erythropoietin (EPO), a hormone that prevents the blood cell progenitors from undergoing programmed cell death, or apoptosis. In EPO's absence, the progenitors all die. The Lodish lab identified a lncRNA called lincRNA-EPS (for long intergenic non-coding RNA-erythroid-pro-survival) that is expressed only during the late stages of red cell formation. Interrupting the expression of lincRNA-EPS in differentiating progenitor cells causes the cells to die. But the opposite occurs when lincRNA-EPS is expressed in maturing red blood cells grown in the absence of EPO. Instead of dying as expected from the lack of EPO, the cells with lincRNA-EPS continue to live, indicating that lincRNA-EPS itself can prevent apoptosis.

Because the inhibition of programmed cell death can cause leukemias and other cancers, the lab is now investigating lincRNA-EPS's function in both normal and diseased human cells to determine whether it affects tumor development and growth. The lab is particularly focused on understanding how lincRNA-EPS turns off the expression of genes that would otherwise cause the cells to undergo apoptosis.

"**Why not** dare to investigate an unexplored area? There are so many fascinating developmental strategies yet to be uncovered, certain to reveal fundamental new insights!" Terry Orr-Weaver

As taught in high school biology, DNA replication occurs immediately before a cell divides, with the DNA replication machinery making a fresh, linear copy of each chromosome from beginning to end. Although technically true, this simplistic description ignores other fascinating ways in which certain cells can bolster their DNA content at key moments in their lifecycle.

One such pivotal period is development, when specific cell types need to expand in size at a rapid rate. Cell layers in the human placenta and skin, for example, must increase their volume while maintaining a boundary between the fetus and its surroundings, and the body and the outside world, respectively. The most efficient way for cells to achieve this growth is by copying their entire genome multiple times in a process known as polyploidization. As the DNA content mushrooms in these cells, nuclear and cellular volume expand accordingly.

The Orr-Weaver lab recently discovered that cells in developing fruit fly brains employ polyploidization as a strategy to maintain the blood-brain barrier, which is essential for shielding the brain from bacteria and viruses and for isolating the brain's specific hormonal and neurotransmitter activity. As the brain grows rapidly during development, subperineurial glia (SPG) cells respond by increasing their ploidy, stretching the blood-brain barrier quickly while preserving the tight junctions between cells that maintain the barrier's integrity. Researchers in the lab observed that when polyploidization is inhibited, the SPG cannot keep pace with the brain's growth, causing the barrier to shatter. The SPG's precise response to the brain's expansion indicates that the brain is somehow able to tell the SPG when to grow and by how much.

For Orr-Weaver, this work raises a host of questions, including whether such communication occurs merely at the cellular level or in larger, organized fashion in the brain and in other organs as the body is formed.

"**Why not** Y? Now that we've successfully defended the honor and dignity of the Y chromosome, we're ready to take it mainstream and usher in a new era of Y biology." David Page

Having waged an arduous battle with proponents of the so-called rotting Y theory, David Page has finally declared victory.

The fatalists argue that the Y's extinction is inevitable because, over the course of 300 million years of evolution, this now tiny chromosome experienced such extensive genetic decay that it retains only 19 of the more than 600 genes it once shared with its ancestral autosomal partner, the X. Surely, they insist, this trend will continue until the Y's gene content is exhausted. Perhaps because of its implicit battle-of-the-sexes story line, the rotting Y theory has persisted.

Over the past decade, Page and his lab have steadily been churning out research debunking the theory. They sequenced the human Y back in 2003, revealing for the first time the unique mechanism it relies on for self-preservation. A subsequent comparison of chimpanzee and human Y chromosomes found that both are evolving more rapidly than the rest of their respective genomes. And most recently—in research to end all arguments—the lab has shown that the human Y has lost only one ancestral gene in the past 25 million years. Conclusion: The Y is here to stay. Case closed.

Although he concedes it's been fun at times, Page says the rotting Y debate has distracted from other important lines of inquiry. He notes that additional cross-species comparisons of Y chromosomes have unearthed a set of widely conserved genes that have no involvement in reproduction or sexual differentiation. "One has to ask the question, 'Why are they conserved? They're trying to tell us something,' " he says.

Another area ripe for exploration is the role of the sex chromosomes in human disease.

"Since the late 1940s, differences in male and female manifestations of disease have been attributed to differences in circulating sex hormones," Page says. "Maybe that's not the whole story. What about these other genes on the Y with no obvious role in the sex differentiation pathway? What if the genetic basis of gender differences in disease is staring us in the face?"

"**Why not** exploit naturally occurring biological processes, perhaps altered by approaches from other scientific disciplines, including chemistry and bioengineering, to elucidate the immune response to invading pathogens?" Hidde Ploegh

Of the many labels that could be used to describe Hidde Ploegh—biochemist, immunologist, microbiologist, even methodologist—"purist" might be among the most appropriate. Throughout a distinguished career spanning four decades at four institutions, Ploegh and his labs have never strayed from one core aspect of immune system behavior.

"We are intrigued by host-pathogen interactions in all their manifestations," Ploegh says. "It's the key focus that shapes who we are. We're driven to pursue anything we can to shed more light on this subject."

Over the years, Ploegh has introduced new tricks to enhance his trade. In collaborating with the lab of Whitehead Founding Member Rudolf Jaenisch, he and his lab have used somatic cell nuclear transfer to clone mice from antigen-specific T cells. It's an approach that allows for the rapid development of animal models to study T-cell behavior during infection. He's now using the same method to produce mice whose T cells specifically recognize an antigen found on the surface of pancreatic cancer cells.

Other work in the lab is exploring how bacterial toxins gain entry into host cells. This line of research is revealing much about host cell biology, spotlighting inherent weaknesses invaders take advantage of as they embark on their pernicious paths. In recent research, members of the lab found 12 new genes required for intoxication by the family of cytolethal distending toxins, which are secreted by multiple pathogenic bacteria, including *Escherichia coli*, *Shigella dysenteriae*, and *Salmonella typhi*. Identification of host factors necessary for infection suggests an alternative to therapeutic development that has traditionally targeted pathogens rather than properties of their hosts.

Ultimately, Ploegh is passionate about solving the puzzle that is the immune response, and although he is resolute in saying it is not necessarily "the desire to cure diseases or make vaccines" that drives his research, it's quite likely that others will leverage his myriad contributions to the field to do exactly that.

"When starting to work on regeneration, well-established model systems were not ideal for studying the process. I thought, '**Why not** use planarians, which naturally regrow body parts, to investigate the molecular basis of regeneration, even though we initially had few tools to study them?'" Peter Reddien

It's readily apparent that planarian flatworms and humans do not have the same regenerative capabilities. Cut a planarian in half, and both halves will regrow any missing tissues and ultimately form two whole worms. Similar injuries to humans can result in considerably less positive outcomes. By studying these tiny worms' amazing ability, the Reddien lab is learning how regeneration works, ultimately allowing one to ask what is different between animals that re-grow missing body parts and humans.

Two key ingredients are necessary for regeneration in any animal: 1) cells with regenerative capacity; and 2) messages that inform such cells which tissues need to be regenerated and where. In the past year, Reddien and his lab have made powerful advances in clarifying the role of specific cells known as neoblasts.

For decades, scientists have known the importance of neoblasts in planarians. After an injury or amputation, neoblasts migrate through the body to the wound site, divide, differentiate, and begin regrowing the missing tissue. If a worm is irradiated to kill all of its neoblasts, its tissues can no longer regrow. Until recently, however, it was unclear whether neoblasts, as a population of cells, contain a singular cell type that can produce all tissues, or multiple cell types, each responsible for regenerating a different tissue type.

In a complex set of experiments, the lab identified a pluripotent neoblast—dubbed a clonogenic or cNeoblast—that can generate all tissue types found in a planarian. The lab also showed, in rather dramatic fashion, that a single transplanted cNeoblast is capable of regenerating an entire worm when transplanted to an irradiated animal lacking neoblasts. Additionally, the lab has found that specialized precursor cells in the neoblast population exist and regenerate specific tissues, such as the optic cup (the planarian version of the retina of an eye) and the protonephridia (the planarian kidney). Intriguingly, genes involved in planarian kidney regeneration are conserved in vertebrates, where they're also active during kidney development. Leveraging the tools developed to study planarian kidneys, the Reddien lab is now exploring the cellular and molecular basis of kidney cell regeneration.

"**Why not** systematically try to understand all of the metabolic pathways in cancer cells? The transformation to a cancer cell is so dramatic that those pathways controlling nutrient sources—one of a cell's most important jobs—have to be involved." David Sabatini

David Sabatini is fascinated by the connection between nutritional state and an organism's physiology. Accordingly, he and his lab study the key pathway in this relationship, the mechanistic target of rapamycin (mTOR) pathway.

To thrive, an organism and its cells must detect and respond appropriately to nutrient levels. Within a cell, the mTOR pathway senses nutrient availability, and, in times of scarcity, scales back metabolic activity at cellular, organ, and organismal levels. When nutrient levels plummet, the mTOR pathway itself is turned off. This initiates an emergency survival strategy called autophagy, which breaks down a cell's organelles and other structures into their elemental molecules and recycles them for immediate use.

During the transformation from a normal to a cancer cell, numerous mutations alter the cell's metabolic pathways. Usually these changes serve to benefit the cancer cell by promoting cell survival, but occasionally, the mutations can also have unexpected consequences. The Sabatini lab recently discovered that human melanoma cells that have a mutation in the RAS/MEK signaling pathway—the most common mutation found in the deadliest form of skin cancer—are unable to sense levels of the essential amino acid leucine. In the melanoma cells in question, the mTOR pathway is unable to detect when leucine levels are insufficient, so mTOR remains active and autophagy never begins. Instead, the cells behave as if there is no nutrient shortage until they reach a metabolic crisis and die. This unexpected Achilles heel may point to new treatments that could mimic leucine deprivation, essentially turning the cancer cell's metabolism against itself.

"In all vertebrates, the central nervous system forms from a tubular structure known as the neural tube. Why a tube? **Why not** a flat structure? It's a paradigm-shifting question." Hazel Sive

Indeed, it's a question that has been propelling exploration in Hazel Sive's lab for years. Sive points out that a number of complex organisms, including fruit flies, develop sophisticated nervous systems from non-tubular structures. In humans, neural tube abnormalities lead to brain and spinal cord defects, but why the tube is important isn't clear. To answer this fundamental question, researchers in the lab have been studying neural tube formation in zebrafish embryos. These studies are revealing what it takes for the tube to form properly and the disastrous consequences that arise when it doesn't.

As the embryonic vertebrate brain develops, the neural tube fills with cerebrospinal fluid (CSF), causing expansion and formation of cavities known as brain ventricles. Appropriate ventricle formation requires both the production and retention of CSF. A few years ago, researchers in the Sive lab identified Na, K-ATPase, a protein complex also known as the sodium-potassium pump, as a key player in the process, finding that a mutation in the gene coding for one of the pump's proteins prevents the brain ventricles from inflating.

Although this work implicated Na, K-ATPase, it was unclear what the pump does during brain development. New research finds that this complex has a role in three discrete processes of ventricle formation. Through a series of experiments with zebrafish controls and mutants, researchers in the lab have shown that Na, K-ATPase is essential for assembly of the neuroepithelium, a cellular sheet whose junctions must be tight enough to retain CSF; modulation of neuroepithelial permeability, which is necessary to maintain proper ventricular volume of CSF; and production of the CSF itself.

The work has implications for understanding a host of developmental disorders and birth defects related to ventricular malformation and CSF disequilibrium, including anencephaly, a severe embryonic malformation, and hydrocephalus, an excess of fluid found both in the embryo and in the adult, where it is associated with Alzheimer's-like symptoms. Sive says additional research into the composition of the CSF itself has found at least 400 proteins in zebrafish CSF. The lab recently identified a protein involved in synthesis of retinoic acid as a specific factor associated with brain cell survival.

"Can we figure out all of the steps of the cancer invasion cascade? **Why not**? It's a question that 10 years ago we would not have dared to have posed, but may now be within our reach."
Robert Weinberg

Knowing that the vast majority of cancer mortality is attributable not to a primary tumor but rather to metastasis, Robert Weinberg and his lab members have dedicated much of their recent research to understanding how cancer spreads throughout the body and identifying ways to stop it.

Weinberg's latest work continues to build on an important discovery emerging from his lab several years ago: that certain tumor cells undergo a physical and behavioral change that confers on them key properties of stem cells, including the ability to self-renew and to form new malignancies. This change, which is known as an epithelial-mesenchymal transition (EMT), also enables the cells to separate from a primary tumor and migrate to distant sites throughout the body.

Through a series of experiments, the lab confirmed that a carcinoma cell that undergoes an EMT essentially becomes a cancer stem cell. Now, for the first time, the lab has found that EMT-derived cancer stem cells can in fact disseminate throughout the body and form significant metastases. Yet, it turns out that cancer stem cells cannot form metastases independently, requiring signals from local inflammatory cells to help them escape from the blood vessels in which they travel. To determine what happens once these cells arrive in a new location, the Weinberg lab is now teasing apart how they integrate into their new surroundings by hooking into the local extracellular matrix.



While these insights into the workings of cancer stem cells—which tend to be relatively resistant to traditional chemotherapies—should lead to the development of novel cancer treatments, they may also have applications beyond the field of oncology. Because normal, healthy cells undergoing an EMT also acquire stem-like traits, Weinberg's research suggests an approach for creating large numbers of patient-specific stem cells that could be used in regenerative medicine.

"**Why not** study embryonic stem cells to gain important new insights into cancer?"
Richard Young

For more than a decade, the Young lab has been focused on drawing the definitive cellular wiring diagram, mapping the circuitry that controls the differentiation, development, and function of all the cells in the body. Taken together, this regulatory circuitry controls gene expression programs, which are akin to software code running the operating systems found in today's most sophisticated computers. When running as intended, cellular operating systems command vital life processes. Defective systems, however, can cause cancer, autoimmunity, and neurological disorders.

Several years ago, Young and members of his lab were the first to describe the key components of the operating system controlling embryonic stem (ES) cells. Because ES cells are pluripotent, that is, capable of giving rise to nearly every cell type in the body, they represent an incomparable tool for understanding the interplay of genes, signaling pathways, and a host of other factors involved in determining whether such cells remain in their pluripotent state or differentiate into other cells, such as nerve, muscle, or blood.

Young's work on ES circuitry has revealed much about mammalian development, from embryo to adult, but it's also revealed yet another ugly truth about cancer—namely, that malignant tumor cells resurrect a key part of the ES cell operating system, enabling them to proliferate rapidly and self-renew. Using powerful tools that decipher the gene expression programs of ES cells and tumor cells, Young's lab is systematically identifying new therapeutic targets.

Says Young: "In the past year, we've gained fundamentally new insights into cancer cells. There are multiple parts of the operating system that we now know are critical for the command and control of cancer cells and can be targeted for therapy."

Whitehead Fellows

The renowned Whitehead Fellows program is the embodiment of the Institute's commitment to future excellence in biomedical research. Free from teaching and other faculty responsibilities, a handful of the world's most promising young scientists receive the kind of support and mentoring sure to produce the next generations of scientific leaders.

Maturation of spermatogonial cells in a mouse testis, from stem state (blue/purple), to modest differentiation (orange/red), to large numbers of fully differentiated germ cells (red) that produce sperm. Supporting Sertoli cells (gray) are distributed throughout the testis.

YANIV ERLICH

Yaniv Erlich has made an art of finding rare, disease-causing mutations in the human genome's 3 billion base pairs. In the recent case of a single Palestinian family whose members suffer from a movement disorder known as hereditary spastic paraparesis (HSP), Erlich and colleagues combined sophisticated sequencing technology with older comparative methods to identify an unknown genetic culprit. In the past, such work required analysis of genetic data from multiple families.

Erlich has also been investigating chimerism in identical twins—a phenomenon in which one twin harbors cells genetically distinct from those in its sibling. Chimerism explains rare cases in which one twin develops a genetic disease while the other remains healthy—despite blood tests indicating the twins share identical genomes. After 30 years' worth of cases reported in the scientific literature, Erlich determined that because developing twins share a circulatory system via the placenta, their blood is actually a chimeric mixture of both twins' genomes. As a result, Erlich has concluded that cheek swabs, rather than blood testing, are a more reliable source of DNA for genetic research in twins.

GABRIEL VICTORA

Gabriel Victora's approach to elucidating the intricacies of the immune system is a classic one: watch and learn. It's an oversimplification, but Victora has advanced his field by developing new imaging techniques to visualize the behavior of the immune system's antibody-generating B cells *in vivo*, in real time.

Using a method known as intravital multiphoton microscopy, Victora has imaged whole mouse lymph nodes, capturing in unprecedented fashion the remarkable path B cells follow, from first contact with a foreign body or antigen, to the development of highly specific antibodies to neutralize an invading pathogen. Along the way, B cells generate a structure known as the germinal center (GC). Within the GC, B cells acquire random mutations in their genes. Those whose mutations lead to enhanced affinity to a particular antigen proliferate, eventually forming either antibody-producing cells or so-called memory cells that reactivate should they encounter the same pathogen in the future.

This activity within the GC is exploited by vaccines and also allows ongoing immunity to certain diseases to develop naturally. Breakdowns in the system, however, can lead to allergies and autoimmune diseases.

Community Evolution

Although cutting-edge research represents Whitehead Institute's immutable core, a community as vital as this is always subject to changes large and small. 2011 had its share of transitions.

Board Member Emeritus Abraham Siegel (left) passed away in January. Joshua S. Boger (center) joined the Board in December. Whitehead Fellow Andreas Hochwagen moved his lab to New York.

BOARD NEWS

The year began on a sad note with the January passing of Board Member Emeritus Abraham J. Siegel. Abe, as he was known, was Dean of the MIT Sloan School of Management when he joined Whitehead's Founding Board of Directors in 1982, and he proved instrumental in steering the Institute through its formative years. Abe was revered for his keen intelligence, profound wisdom, and wonderful personality. Former Whitehead Director Gerald Fink credits Abe's counsel and leadership on the Board with helping to guide the Institute through a number of critically important strategic initiatives, including a building expansion and the establishment of the Whitehead/MIT Center for Genome Research. Abe's unique understanding of the culture of an academic research institution was the impetus for the establishment of the Abraham J. Siegel Fellowship, awarded annually to a graduate student training at Whitehead Institute. Abe served on Whitehead's Board of Directors for 10 years before becoming its first Member Emeritus. Upon learning of Abe's passing, Whitehead Founding Director David Baltimore wrote: "Abe was a great person and a great friend of Whitehead Institute. His judgment was so sound and his wisdom so deep."

At the close of 2011, biotechnology executive Joshua Boger was elected to the Whitehead Institute Board of Directors. Joshua founded Vertex Pharmaceuticals in 1989, serving as its CEO from 1992 until his retirement in May 2009. He remains a member of the Vertex Board of Directors. Prior to founding Vertex, he served as Senior Director of Basic Chemistry at Merck Sharp & Dohme Research Laboratories. He holds a BA in chemistry and philosophy from Wesleyan University as well as an MS and PhD in chemistry from Harvard University.

INSTITUTE NEWS

In the fall of 2011, after five and a half years as a Whitehead Fellow, Andreas Hochwagen moved his laboratory to lower Manhattan to become an assistant professor of biology at New York University.

At NYU, Hochwagen is continuing his study of meiotic cell division, the intricately complex process he began investigating as a graduate student at MIT (in the lab of former Whitehead Fellow Angelika Amon) and established himself in the field during his own stint as a Whitehead Fellow. He's not about to stop now, and, as a result of his training, he hasn't even had to pause.

"The transition to running my own lab has been incredibly smooth," he says. "The Whitehead Fellows program prepared me so well for all of this. It was a fantastic opportunity to be independent and yet be included in meetings of other labs and have faculty mentors. As Thijn [former Whitehead Fellow Thijn Brummelkamp] used to say, 'It's the best job in the world.'"

PUBLIC OUTREACH

For more than two decades, Whitehead Institute has been a leader in the development of STEM-related (science, technology, engineering, and math) programming. Through Whitehead's Partnership for Science Education, which brings together teachers and students from the greater Boston area, the Institute has maintained its enduring commitment to science education and outreach.

The Partnership's longest running programs are Whitehead's Seminar Series for High School Teachers and its Spring Lecture Series for High School Students. The 2011 series, Reassessing the Threat: Infectious Diseases in the 21st Century, attracted 60 teachers to monthly lectures on emerging and re-emerging pathogens and their implications for biomedical research, drug development, and public health policy.

More than 100 high school students spent part of their spring school vacation at the Institute for *Taking Stock of Stem Cells*, a three-day program on developments in adult and embryonic stem cell research, advances that are bringing stem cell-based therapies closer to clinical use, and the many challenges that must be met for potential to become reality.

In June, Whitehead Institute joined forces with 19 Massachusetts-based biotechnology companies and research institutions for the second annual Massachusetts Statewide Biotechnology Job Shadow Day. The Institute hosted 12 Boston-area high school students who were placed in nine laboratories within the Institute. The day included an introduction to Whitehead, special tours, and one-on-one mentoring, all aimed at exposing students to the breadth of career opportunities in the life sciences and encouraging them to pursue science education.

Also in June, Whitehead piloted a program for middle school girls, A Girl's Guide to Understanding Life Science. Supported by Whitehead Member Susan Lindquist—long a supporter of science education for young women—this one-day workshop for 7th and 8th grade girls offered hands-on activities, laboratory demonstrations, and discussions with female scientists in an effort to showcase the ways researchers are addressing some of biology's most challenging questions.

*Scenes from the Whitehead Spring Lecture Series for High School Students, **Taking Stock of Stem Cells**. More than 100 students participated in the 2011 program.*

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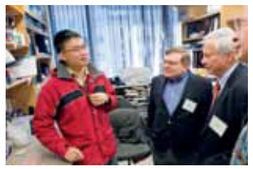


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2010

Research
45.5 million (63%)

Administrative
Salaries and Benefits
8.9 million (12%)

Capitalized Plant
and Debt-Related
6.1 million (9%)

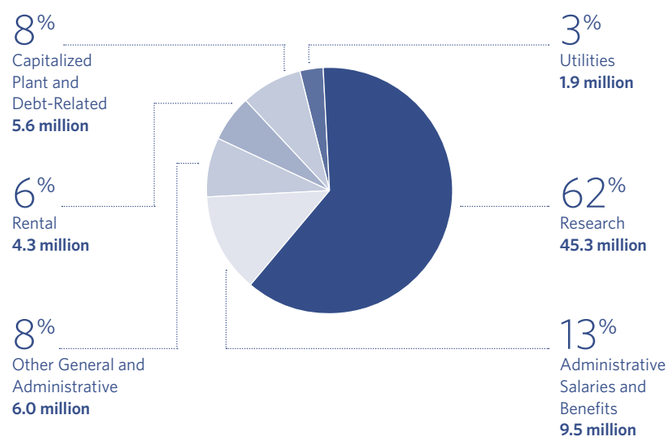
Rental
4.7 million (7%)

Other General and
Administrative
4.6 million (6%)

Utilities
1.8 million (3%)

TOTAL
$71.6 million (100%)

2011 EXPENDITURES & DISBURSEMENTS 2011 Total: **$72.6 million**



2010

Corporate and
Foundation Support
13.9 million (19%)

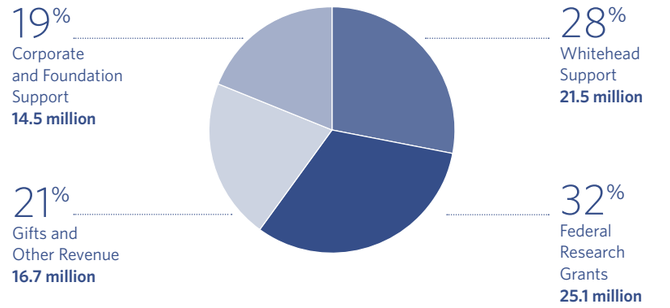
Gifts and
Other Revenue
17.3 million (23%)

Federal Research Grants
23.5 million (32%)

Whitehead Support
19.2 million (26%)

TOTAL
$73.9 million (100%)

2011 REVENUES & SUPPORT 2011 Total: **$77.8 million**



Tumors comprise a mosaic of cell types. Here, cancer cells labeled with different colors are seen passing their coloring to subsequent generations, making it possible to trace the cells' lineage and monitor spatial relationships.

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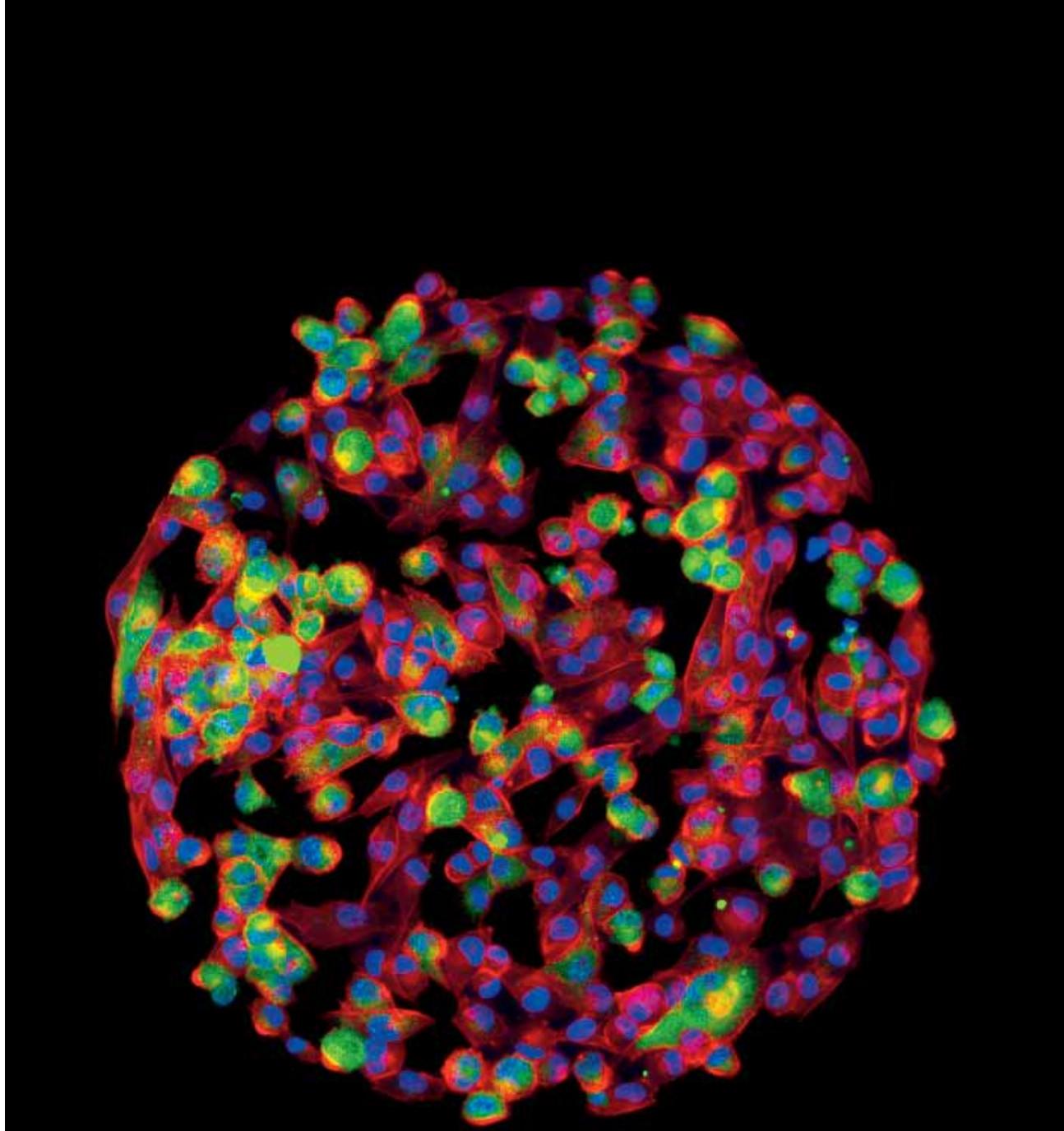
FACULTY AND FELLOWS

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

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

FACULTY ACHIEVEMENTS

Whitehead faculty includes the recipient of the 2011 National Medal of Science (Jaenisch), the 2010 National Medal of Science (Lindquist), the 1997 National Medal of Science (Weinberg), nine members of the National Academy of Sciences (Bartel, Fink, Jaenisch, Lindquist, Lodish, Orr-Weaver, Page, Weinberg, and Young), 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).



Within this cluster of melanoma cells, those that glow green have an active signaling pathway critical for the cancer's growth and survival. Nuclei (blue) and cystoskeletons (red) are seen as well.

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