



Whitehead Institute

ANNUAL REPORT 2013

Not safe. Not sorry.



More than 50 years ago, in a speech meant to rally support for this country's space program, President John F. Kennedy famously stated: "We choose to go to the moon in this decade and do the other things, not because they are easy, but because they are hard..."

This same spirit drives Whitehead Institute's scientists, who have always known that the most impactful pursuits are often the riskiest.

Where safety doesn't always come first



Four years ago, we concluded an exhaustive search for new junior faculty members by hiring two exceptional young scientists: Piyush Gupta and Mary Gehring. One could certainly have predicted that we would select individuals of their caliber, but what surprised many in the greater scientific community is that Mary just happens to be a plant biologist.

Whitehead Institute hadn't been a major player in plant biology in more than a decade. In fact, at the time of our search, we were considering converting the empty greenhouse on our seventh floor into new lab or core facility space. And yet, in Mary and her proposed research program, we saw an opportunity for our Institute that, though seemingly unorthodox, could not be missed. Knowing that Mary's work in epigenetic reprogramming in *Arabidopsis thaliana* has implications far beyond the plant world, we were convinced that we had placed the right bet. Within a year of her start here, Mary was named a Pew Scholar in the Biomedical Sciences, receiving four years of funding from a prestigious program that supports risk-taking research by creative young investigators. Apparently we weren't alone in our assessment.

This past year, we did it again, welcoming plant biologist Jing-Ke Weng as our newest junior faculty member. Jing-Ke, who can also be described as a natural products chemist, is studying how certain plant-derived products can be effective in treating human diseases. It's a somewhat unexpected approach, but the Pew Charitable Trusts has high expectations and, accordingly, has now named Jing-Ke a Pew Scholar as well.

Throughout 2013, Whitehead scientists at very different stages of their careers saw this kind of embrace of the unconventional validated in meaningful ways. Our two newest Whitehead Fellows, Sebastian Lourido and David Pincus each received a National Institutes of Health (NIH) Director's Early Independence Award (EIA), aimed at accelerating the careers of exceptionally creative junior scientists. (It's worth adding that Whitehead Fellow Gabriel Victora was an EIA recipient in 2012.) The EIA is a part of the so-called High Risk-High Reward program supported by the NIH Common Fund.

In the meantime, Whitehead Founding Member Bob Weinberg received an inaugural Breakthrough Prize in Life Sciences. Sponsored by a group of entrepreneurs that includes Google co-founder Sergey Brin and personal genetics information pioneer Anne Wojcicki, the prize recognizes research excellence. As Wojcicki put it: "We are thrilled to support scientists who think big, take risks and have made a significant impact on our lives."

Is there a pattern here? Absolutely, and it's one that mirrors this report's theme: "Not safe. Not sorry." We have never played it safe here, and, given our track record of scientific achievement, we're certainly not sorry. We are, however, exceedingly grateful to our friends, faculty, staff, and supporters for helping us live this philosophy daily.

David C. Page

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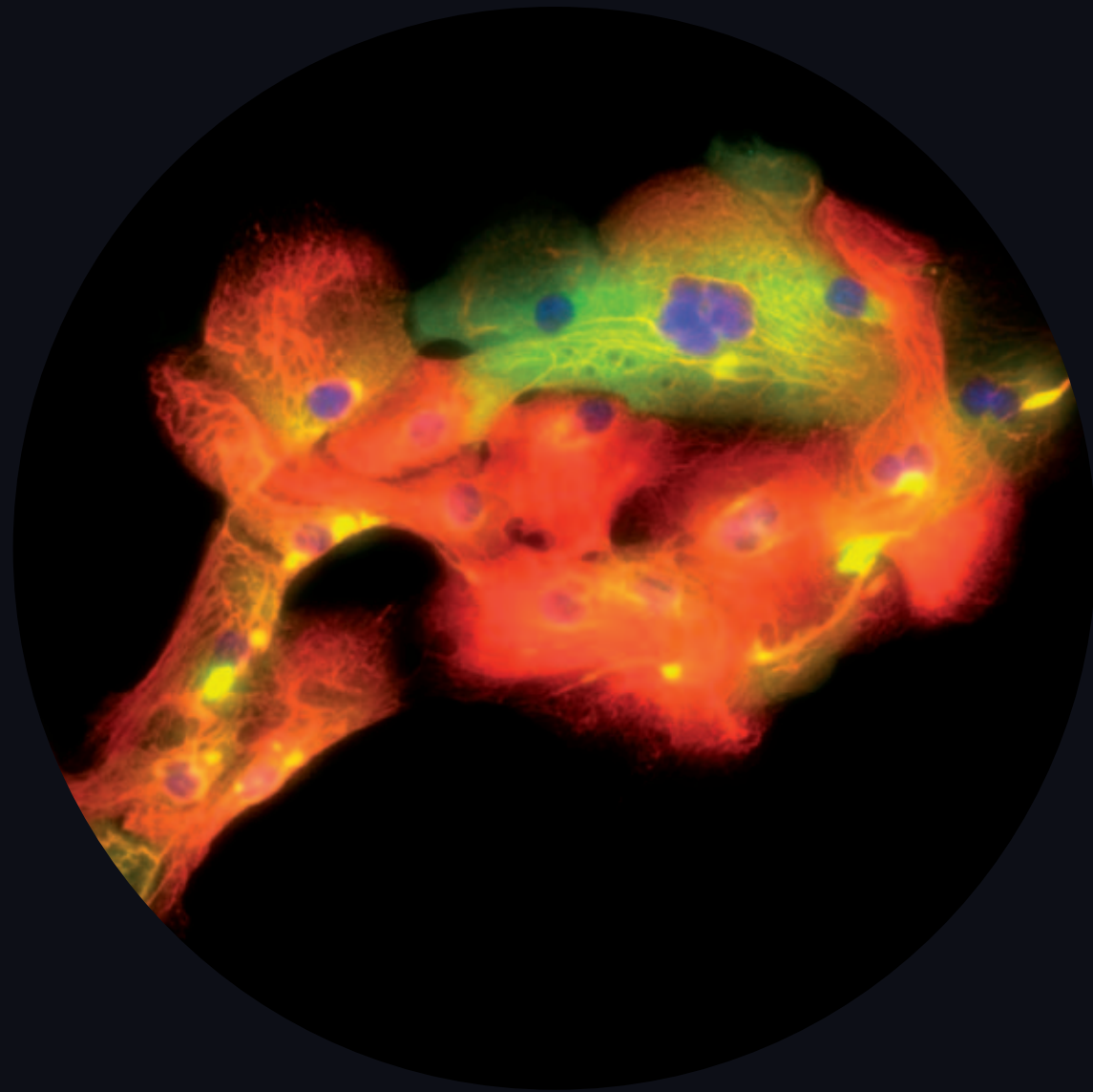
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Each year, research emerging from Whitehead Institute laboratories enhances our understandings in arenas ranging from evolution and developmental biology, to genetics, genomics, stem cells, cancer, and beyond. Although the full effects of such work may not be realized for decades, its promise— and those performing it— are recognized in a more timely fashion.

Shocking Responses, Controlled Aggression

Organisms from yeast to worms to humans rely on a highly conserved stress response—known as the heat shock response—to help their normal cells adapt to harsh environments, including the presence of heavy metals, high salt concentrations, low oxygen levels, and of course increased temperatures.

Unfortunately, cancerous cells rely on it too, having long ago figured out how to co-opt the response and its master regulator, heat shock factor 1 (HSF1), to support the production of vast quantities of proteins and the high-energy demands needed to propel malignancy. Accordingly, researchers have envisioned HSF1 as a potential therapeutic target, but such transcriptional regulators have been notoriously difficult to target.

However, researchers in the lab of Whitehead Member **Susan Lindquist** recently determined that protein production or translation in cancer cells is tightly linked to HSF1 activity. It's a

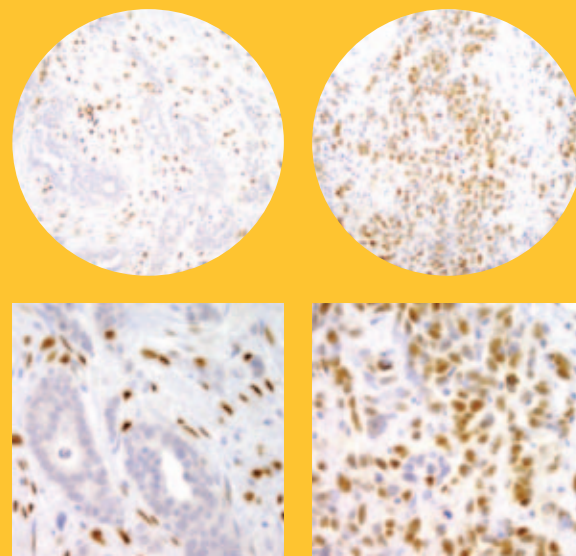
finding that lab members suspect may point to a novel approach to controlling cancer cells' overactive heat shock response. To wit, they found that in mouse models of cancer, targeted therapeutic inhibition of translation disrupts the response, dramatically slowing tumor growth and potentially rendering drug-resistant tumors vulnerable to other therapies.

While those in the Lindquist lab were studying aberrant cell behavior across a range of tumor types, scientists in the lab of Whitehead Founding Member **Robert Weinberg** were shedding new light on the aggressiveness of certain breast cancers by identifying a transcription factor, known as ZEB1, that is capable of converting non-aggressive basal-type cancer cells into highly malignant, tumor-forming cancer stem cells (CSCs).

ZEB1 is a key player in the so-called epithelial-to-mesenchymal transition (EMT), during which epithelial cells

acquire traits of mesenchymal cells, including the ability to move about within tissues. Earlier work in the Weinberg lab had shown that cancer cells passing through an EMT are able to self-renew and to seed new tumors with high efficiency, hallmark traits of CSCs. In this latest research, lab members discovered that in basal non-CSCs, the ZEB1 gene is held in a poised state, ready to respond rapidly to environmental cues that consequently drive those non-CSCs into the dangerous CSC state. Intriguingly, luminal breast cancer cells, which are associated with a much better clinical prognosis, carry ZEB1 in a state of permanent suppression.

Says Weinberg: "We may have found a root source, maybe the root source, of what ultimately determines the destiny of breast cancer cells—their future benign or aggressive clinical behavior."



BASAL BREAST CANCER CELLS (RIGHT) HAVE SIGNIFICANTLY HIGHER EXPRESSION OF THE TRANSCRIPTION FACTOR ZEB1 (STAINED BROWN) THAN DO LESS AGGRESSIVE LUMINAL BREAST CANCER CELLS (LEFT).

Facing Strange—and Rapid—Changes

In the classical view of evolution, species experience spontaneous genetic mutations that produce novel traits—some helpful, some detrimental. Nature selects for those most beneficial, passing them along to subsequent generations.

It's an elegant model, but an extremely time-consuming process of little help to organisms facing sudden, life-threatening changes in their environments. Surely another mechanism could enable more rapid adaptive response. With researchers from Harvard Medical School, Whitehead Member **Susan Lindquist** showed that at least in the case of one variety of cavefish, the other agent of change is the heat shock protein HSP90.

Thousands of years ago, *Astyanax mexicanus* (a fish indigenous to north-eastern Mexico) was swept from its hospitable river home into the unfriendly confines of underwater caves. Now in darkness, the fish dispensed with pigmentation, developed heightened

sensory systems and, perhaps most strikingly, lost their eyes. Eye loss is actually thought to be an "adaptive" or beneficial trait, as the maintenance of a complex but now useless organ would come at a high metabolic cost. Thus, the fish could reallocate limited resources to more useful functions.

This eye loss exemplifies the theory of "standing genetic variation," which argues that normally silent genetic mutations exist in a given population. Lindquist had shown that HSP90 silences such variation in organisms ranging from fruit flies, to yeast, to plants, but that the normal cellular reservoir of HSP90 is depleted during physiological stress. The loss of HSP90 allows for rapid phenotypic changes. In this latest work she showed HSP90 was doing the same thing in these fish. The result marks the first time this HSP90-mediated mechanism was associated with adaptive traits in vertebrates.

In an intriguing study of human evolution, Whitehead Director **David Page** recently conducted a painstaking analysis of the genetic sequence of the X chromosome and came to a shocking conclusion: Large portions of the X—long perceived as the "female" counterpart to the male-associated Y chromosome—have evolved to play a specialized role in sperm production. Moreover, the lab showed that despite its reputation as the most stable chromosome of the genome, the X has undergone relatively swift change.

Says Page: "We view this as the double life of the X chromosome. The story of the X has been the story of X-linked recessive diseases. But there's another side to the X, a side that is rapidly evolving and seems to be attuned to the reproductive needs of males."



IN SURFACE POPULATIONS OF THE CAVEFISH *ASTYANAX MEXICANUS*, DECREASES IN THE LEVELS OF THE HEAT SHOCK PROTEIN HSP90 LEAD TO REDUCTIONS IN EYE SIZE COMPARED WITH THE NORMAL CONTROL SHOWN AT UPPER LEFT.

Playing Offense and Defense

To help a host win a battle against a pathogen, you've got to understand what each of the combatants brings to the field. At Whitehead, two labs have been doing just that, exploring the activities of both the way a football coach might study film of offensive and defensive units.

On the offensive front, Whitehead Member **Hide Ploegh** and his lab recently revealed that the influenza virus infects its host by first killing off the cells of the immune system that are actually best equipped to neutralize it.

Confronted with a virus, the immune system generates cells producing antibodies customized to disarm the invader. A population of these virus-specific B cells retains the information needed to neutralize the virus and resides in the lung to fight secondary infection from re-exposure via viral inhalation. On the surface of these "memory B cells" are specific receptors that bind virus

particles to reduce spread. While such cells should serve as first-line defenders, it turns out that influenza exploits the specificity of the cells' receptors to gain entry, disrupt antibody production, and ultimately kill the cells. By dispatching its enemies this way, the virus replicates quickly before the immune system can mount a second defensive stand.

Meanwhile, Whitehead Fellow **Gabriel Victora** is shedding new light on how the immune system defends against constantly-changing invaders.

When the body detects a foreign virus or bacteria, structures known as germinal centers (GCs) form in the lymph nodes. Within the GCs, antibody-producing B cells move continually through mutation cycles to generate appropriate antibodies. Because production of these high-affinity antibodies requires diversity, multiple GCs arise in a single lymph node, with each GC housing an exclusive population of B cells.

During the mutation cycles, most of the B cells in a GC fail to achieve sufficient antibody affinity and are eliminated. A few, however, are selected to proliferate, leave the GC, and attack the offending pathogen. This selection is driven by T follicular helper (Tfh) cells, which essentially cherry-pick the best B cells. Yet the behavior of Tfh cells has largely been a mystery. But Victora recently found that unlike B cells, Tfh cells move from GC to GC within a lymph node, thereby enhancing the diversity of antibody production by introducing static B cells to a range of dynamic Tfh cells.

"We think this could be the way our immune system maintains a targeted immune response, even when the target is moving," he says.

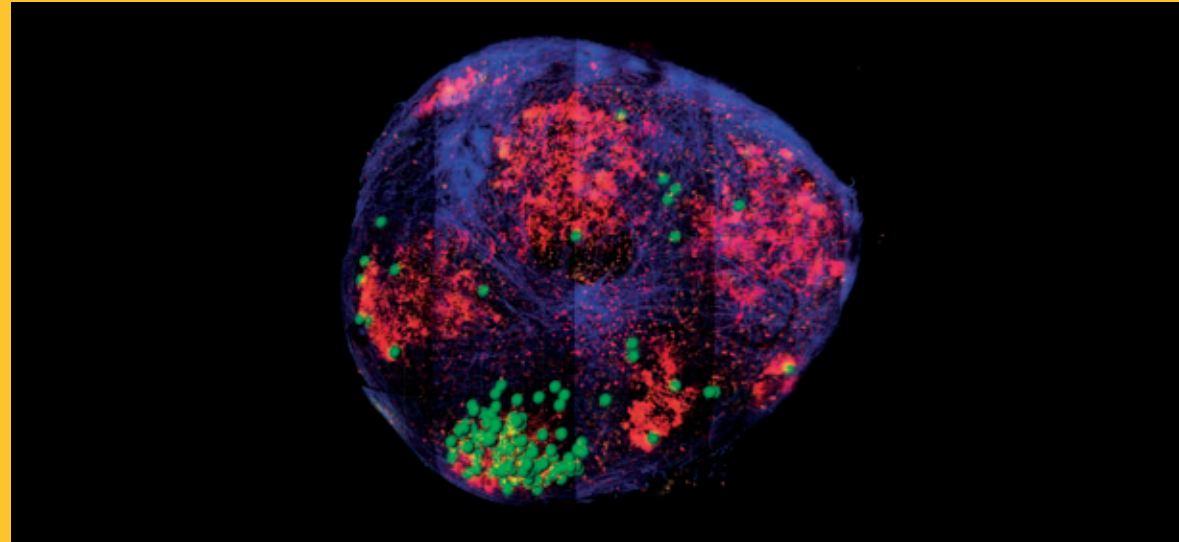


IMAGE OF A LYMPH NODE (BLUE CAPSULE) CONTAINING SEVERAL GERMINAL CENTERS (RED CLUSTERS). T FOLLICULAR HELPER CELLS WERE PHOTOACTIVATED WITHIN A LIVING MOUSE 20 HOURS PRIOR TO IMAGING. GREEN SPHERES WERE DIGITALLY PLACED OVER PHOTOACTIVATED CELLS AND SHOW THE EMIGRATION OF T CELLS FROM THE ORIGINAL GERMINAL CENTER (CENTER BOTTOM) TO OTHER REGIONS OF THE LYMPH NODE.

Dishing Up a Viable Model of Disease

A major pursuit of research with induced pluripotent stem (iPS) cells has been the so-called disease-in-a-dish paradigm; that is, the establishment of disease models using patient-derived cells. Among the diseases of greatest interest are neurodegenerative disorders, such as Parkinson's disease (PD). However, because such disorders are largely diseases of aging, modeling a realistic progression of pathology and identifying therapeutic targets in the confines of a culture dish is exceedingly challenging.

However, scientists in the lab of Whitehead Member **Susan Lindquist** recently deployed a discovery platform—whose components range from yeast cells to human stem cells—to uncover a novel PD target and a compound capable of repairing PD patient-derived neurons.

PD and other diseases such as Huntington's and Alzheimer's are characterized by protein misfolding, resulting in toxic accumulations of proteins in the cells of the central

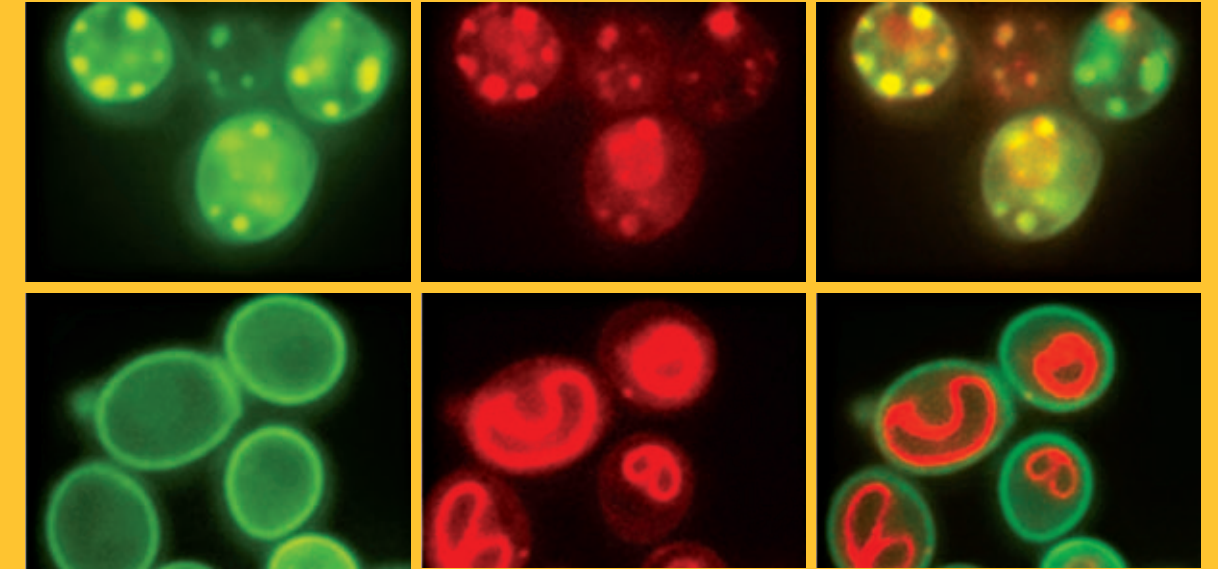
nervous system. Buildup of the protein alpha-synuclein, for example, has long been associated with PD, making this protein a potential target for therapeutic intervention. When searching for compounds that alter a protein's behavior or function—such as that of alpha-synuclein—drug companies often rely on so-called target-based screens that test the effect large numbers of compounds have on the protein in question. Though efficient, the approach is limited by the fact that it essentially occurs in a test tube. Compounds emerging from a target-based screen may act quite differently when tested *in vivo*.

To overcome this limitation, Lindquist's lab uses phenotypic screens, in which candidate compounds are studied within a living system. In this case, yeast cells—which share the core cell biology of human cells—serve as living test tubes in which to study protein misfolding and to identify possible solutions. Yeast

cells genetically modified to overproduce alpha-synuclein serve as robust models for the toxicity of this protein that underlies PD.

In a screen of nearly 200,000 compounds, researchers identified one chemical entity that not only reversed alpha-synuclein toxicity in yeast cells, but also partially rescued neurons in the model nematode *C. elegans* and in rat neurons.

But would these findings apply in human cells? To answer that, lab members examined neurons derived from iPS cells generated from PD patients. The cells and differentiated neurons (of a type damaged by the disease) were derived from patients that carried alpha-synuclein mutations and develop aggressive forms of the disease. In a strikingly positive result, exposure to the compound identified via earlier yeast screens reversed the damage in these neurons.



THE OVEREXPRESSION OF THE ALPHA-SYNUCLEIN GENE FORMS CLUMPS WITHIN THE CELLS OF A YEAST MODEL OF PARKINSON'S DISEASE (TOP ROW). THE ADDITION OF THE COMPOUND NAB2 RESCUES THESE CELLS BY RESTORING ENDOCYTOSIS AND REDUCING ALPHA-SYNUCLEIN PROTEIN INCLUSIONS (BOTTOM ROW).

A CRISPR, more precise approach to editing the genome

For the Human Genome Project to deliver ultimately on its considerable promise—if not hype—in the clinic, scientists require better tools with which to manipulate and study the functions of genes, both individually and in multiples.

Since the late 1990s, a method known as RNA interference (RNAi), has been the most widely used approach for studying gene function. By delivering short RNA strands known as shRNA, which destroy the messenger RNAs (mRNAs) that translate DNA into the proteins that carry out cellular functions, scientists have been able to “knock down” specific genes and observe the impact. However, the naturally-occurring RNAi pathway, which protects cells from viruses and genomic parasites known as retrotransposons, doesn't exist in all organisms. Moreover, because the approach targets mRNA rather than DNA, it cannot completely “knock out” all gene function.

More recently, methods relying on proteins known as zinc finger nucleases (ZFNs) and transcription activator like effector nucleases (TALENs) have been used successfully to target specific genes. Nevertheless, both ZFNs and TALENs can be quite costly, complex, and time-consuming to produce, making them less than ideal for labs anxious to perturb genes and assess the effects rapidly. This is why over the past two years, the development of a novel genome editing system known as CRISPR (for clustered regularly interspaced short palindromic repeat) has been hailed as a breakthrough technology.

CRISPR taps into a bacterial defense system against viral intruders. The most widely used version of the system is known as CRISPR/Cas, (for CRISPR-associated). It relies on the enzyme Cas9, which cuts DNA at locations specified by single guide RNAs (sgRNAs). This DNA-editing complex is highly precise, allowing scientists to select specific genes for disruption simply by changing the sequence of a given sgRNA.

Whitehead Member **Rudolf Jaenisch** and his lab were among the first to demonstrate the transformative power of the system in the biomedical research space by using it to

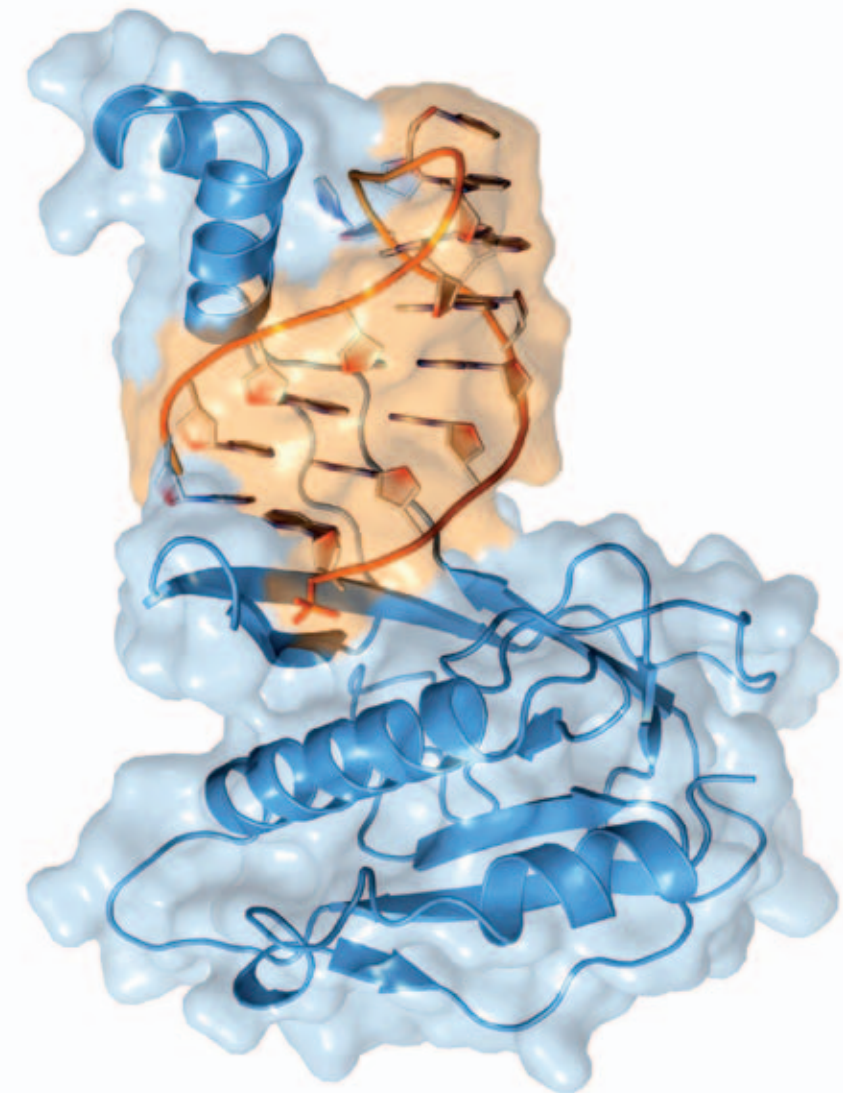
generate mice with alterations in multiple genes in a single step for use in disease modeling. Scientists create such mouse models by altering specific genes associated with a given disease. The models allow for the study of the development and course of the disease and the effects of various interventions, including genetic and chemical. For decades, the approach to generating these animals has remained largely unchanged: scientists insert a piece of DNA into a mouse embryonic stem (ES) cell, inject the modified cell into a very early-stage embryo, then implant the developing embryo in a foster female mouse. The process can take years and tens of thousands of dollars to establish a mouse strain with, for example, a single copy of a gene “knocked out”.

“This new method is a game changer,” says Jaenisch. “We can now make a mouse with five mutations in just three to four weeks, whereas the conventional way would take three to four years. And it's rather straightforward, probably even easier than the conventional way.”

Jaenisch's lab also recently created a modified system known as CRISPR-on, which enables researchers to increase the expression of multiple genes simultaneously and precisely manipulate each gene's expression level. The system, which is effective in both mouse and human cells as well as in mouse embryos, should bolster understanding of multigenic activity underlying a variety of diseases.

“Many diseases, especially complex diseases, involve multiple genes, and this system could be used therapeutically to target and activate multiple genes together and rescue these disease phenotypes,” says Albert Cheng, a graduate student in the Jaenisch lab working with the CRISPR-on system.

Concludes Jaenisch: “CRISPR-on is a tool that will be very useful for studying many biological processes, particularly for studying gene functions and gene networks. In contrast to RNA interference, which is commonly used to inactivate gene activity, the CRISPR-on system allows activation of cellular genes. The technology substantially expands our ability to change gene expression in cultured cells and animals.”



THIS COMPUTER MODEL OF A MICROBIAL IMMUNE SYSTEM MOLECULE DEPICTS A TEMPLATE OF A SECTION OF A CRISPR (CLUSTERED REGULARLY INTERSPACED SHORT PALINDROMIC REPEAT) DNA UNIT (IN ORANGE) THAT HAS HAD DNA FROM AN INVADING PATHOGEN INSERTED INTO IT. HERE, THE CRISPR UNIT BINDS PRECISELY WITHIN AN ENZYME (IN BLUE), CUTTING RNA INTO MANY SHORT SECTIONS THAT CAN MATCH UP TO THE PATHOGEN'S DNA AND BIND TO IT. THIS STOPS THE CELLULAR MACHINERY FROM READING THE PATHOGEN'S DNA AND SO SUPPRESSES THE INFECTION.

“Super-enhancers” have their say, in sickness and in health

In little more than a year’s time, Whitehead Member **Richard Young** and his lab have managed to change not only the way we think about the mechanisms of cellular control, but the way we speak of them as well.

This shift began with the discovery of a set of powerful gene regulators that control cell state and identity. In a bold act of neologism, Young dubbed them “super-enhancers”. It turns out that healthy cells use super-enhancers to control genes responsible for cellular functions and developmental transitions, but cancer cells are able to assemble their own insidious super-enhancers to overproduce harmful genes that lead to aggressive tumors.

“We have been marveling at the complexity of cellular control, with millions of enhancers controlling tens of thousands of genes in the vast array of cells that comprise human beings,” says Young. “So it was a surprise to find that only a few hundred super-enhancers control most key genes that give each cell its special properties and functions, and furthermore, that these special controls are hijacked in cancer and other diseases.”

During 2013, Young’s lab produced publications documenting the power of super-enhancers. In one work, the lab established a model of gene regulation in normal cells that appears to be dramatically less complex and more solvable than previously thought. A vast body of research—including that of the much heralded ENCODE (Encyclopedia of DNA Elements) project—has identified more than one million enhancers or “switches” that control gene expression in mammalian cells. Yet, Young and colleagues appeared to have found a shortcut to solving the core gene control circuitry. They showed that only a few hundred special switches—that is, super-enhancers—control the key genes that actually make each cell different.

“What is fantastic about this concept is its simplicity,” says Denes Hnisz, a Young lab postdoctoral scientist and a co-author of one of the publications. “We found that genes that are especially important for each cell are regulated by these specialized enhancers. But we also discovered that the super-enhancers are especially quick to change during development, and thus loss of old super-enhancers and establishment of new ones drives cell identity changes during development.”

Young believes such changes in cell identity probably begin and end with the super-enhancers, which, though powerful, are also exquisitely sensitive to alterations in their environment. As differentiation begins, active super-enhancers are decommissioned, leading to changes in gene expression programs that fall under the control of newly established super-enhancers. It’s a process that adds remarkable insight to our understanding of how a fertilized egg eventually gives rise to the more than one trillion cells of the human body.

Says Young: “The discovery of super-enhancers promises to help us solve the regulatory circuitry of all human cells.”

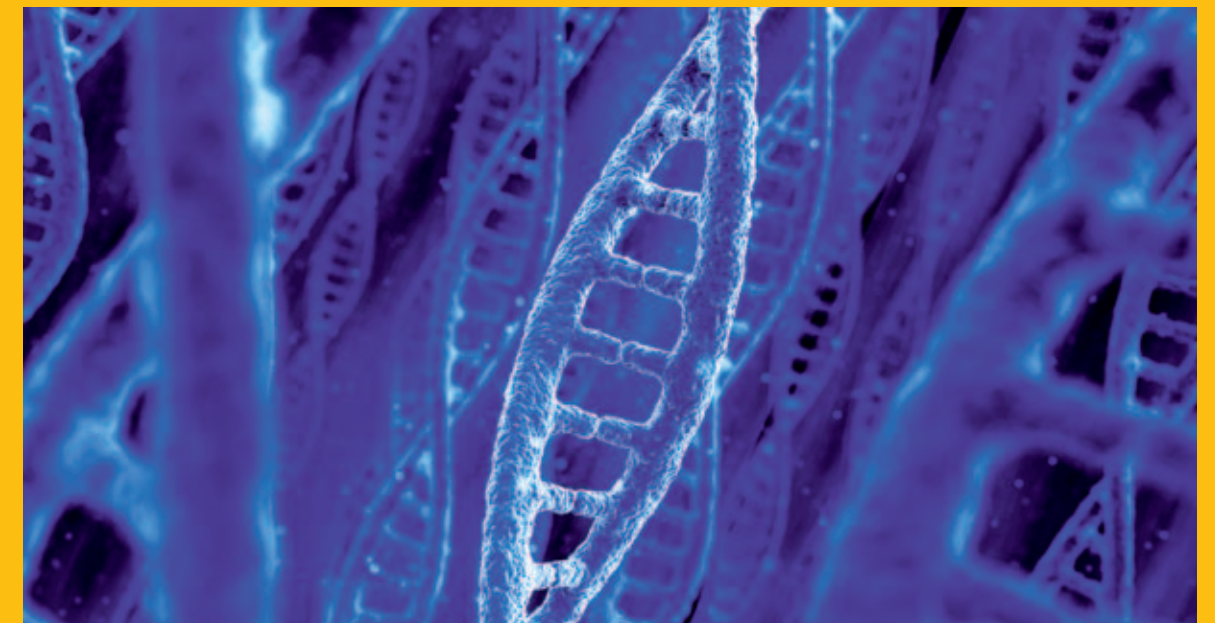
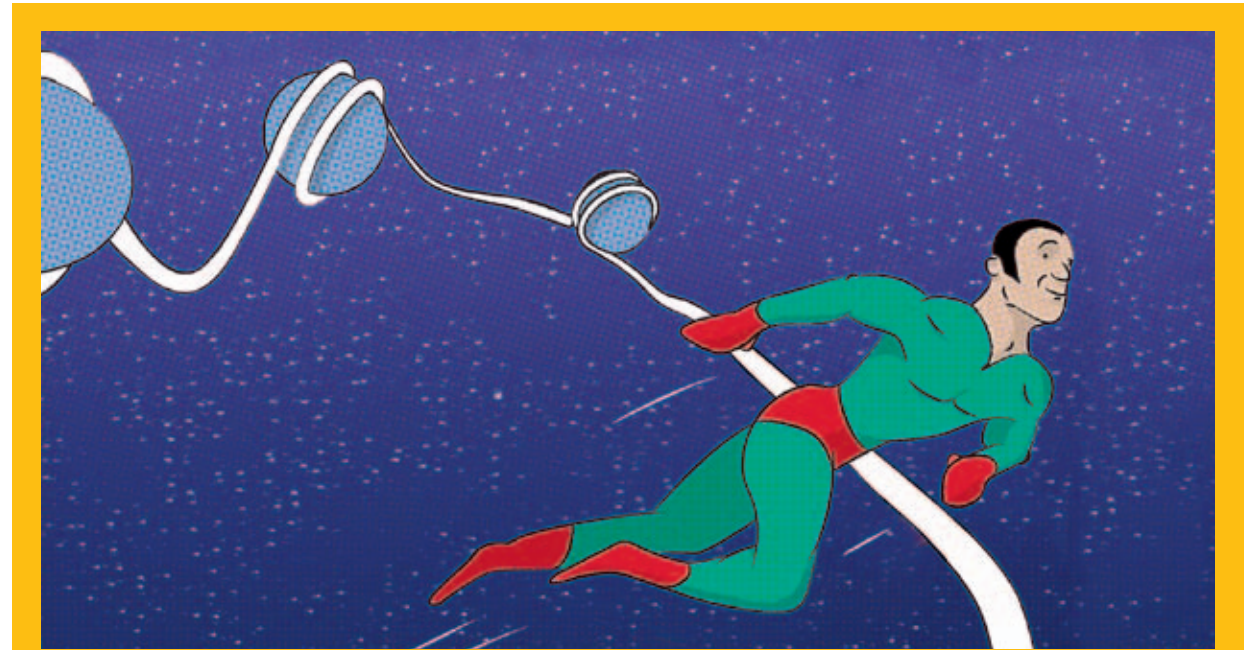
That includes cancer cells. While mapping the locations of super-enhancers along the genome of multiple myeloma (MM) cells, which are especially aggressive blood cancer cells, Young lab members found them in areas associated with known cancer-causing genes, including the notorious MYC oncogene. It turns out these MM cells were forming their own super-enhancers to drive dangerous overexpression of their oncogenes. Moreover, this phenomenon was not limited to MM cells, as the researchers identified super-enhancers at key tumor genes in small-cell lung cancer and the brain cancer glioblastoma multiforme.

Having observed how sensitive super-enhancers are to disruptions in their surroundings, Young and colleagues hypothesized that this sensitivity might represent a vulnerability in cancer cells whose oncogenes are in overdrive. Young and collaborator James Bradner of Boston’s Dana-Farber Cancer Institute found that an experimental drug known to selectively inhibit MYC expression in MM cells was acting at the MYC super-enhancer.

“It’s difficult not to be excited about the prospect of identifying super-enhancers in patient tumors and developing novel therapeutics to disrupt their control of key oncogenes,” says Bradner.

Young meanwhile is increasingly confident that this super-enhancer paradigm of gene regulation has important implications across human disease states.

“Looking at large genome association studies, one can find disease-related mutations occurring in super-enhancers,” Young says. “It’s possible that super-enhancers could become biomarkers that identify key disease genes and help guide the development of approaches to treatment.”



ALTHOUGH THE NAME “SUPER-ENHANCERS” MAY EVOKE IMAGES OF CARTOON SUPERHEROES, THE EFFECTS OF THESE RECENTLY DISCOVERED, EXTRA-POTENT GENE REGULATORS ARE QUITE REAL. THEY NOT ONLY HOLD THE KEY TO THE CONTROL OF CELL STATE AND IDENTITY IN NORMAL CELLS, BUT ARE ALSO CO-OPTED WITH DISASTROUS CONSEQUENCES IN A VARIETY OF DISEASES, INCLUDING CANCER.

Honors and Awards

Yaniv Erlich

In June, the Burroughs Wellcome Fund named Whitehead Fellow Yaniv Erlich a recipient of one of its Career Awards at the Scientific Interface (CASI). Intended to foster early career development, CASI grants provide \$500,000 to support researchers over their first three years between postdoctoral training and a faculty appointment. Grantees are those who have transitioned or are transitioning in the physical/mathematical/computational sciences or engineering into postdoctoral work in the biological sciences, and who are dedicated to pursuing a career in academic research. Erlich, who was awarded for his research on dissecting complex phenotypes using web 2.0 social networks, was one of 10 young scientists to receive a CASI grant in 2013.

Gerald Fink

In late January, the American Association for the Advancement of Science (AAAS) announced that Whitehead Institute Founding Member Gerald Fink had been chosen as its President-elect for 2013. With his election, Fink began a three-year term as an officer and member of the Executive Committee of the AAAS Board of Directors and assumed the role of President of AAAS in February 2014. Upon his election, Fink stated: "It's an honor to be elected to the presidency of AAAS, which serves as the voice of American science to the world. I am prepared to tackle a number of daunting

challenges facing us today, not least of which is the waning support for American science by the Federal government. As the eventual leader of AAAS, I intend to work hard to protect our most vulnerable group in science—today's students, fellows, and young faculty—and to ensure that the world's population has the benefit of their insights and ideas in the decades ahead."

Rudolf Jaenisch

Also in January, the Baltimore-based Passano Foundation, whose mission is to recognize members of the medical and scientific community who have made an outstanding research contribution, selected Whitehead Founding Member Rudolf Jaenisch as its 2013 Laureate. Named for its founder, the late Edward Boetler Passano, former Chairman and CEO of medical publisher Williams & Wilkins, the foundation has been bestowing this honor annually since 1945. According to the foundation, Jaenisch was being recognized for his "groundbreaking contributions in the field of transgenic science, therapeutic cloning, and cell biology."

In November, the New York Academy of Medicine awarded Jaenisch its 2013 Academy Medal for Distinguished Contributions in Biomedical Science. The Academy, which was established in 1847, has been awarding the medal to an eminent scientist in biomedicine since 1929. In announcing the award,

Academy President Jo Ivey Boufford, MD, stated: "Dr. Jaenisch's groundbreaking research is vital to the field of biomedical science and has advanced progress toward finding cures for numerous life-threatening diseases. We are pleased to honor him with this year's medal."

Sebastian Lourido and David Pincus

In September, Whitehead Fellows Sebastian Lourido and David Pincus were each named a recipient of a 2013 National Institutes of Health (NIH) Director's Early Independence Award (EIA), aimed at accelerating the careers of exceptionally creative junior scientists. The awards enable qualified recipients to conduct independent biomedical or behavioral research by skipping the traditional postdoctoral training period. The EIA is a part of the so-called High Risk-High Reward program supported by the NIH Common Fund. Lourido and Pincus, two of the 15 awardees selected nationwide, will receive five years of funding from the NIH.

Peter Reddien

In May, the Howard Hughes Medical Institute (HHMI) announced that Whitehead Member Peter Reddien was among 27 biomedical researchers nationwide to be appointed as HHMI investigators. The new HHMI investigators were identified in a rigorous selection process that winnowed an original field of nearly 1,200 applicants to approximately 60 semifinalists

asked to give brief scientific presentations at an HHMI research campus in Virginia. Chosen for their individual scientific excellence, Reddien and the 26 other new investigators will each receive five years of research support intended to fuel creativity and audacity in the lab. Notably, Reddien became the fifth HHMI investigator at Whitehead Institute, joining Whitehead Members David Bartel, Susan Lindquist, David Sabatini, and Whitehead Director David Page.

Robert Weinberg

In February, Whitehead Institute Founding Member Robert Weinberg was among 11 scientists to receive the new Breakthrough Prize in Life Sciences, intended to recognize excellence in research aimed at curing intractable diseases and extending human life. The prize—whose founding sponsors include Google co-founder Sergey Brin, Anne Wojcicki, founder of the personal genetics information company 23andMe, Facebook founder Mark Zuckerberg, and Russian entrepreneur Yuri Milner—awards each recipient \$3 million for "past achievements in the field of life sciences, with the aim of providing the recipients with more freedom and opportunity to pursue even greater future accomplishments."

The value of the Breakthrough Prize is more than double that of the Nobel Prize. Arthur Levinson, Chairman of the Board of Apple and Chairman and former CEO of Genentech, chairs the foundation

that oversees administration of the prize. In announcing the inaugural recipients Levinson stated: "I believe this new prize will shine a light on the extraordinary achievements of the outstanding minds in the field of life sciences, enhance medical innovation, and ultimately become a platform for recognizing future discoveries."

The foundation has dedicated itself to supporting groundbreaking research, celebrating scientists, and inspiring the pursuit of careers in science. "We are thrilled to support scientists who think big, take risks, and have made a significant impact on our lives," Wojcicki said. "These scientists should be household names and heroes in society."

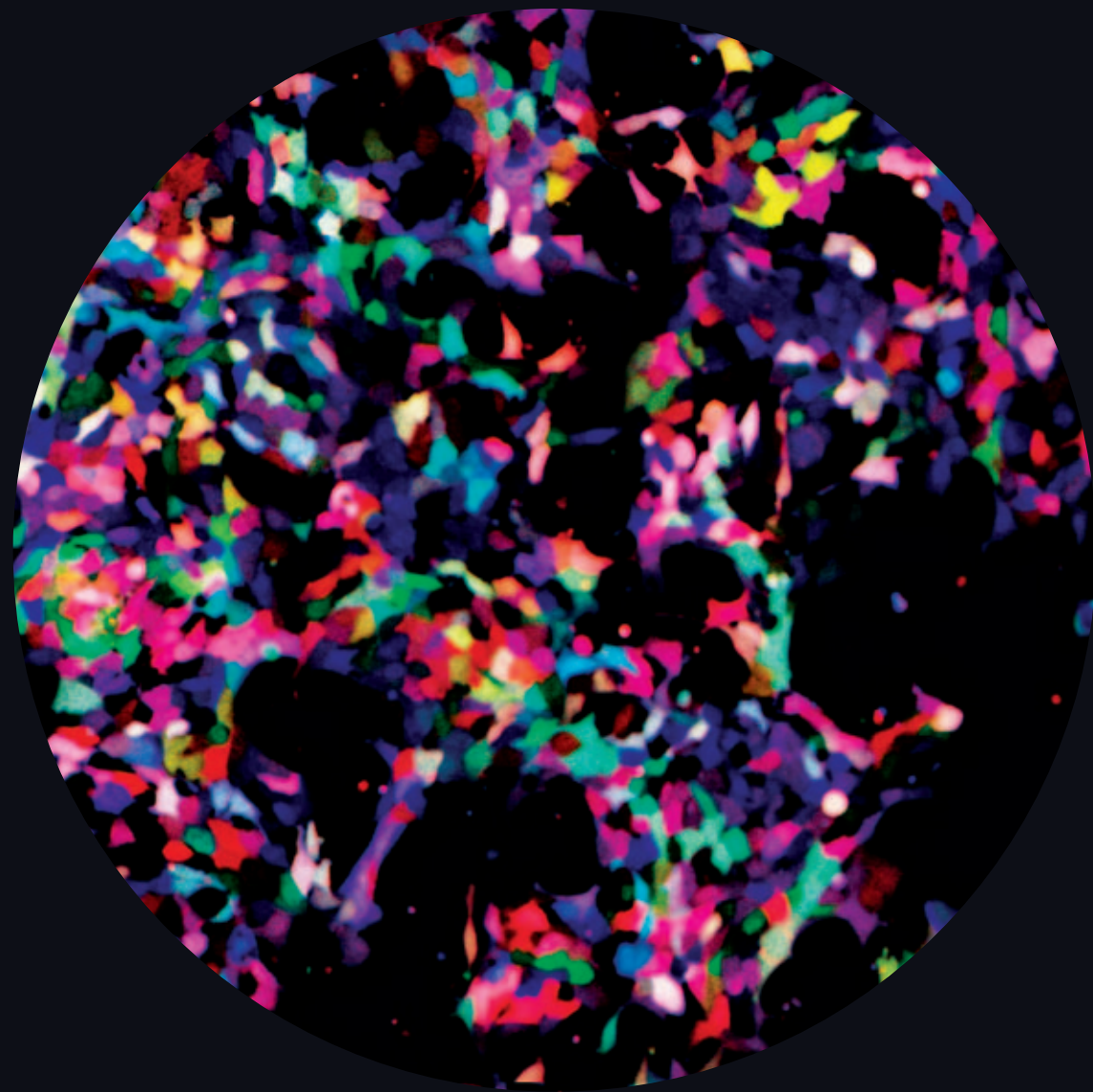
Awardees in addition to Weinberg, include: Eric Lander, a former Whitehead Member and Whitehead Fellow who is now Director of the Broad Institute; Rockefeller University professor and Howard Hughes Medical Institute investigator Cornelia Bargmann, who trained under Weinberg in the 1980s, and induced pluripotent stem cell pioneer and Nobel Laureate Shinya Yamanaka of Kyoto University and Gladstone Institutes.

In late March, the American Association for Cancer Research (AACR) announced that Weinberg would become a member of its inaugural class of Fellows of the AACR Academy. AACR established its Academy "to recognize and honor distinguished scientists whose major

scientific contributions have propelled significant innovation and progress against cancer." The first class included 106 Fellows—a number equal to AACR's years in existence—chosen in what AACR describes as a rigorous peer review process. Subsequent classes will include 11 new Fellows annually. Other inaugural Fellows of the AACR Academy with ties to Whitehead Institute include: Nobel Laureate Aaron Ciechanover (Technion-Israel Institute of Technology), a former postdoctoral fellow in the lab of Whitehead Founding Member Harvey Lodish; Tyler Jacks (David H. Koch Institute for Integrative Cancer Research at MIT), a former postdoctoral researcher in Weinberg's lab; and Nobel Laureate Phillip Sharp (MIT), a member of Whitehead Institute's Board of Directors.

Whitehead Institute

In the final year of its "Best Places to Work: Postdocs" ranking, *The Scientist* magazine announced in April that Whitehead Institute had again emerged as Number 1. This was the third straight year, and the fourth time in the 10 years the rankings were conducted, that Whitehead came out on top—more than any other institution in the history of the annual exercise.



PRINCIPAL INVESTIGATORS

*They are 17 of the world's most accomplished
and most creative scientists, all dedicated to
conducting transformative research while shaping future
generations not just to follow in—
but to one day outpace—their formidable footsteps.*



David Bartel

Current scientific research rests on a foundation of earlier findings, some often decades or more in the making. Once a conclusion is supported by corroborating research, scientists base future experiments on the assumption that a tenet is correct. But what happens when a tenet's scope is more restricted than originally thought? The Bartel lab recently tackled this issue when it overturned our understanding of messenger RNA (mRNA) translation rates occurring in early development.

Years of work in oocytes and new embryos had shown that chains of adenosine molecules called poly(A) tails added to mRNAs determine how often the mRNAs are translated to make proteins. The longer an mRNA's poly(A) tail, the more frequently it would be translated. This control of translation provides a mechanism for regulating gene expression in oocytes and very early embryos and was thought to do the same in older embryos and adult cells as well. That is, until the Bartel lab investigated further, aided by their newly developed technique that measures the tail lengths of millions of individual mRNAs in a sample.

To their surprise, lab members found that previous findings were accurate only through the earliest stages of embryogenesis, after which tail length becomes irrelevant for mRNA translation rates.

Bartel hypothesizes that the timing of this shift relates to the changing possibilities for gene regulation available to an embryo as it develops. Oocytes and very early embryos are unusual in that they operate without making any new mRNAs, instead using old mRNAs inherited from the mother. Without the ability to change gene expression by making new mRNAs, the cells lengthen or shorten tails of pre-existing mRNAs, and in this way favor the translation of some mRNAs over others.

Later, as the embryo acquires the ability to create new mRNAs, there is less need for this regulatory mechanism. There are also more opportunities for regulating genes by changing the stability of their mRNAs. Accordingly, tail length becomes unimportant for translation rates and more important for mRNA stability, with very short tail lengths flagging mRNAs for destruction. Bartel speculates that after reaching this more typical state in which control of mRNA stability plays a major role in gene regulation, translating the mRNAs equally regardless of their tail length has the advantage of enabling the cell to fully utilize long-lived mRNAs, which tend to have shorter tails because tails shorten as mRNAs age.

NOT SAFE. NOT SORRY.

*Developing a new method can be difficult, with plenty of risk and frustration,
but it's a real thrill when that method works,
and a previously inaccessible aspect of biology is suddenly revealed.*

With more than 30 trillion cells in the human body, cells must divide countless times to generate each person. By precisely dividing its contents, a mother cell ensures that both of its daughter cells have the information and resources to survive and produce the next generation. Iain Cheeseman's lab studies cell division by focusing primarily on the role the protein complex known as the kinetochore plays in this finely tuned process. Occasionally, however, the simple act of carefully observing cell division can lead to unexpected discoveries.

In preparation for mitosis, a human cell copies its 46 chromosomes (units of DNA). Each replicated chromosome is composed of two identical chromatids held together. As mitosis progresses, thin protein filaments, called microtubules, extend from spindle poles on either end of the cell and hook onto the kinetochores, located at the centromeres, forming a structure called the mitotic spindle. Once the microtubules align the chromosomes in the middle of the cell, they pull the chromosomes apart into separate chromatids. The chromatids are then dragged to opposite ends of the cell, and the cell membrane pinches together between the two chromatid deposits.

The location of the pinching point that divides the cell depends on the position of the mitotic spindle within the cell. If the spindle structure is in the middle of the cell, the cell will divide symmetrically, resulting in equal-sized daughter cells, as is the case in almost all human non-stem cells. In contrast, asymmetric cell division can result in two daughter cells with very different fates—one large cell that divides again prematurely and a much smaller cell that grows very slowly or dies.

As Tomomi Kiyomitsu, a researcher in Cheeseman's lab, carefully watched cells divide, he noted that as they progress through mitosis, some cells' spindles are off-center. In most cases, the cells correct this positioning by moving their spindles into proper alignment. But about 25% of the time, the cells perform a feat not thought possible—they adjust their membranes to accommodate the spindles' position. Cheeseman says that this unexpected phenomenon happens in virtually every plate of dividing human cells, yet no one had paid attention to how one-quarter of those cells corrects a potentially disastrous situation.



Iain Cheeseman

NOT SAFE. NOT SORRY.

On a daily basis, we're making research decisions where we don't know what the final outcome will be.

You have a gut instinct that what you're studying is going to be interesting and worth looking at, and you're sure you can work out any issues, but there are no "safe" projects.

Overall, science as a career is like this, too. It's not about success, fame, or money, and at times it can feel like a risky choice, but I have never been sorry.



How does a biologist decide which organism to study? Gerald Fink chose to study yeast, much to the surprise of his mentor, who tried to convince him to work on a better-studied beast.

“He thought it was an odd choice because so few people had studied this microorganism, and it wasn’t in the mainstream,” Fink recalls. “But yeast’s lifestyle fit my own research tempo. I don’t have the patience to wait for mice to breed. Even fruit flies take too long for me. I like to see results the next day.”

Fink’s yeast studies spawned what would become a burgeoning field. He’s perhaps best known for developing a technique allowing researchers to put any gene from any organism into the yeast genome. This finding launched yeast first as the premier model for eukaryotic molecular biology and later as the model organism driving newer fields such as functional genomics and systems biology.

Now Fink is adding to yeast’s vast job description by introducing it as a system in which to explore one of molecular biology’s great mysteries—post-transcriptional modification—the study of chemical changes to RNA occurring after synthesis. One of the major post-transcriptional changes is methylation, the addition of a

chemical methyl group to messenger RNAs at specific sites on the RNA molecule.

One change, m6A methylation, was actually discovered nearly 40 years ago, but until recently was considered insignificant. Yet, this m6A modification, or “mark,” is found on mRNAs in nearly all eukaryotic organisms, including humans. Its ubiquity spurred Fink to discover its function in yeast, believing it would again be the quickest way to resolve the puzzle.

Fink and colleagues recently conducted a comprehensive, high-resolution mapping of m6A sites on the messenger RNA in yeast, revealing for the first time clues about this mark’s function. The researchers discovered that the m6A modification has profound effects on the sex cycle of the organism. Without it, the yeast fails to go through meiosis. There are hints it may also affect the sexual cycle in other organisms.

Having linked m6A methylation to such a critical developmental event, and knowing the ubiquity of m6A methylation across species, Fink believes this latest mapping once again makes yeast the pioneer organism for exploring the unknown.

Gerald Fink

NOT SAFE. NOT SORRY.

I’ve never been safe, and I’ve never been sorry. At the time I decided to work on yeast, there were probably only 20 labs in the world doing so. Now there are several thousand. This has happened because yeast allows you to answer questions rapidly. This has been important not only for research labs, but for development of biofuels and for manufacture of drugs in yeast.

Mary Gehring

The plant *Arabidopsis thaliana*, a relative of cabbage and mustard, stands just a few inches tall and can often be seen popping up through sidewalk cracks and among rocks in temperate climates. With its thin stems, petite leaves, and small, white flowers, *A. thaliana* may look at best delicate and at worst like a weed that needs to be eradicated. Yet a few of this plant's characteristics—including its short lifecycle, prolific seed production, and surprisingly small genome—make *A. thaliana* an ideal model organism and the basis for Mary Gehring's research on epigenetics.

Gehring's space in Whitehead Institute's greenhouse is home to several strains of *A. thaliana*, each with its own special traits: the Columbia line was the first to have its genome sequenced and is the most commonly studied strain; the Landsberg strain has spawned about 50 years' worth of research; and the Cape Verde Islands line is much less methylated in the coding segments of its DNA than the other two strains, one of Gehring's findings that has made the Cape Verde Islands line a key player in some of her work.

Methylation is an epigenetic modification that promotes or suppresses gene expression by adding collections of atoms, called methyl groups, to certain bases within the DNA. Methylation of certain genes can change as a cell or organism matures—for example from an embryonic stem cell to a muscle cell or from a seedling to a leaf. This process is tightly controlled, as activating the wrong methylation profile can lead to cell death or cancer in humans and animals.

Methylation patterns can also be passed from one generation to the next in a process called gene imprinting. This can occur between female and male gametes to their zygote. By crossing the Cape Verde Islands strain with the other strains, Gehring is using the plant lines' natural variation in methylation levels to study how gene imprinting at the base pair level across the genome is maintained or lost from parent to progeny and how this alters gene function.

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We are betting that a simple weed will allow us to gain fundamental insights into epigenetic inheritance not only in plants, but more broadly in all multicellular organisms.





“One thing you’re always told is that the third rail of chemical biology is ‘target ID,’” says Piyush Gupta, referring to the strategy of trying to determine a specific chemical’s activity or target in a cell. “The experts insist that it’s much safer to start with a target—for example a protein of interest—and find the things that bind to it, rather than to look for chemicals that have a cellular phenotype of interest—for example killing cancer stem cells—and try afterward to figure out what the chemical is doing. The problem with this is that you often end up with a chemical with known binding properties that doesn’t do anything interesting in actual cells. So we decided to not play it safe.”

While that daring research strategy may have cost Gupta some measure of funding from the National Institutes of Health, it also led to one of the most important discoveries of his career thus far.

A few years ago, Gupta ran a large screen of more than 300,000 chemicals to see if any had an effect on cancer stem cells (CSCs), which are resistant to almost all current therapies, capable of traveling around the body, and able to seed new tumors. Two compounds in the screen were selectively toxic to CSCs.

Gupta and his lab recently determined that the compounds kill otherwise invincible CSCs by stressing their endoplasmic reticulum (ER); the compounds did not affect the ER of non-CSCs, leaving those cells unscathed.

CSCs require their ER to pump out vast amounts of proteins that are needed for the CSCs’ mobility, and these demands push the ER to their capacity. Adding either of the compounds or any other ER stressors to the CSCs pushes the ER beyond their limits, and the cells die.

The PERK pathway in the ER may be particularly important for CSCs, as it helps cells cope with massive protein production. In studying roughly 800 patient tumors across a range of cancer types, Gupta’s lab found that the expression of the CSC genetic profile is tightly correlated with PERK pathway activity. Perhaps PERK pathway activity could be used as a marker for therapy, as cancers with higher PERK activity seem more sensitive to further ER stress.

Piyush Gupta

NOT SAFE. NOT SORRY.

I have no regrets about taking the approach we did, even if we didn’t always know everything would work out. And I’m grateful to be at an institution where I am free to take these kinds of risks, because not everyone is so lucky, and because science without risks is often incremental and unlikely to lead to real breakthroughs.

Rudolf Jaenisch

It takes an awful lot to impress Rudolf Jaenisch. Over a distinguished research career spanning nearly 50 years, he's seen plenty of techniques and discoveries initially touted as breakthroughs come and just as quickly go. So when a little more than a year ago he described a novel gene-editing technique called CRISPR/Cas as "a game changer," the scientific community took notice.

Then he proved it, using CRISPR/Cas to forever change the way mice can be genetically altered to model human disease. Jaenisch, who helped transform the study of genetics by creating the first transgenic mouse in 1974, had long known the drawbacks of conventional mouse models. In fact, for more than two decades, the creation of such models had remained relatively unchanged: scientists inserted a piece of DNA into a mouse embryonic stem (ES) cell, injected the modified cell into a very early-stage embryo, called a blastocyst, and then implanted this developing ball of cells into a foster female mouse. The process is slow and expensive, often taking many years and costing tens of thousands of dollars. Moreover, these models' utility is often restricted to the study of monogenic diseases; that is, those whose manifestations

are associated with mutations of a single gene. However, many of our most prevalent and devastating diseases are multi-genic, influenced by changes in multiple genes.

Using the CRISPR/Cas system, the Jaenisch lab was able to generate ES cells with as many as five mutated genes in a matter of weeks. It was the first time that the approach was used to alter multiple genes in a single step. Moreover, the CRISPR/Cas technique can generate mutant mice even without using time-consuming ES cell technology. In fact, because, in contrast to the conventional method for making models, ES cells are not required, genetic research may no longer be confined to a limited list of model species—those for which ES cells exist.

Jaenisch was so impressed with the efficiency and precision of the method that he drove the creation of a CRISPR core facility at Whitehead that is now serving not only his lab, but others within the Institute. The facility is allowing researchers to conduct extensive gene editing experiments, creating deletions and insertions in mouse embryos and the direct generation of adult mice carrying multiple genetic alterations.

NOT SAFE. NOT SORRY.

When I applied for my first grant to produce transgenic mice 40 years ago, it was funded immediately. That's a project that would never be funded today.

Now you are likely to get money from traditional sources only if you have safe, predictable projects.

There can be no risk involved. This is not what drives science.

This philosophy does not produce technological advances like CRISPR, for example.





Susan Lindquist

Among the hallmarks of Susan Lindquist's prolific research career has been her ability to challenge—and eventually overturn—conventional wisdom. In her studies of the evolution of novel traits, one of her proudest achievements has been to show that prions, the proteins best known for causing “mad cow” disease and Creutzfeldt-Jakob disease, can also induce potentially beneficial traits.

A few years ago, her lab became the first to identify such prion behavior in naturally occurring yeast strains, discovering proteins that switch from a normal shape to a self-perpetuating prion conformation and back again. This switch, found to cycle more rapidly in environmentally stressful conditions, alters protein function, leading to the emergence of new traits. About half of the new traits proved to be beneficial. Moreover, such traits can be hard-wired into the genome and passed down to subsequent generations, indicating that this protein-based mechanism of inheritance is part of a survival mechanism helping yeast adapt to changes in their surroundings.

More recently, members of her lab added to the job description of prions as agents of change, discovering a prion capable of triggering a transition in yeast from its conventional single-celled form to a cooperative, multicellular structure. This change, which also appears to

improve yeast's chances for survival in the face of hostile environmental conditions, is an epigenetic phenomenon—a heritable alteration brought about without any change to the organism's underlying genome.

By testing yeast cells against a variety of stressors, the scientists discovered that exposure to a concentration of ethanol akin to that occurring naturally during fermentation increased the formation of a prion known as [MOT3+] by a factor of 10. They also found that as the cells exposed to ethanol shifted their metabolism to burn surrounding oxygen through respiration, the prions reverted to their non-prion conformation, and the yeast returned to the unicellular state. In essence, prion formation drove a shift to multicellularity, helping the yeast to ride out the ethanol storm.

“We see such prions as part of a bet-hedging strategy that allows the yeast to alter their biological properties quickly and to try out new survival mechanisms when their environments turn unfavorable,” Lindquist says. She also theorizes that prions are playing such roles beyond yeast and has been investigating prions and prion-like mechanisms at work in other organisms as well as in diseases of protein misfolding.

NOT SAFE. NOT SORRY.

I believe we need to use the power of evolution to unlock the secrets for medical cures. It's not necessarily the safest approach one could take, but simple cells like yeast have evolved to cope with adversity in very complex ways. We're finding that we're able to exploit these cells to accelerate our understanding of the pathologies associated with a number of human diseases.



Until a few years ago, the spotlight of RNA research focused on messenger RNAs (mRNAs), which act as templates for protein production. We now know, however, that these represent a mere one-fifth of the RNA sequences generated in mammalian cells. The remainder—comprising primarily long non-coding RNAs (lncRNAs)—lurked in the shadows, invisibly regulating gene expression during development and other processes.

Only recently have scientists recognized lncRNAs' existence and appreciated their importance. Harvey Lodish is one of those scientists, and his lab has been identifying lncRNAs' roles in the developmental pathways that generate fat and red blood cells (RBCs). The lab has found some lncRNAs that operate only in brown fat, which is primarily found in babies, and several that support white fat exclusively. Others are active in RBCs but not in other tissue. Most importantly, the lab has shown that many of these lncRNAs are essential for normal production of these cells.

“This is part of a new regulatory circuitry that we are just beginning to uncover and understand,” says Lodish. “How lncRNAs act within the cells and why they are crucial for many developmental pathways is a puzzle, a very big puzzle, that we and several other labs are trying to work out.”

The Lodish lab is also working on repurposing existing drugs to treat Diamond-Blackfan anemia (DBA) and other anemias that are currently considered untreatable with standard therapy, the hormone erythropoietin (EPO). Currently, patients are prescribed glucocorticoid steroids, such as prednisone or prednisolone, which increase the number of RBC progenitor cells that respond to EPO. Although helpful, these drugs cause a host of negative side effects, including decreased bone density, immunosuppression, stunted growth, and cataracts, so lowering or eliminating glucocorticoid use is desirable.

The lab is making impressive strides toward this goal. First, it has identified the mechanism that glucocorticoids activate to stimulate the self-renewal of early RBC progenitors. By tapping into this system, they have increased RBC production from stem cells to over 30,000-fold. Now, Lodish has identified a receptor that synergizes with the glucocorticoid receptor to increase the production of early RBC progenitors even more. Stimulating both receptors with existing drugs produces an astonishing 120,000-fold expansion of RBC production. Perhaps this discovery is a step toward improving the outcome of DBA patients while allowing for lower doses of glucocorticoids.

Harvey Lodish

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It's not that we necessarily do crazy experiments ourselves, but we train people to go off in their own directions. That's what my postdoc in the 1970's, Jim Rothman, did. He used a system we had developed for studying membrane protein synthesis in a completely novel way to identify the proteins in vesicular traffic. For that, he won the 2013 Nobel Prize in Physiology or Medicine.

Terry Orr-Weaver

Understanding the earliest steps in development is one of Terry Orr-Weaver's passions.

"For me, how you start embryogenesis at fertilization is such a fascinating question," she says. "How do you take a quiescent, arrested, differentiated oocyte and turn it into a totipotent embryo? It's the start of life. It's asking, 'how do you start life', and what could be more profound or interesting?"

Usually such transitions in cell state are regulated by changes in transcription of DNA. But during the shift in animals from an immature egg cell to embryo, transcription is halted, so some other mechanism must be in control. To help her identify the processes in action, Orr-Weaver looked to her preferred model organism, the fruit fly. After examining mutants that are unable to complete the oocyte-to-embryo transition, she found that some proteins must be purged from the oocyte whereas others must be translated before embryogenesis can commence.

Orr-Weaver and her lab identified these massive changes in proteins that activate the change from oocyte to embryo by analyzing both protein levels and the translation of mRNAs. This is the first time one lab has defined both the proteome and the translome changes accompanying a developmental transition. The results were surprising. mRNA levels in the egg do not change, but how those mRNAs are translated does, and one protein kinase complex, called PAN GU, controls which mRNAs are translated during this transition. PAN GU was known to be active during this window of development, but it was thought to control only a handful of targets. Moreover, many proteins present in the oocyte are turned over and newly synthesized at egg activation, a likely mechanism to reset the state of the proteins for embryogenesis without changing their abundance.

Although the switch that starts the process of remodeling the protein content at the oocyte-to-embryo transition is not yet known, the comprehensive study by Orr-Weaver and her lab has uncovered a group of candidates that may be the critical regulators. The lab is actively pursuing the function of these genes.

NOT SAFE. NOT SORRY.

It certainly did not feel safe changing from looking at a single gene at a time to a global view of how every mRNA and protein in the oocyte changed at the transition to the embryo, and it would not have been possible without the advice of my colleagues here and the computational support provided by Whitehead's Bioinformatics and Research Computing (BaRC). But shifting our focus to a global level provided critical unexpected insights.



Those who know him well would regard David Page as a most unlikely instigator of a sexual revolution. And yet, a growing body of research emerging from his lab may trigger just that, at least when it comes to how we view sex and disease.

Page has built a celebrated career studying mammalian sex chromosomes, and his painstaking, decade-long, airtight defense of the human Y chromosome against those who prophesy its eventual extinction is well-documented. Now Page says he's ready to usher in a new era of Y biology, one that, of necessity, includes the X chromosome (or, as Page puts it, the "foil" to the Y).

Page's lab recently reported that the human Y chromosome has over the course of millions of years of evolution managed to preserve a small set of genes that has ensured not only its own survival but also the survival of men. The lab also found that most of these tenacious genes are expressed widely throughout the body and appear to have little if any role in sex determination or sperm production. Taken together, the findings suggest that these dozen or

so genes may actually be contributing to differences in disease susceptibility and severity observed between men and women.

Driven by this hypothesis, the lab is now investigating the expression and function of these genes. Fueling Page's intuition is the understanding that throughout the animal kingdom, male and female genomes, though largely similar, are actually "read" differently; that is, the same genes in both sexes don't always perform the same way, leading to unique outcomes in each. In humans, the sex chromosomes cue up the alternate male and female readings. The implications are as potentially significant as they are intriguing.

"It may be that all differences in disease prevalence and severity find their origins in the X and Y chromosomes," says Page. "We need to rewrite the book from the most basic level of the sex chromosomes. We need to build from that to find explanations. Starting from the disease state and working backwards hasn't led to any great understanding."

David Page

NOT SAFE. NOT SORRY.

There's enormous risk in all of this. What's unsafe about this is that I have no idea whether I'm right.

I don't know if it's going to turn out the way I want it to, that we'll find these links between the sex chromosomes and differences in disease, but I am convinced there's a connection.

There's no roadmap to filling this enormous gap in our understanding, but the invisibility of the path is really what's most appealing.





Hidde Ploegh

Investments in developing seemingly unorthodox approaches for studying the immune system and its response to invading pathogens have long paid dividends for Hidde Ploegh, the members of his lab, and the greater scientific community. One of his most recent forays is no exception.

Over the past few years, Ploegh has established a research platform that exploits single-domain antibodies—extremely small antibodies produced by the immune systems of a family of animals known as camelids. In addition to their small size, these unique camelid antibodies are thermally stable and can be easily modified by sortagging, a highly specific protein-labeling technique developed in the Ploegh lab. Ploegh’s vision was to immunize alpacas—his camelid of choice—to generate single-domain antibodies that could be used to probe the inner workings of cells with remarkable precision.

Today, that vision is reality, and Ploegh’s single-domain antibodies are being used at Whitehead, MIT, and beyond in a range of pursuits, from the study of viral replication and trafficking to the development of novel imaging applications that could enable clinical monitoring of the human immune response via PET (positron emission tomography)

scanning. Convinced of the potential of the single-domain platform, Ploegh recently spun off a small biotech company to commercialize the technology.

In other research in the lab, scientists have been studying the influenza virus, recently discovering the insidious way it establishes infection in its hosts. Leveraging Ploegh’s sortagging, researchers were able to attach a fluorescent label to identify flu-specific B cells whose nuclei were then introduced into enucleated mouse egg cells via somatic cell nuclear transfer (SCNT)—a cloning technique borrowed from Whitehead Founding Member Rudolf Jaenisch’s lab—to generate a line of mice with virus-specific B cells and cell receptors. The generation of mice with B cells specific for a known pathogen allowed the researchers to track the virus’s interactions with the cells in unprecedented fashion, revealing that the virus infects by first killing off the cells of the immune system that are normally best equipped to neutralize the virus.

Because the infectious process discovered in this research is likely not exclusive to influenza, this approach could have implications for other viruses as well, as the same methods could be employed to create mouse models for a variety of pathogens.

NOT SAFE. NOT SORRY.

It’s fair to say that at the outset, the single-domain antibodies project was a huge gamble, but I’m happy I made it.

If I had been thinking safely or conservatively, I probably wouldn’t have started it.

Peter Reddien

In 2001 Peter Reddien chose to focus his postdoctoral research at the University of Utah School of Medicine on the regenerative capacity of planarian flatworms. It was an exciting time, as regeneration was largely a black box, with little known about the molecules and mechanisms that control it.

The planarian seemed to be a promising model organism for studying tissue regrowth. The worms are so adept at regenerating body parts that they use this process for routine tissue turnover and for a form of asexual reproduction in which the worms tear themselves in half. But many of the workhorse tools used to study other model organisms, such as mice and fruit flies, lacked planarian counterparts.

More than a decade later, much has changed. Many of the desired tools have become a reality, thanks in part to Reddien's dedication. With better tools came a better understanding of the mechanisms driving regeneration, including the identification of several signaling pathways that determine whether a head or a tail grows at an amputation site.

Yet, scientists still didn't understand how stem cells known as cNeoblasts, which are responsible for tissue regeneration, sense their own location within the worm and "know" which cells are needed to recreate missing tissues.

To address this, Reddien's group leveraged its earlier research that identified genes involved in imparting positional information during regeneration, including the regulators of the head-or-tail signaling pathways. Reddien hypothesized that a certain type of cell must express these position control genes. After screening cells for these genes' expression, the Reddien lab found one type of cell that expressed all of them plus one additional cell marker, collagen, a telltale marker of planarian muscle cells.

"The knowledge that muscle cells, which run throughout the planarian body, act as a GPS-like system is fascinating in its own right," says Reddien. "But it also allows us to understand how instructions are guiding tissue turnover and regeneration, and opens the door to molecular dissection of regeneration instructions."

NOT SAFE. NOT SORRY.

I took a major leap when I decided to work with an unconventional model system and to develop approaches for understanding how regeneration works.

At the time, it was not at all clear how well it would work.

But as a system, it has yielded spectacular insights into regeneration.

I'm really glad I have taken this path.





What happens to our bodies when food is scarce? If you're like most folks, you might respond to this seemingly simple question with a similarly facile reply, such as, "We lose weight."

If you're David Sabatini, however, you take this question very seriously. So seriously, in fact, that you devote a large portion of your research to it, knowing that the full answer will help us understand how we age, develop such diseases as diabetes and cancer, and how we might forestall it all.

Sabatini has been investigating the physiological changes that occur in response to varying availability of food. Central to such changes is the cellular signaling pathway known as mTOR (for mechanistic target of rapamycin), which senses the presence of nutrients and adjusts metabolism at the cellular, organ, and organismal levels accordingly. Sabatini has shown that mTOR exerts its effects globally via the activity of two protein complexes, known as mTORC1 and mTORC2, and that mTORC1 signaling is suppressed during periods of reduced caloric intake.

Sabatini's lab recently examined how the gastrointestinal (GI) tract itself reacts to fluctuations in nutritional state and revealed an intriguing dynamic among its inhabitants. Lining the walls of the intestine are crypts or "niches" that house the intestinal stem cells (ISCs) that replenish the various cell types that are essential for proper GI function but that turn over quite quickly. Lab members discovered that caloric restriction (CR) increases ISC self-renewal, which in turn leads to a larger number of ISCs in the niche. The route to increased ISC activity is indirect, however. CR causes a reduction in mTORC1 signaling in Paneth cells—co-occupants of the niche that sense a loss of nutrients and prompt the behavioral change in the neighboring ISCs. The same effect is seen when the niche is exposed to the drug rapamycin, an mTOR inhibitor that has been shown to mimic CR.

This documented change in stem cell function in response to CR raises other key questions. Notes Sabatini: "Obesity is the flipside of this. How does obesity upset stem cells in the niche? We know obesity is linked to cancers of the GI tract. What's the connection between obesity's effect on stem cells and these cancers?"

David Sabatini

NOT SAFE. NOT SORRY.

We need to preserve a culture of high-risk experimentation.

We need to be able to pursue experiments that seem almost certain to fail, and we need to have the ability to attract people willing to try.

Our caloric restriction studies are a great example. They've been successful, but they're also difficult and expensive. Early on, we could never have gotten grants for them.

Hazel Sive

More than a decade ago, Hazel Sive's plan to use developing zebrafish embryos as a tool with which to study schizophrenia and autism spectrum disorders was met with more than a little skepticism. Undaunted, Sive and her lab went on to show that because these tiny fish have genes that correspond (that is, are homologous) to mental health disorder risk genes in humans, they can indeed bolster our understanding of how such genes may contribute to the development of abnormalities.

Today, she's casting an even wider net, using her zebrafish research platform to investigate not only the origins of a number of psychiatric and neurodevelopmental disorders but also the vexing co-morbidities that accompany them. Sive notes that patients on the autism spectrum often experience immune dysfunction and gastrointestinal issues, including pain, constipation, and malabsorption. Other disorders can bring with them craniofacial malformation and seizures.

"These co-morbidities are difficult to separate from the mental aspects of a disorder, and they're almost always there," says Sive. "They can be as debilitating as the brain aspect of a disorder. How do the genes that control mental health also control these co-morbidities?"

Here again, the utility of the zebrafish is remarkable. Beyond its gene homologs, the fish brings to the table its transparent body, meaning that all its organs can be

studied at once. As a result, candidate genes can be manipulated and the effects observed throughout the living animal. Lab members can thus study brain formation and intestinal development simultaneously or track the passage and absorption of food while monitoring brain function for signs of seizure activity.

In perhaps the best example of this approach, researchers in the lab are studying a genetic interval known as 16p11.2—a region on chromosome 16 carrying genes strongly associated with autism. Previously the lab identified 20 genes (with human homologs) on the interval that are highly active during brain development and that when silenced individually, could result in defects in nerve growth, neuromuscular connections, and brain structure.

Based on extensive human genetic studies indicating that autism spectrum disorders and their comorbidities are multigenic, lab members are now searching for 16p11.2 genes that work together to create abnormalities. To date, in an unprecedented effort, 162 gene pairs have been knocked down, with nine pairs shown to create distinct brain phenotypes. The effects of these pairs beyond the brain are now being investigated. Sive feels that this bold approach in zebrafish, coupled with studies of patient-derived induced pluripotent stem cells, could pinpoint which genes are contributing to disease manifestations and in what fashion.

NOT SAFE. NOT SORRY.

I've never been safe, and I've never been sorry. Science is an exploration, and I've always embraced the power of new thought. I've never felt constrained. To address profound human diseases with something as crazy as a fish, you have to have the confidence and courage to keep going on that track.





It was a seminal discovery, to be sure, but, as with many scientific advances, it was only the beginning.

In 2004, the Weinberg lab first reported that certain cells in cancerous tumors tap into a long-dormant embryonic development program that changes both their shape and, perhaps more importantly, their behavior. Known as the epithelial-mesenchymal transition or EMT, the program enables the cells to break away from a primary tumor and migrate to distant sites throughout the body.

Four years later, the lab discovered that the EMT program also confers on such cells key properties of stem cells, including the ability to self-renew and to seed new malignancies. The EMT program remains a focus of the lab, as its complexities continue to reveal themselves. Where once it was thought that the EMT might merely be dispatching cancer cells to remote venues, it now appears that the program also drives metastatic colonization. In recent research, members of the lab have determined that signaling pathways inherent in the process enable disseminated cancer cells to form entire new tumor cell colonies; that is, metastases. The EMT empowers a cell to exit a distant blood vessel and produce finger-like projections known as filopodia, allowing the cell to anchor in tissue and begin to proliferate.

Still, an active EMT program and the presence of filopodia are probably not enough on their own to ensure the outgrowth of life-threatening metastases. A would-be colonizing cell must also strive to maintain its active EMT program in the distant tissue. Without encountering an activated, inflamed tissue microenvironment, the migrant cell may revert to a more benign, epithelial, non-stem like state and thereby lose the opportunity to seed a new tumor. Hence, metastasis formation depends on a delicate balance of epithelial and mesenchymal traits in the disseminated cancer cell.

In other work that represents something of a departure for the Weinberg lab, at least one scientist has begun to explore the potential relationship between wounding and the growth of distant metastases. At play is the question of whether wounding and wound-healing—such as that experienced by patients whose primary tumors are removed surgically—suppress an immune response that would ordinarily keep disseminated tumor cells from forming malignancies. Accumulating evidence indicates that, indeed, this is the case, raising the question of whether cancer surgery is accompanied by risks that have not been adequately explored.

Robert Weinberg

NOT SAFE. NOT SORRY.

To be honest, tumor immunology is a big leap for us. Historically, it's not part of our lab.

This is more of an intuition because the evidence to date is not overwhelming.

But, we have seen that if you make a wound in a mouse, you promote tumor growth in another part of the mouse. It's an important enough question to investigate.

Jing-Ke Weng

As Whitehead's newest Member, Jing-Ke Weng has transitioned seamlessly from accomplished postdoctoral scientist to promising principal investigator. His lab equipment is in place, as are two new postdocs and three graduate students, all poised to execute a compelling research plan to determine how certain plant-derived products can be effective in treating human disease.

Not timid in the least, Weng is starting with one of the most important diseases of our time—diabetes, whose incidence and prevalence are rising in dramatic fashion globally. Among the most widely prescribed treatments is the drug metformin, which is closely related to a chemical found in the French lilac. In Medieval times, this plant was used to treat people suffering from painful urination and excessive thirst, key manifestations of diabetes. While the central molecule responsible for the French lilac's antidiabetic properties was later refined and synthesized into the drug we know today, its exact mechanism of action remains a mystery.

Now the Weng lab is planning to solve this ancient riddle with next-generation tools and methods, including RNA sequencing, high-end mass spectrometry, complex

molecular genetics, and bioinformatics. As Weng puts it, "We want to go back and determine why this chemical is important in the French lilac. How is it biosynthesized? In an ecological setting, why does the plant make this molecule? What purpose does it serve?"

Preliminary investigations are already yielding clues. Weng has found that when grown in a medium with a high concentration of glucose, the model plant *Arabidopsis thaliana* suffers significant stress. The addition of metformin to the medium relieves the stressed plants, a finding that is leading the lab to investigate how the drug affects glucose metabolism at a molecular level.

Weng believes this work could lead to the development of novel diabetes therapies that are more efficacious, better tolerated, or both. In a related aside that conveys not only the validity of his approach but also the need for precision in such endeavors, he notes that the drug phenformin—a member of the same chemical class as metformin—was prescribed to diabetic patients for nearly two decades before being withdrawn from most markets worldwide in the late 1970s for causing an often fatal side effect. Phenformin, it turns out, is toxic to *Arabidopsis*.

NOT SAFE. NOT SORRY.

For me, it's important to be surrounded by a faculty that's not afraid to think outside the box. Susan Lindquist's idea to use yeast as a model for studying human disease, for example, was really attractive to me. This is an environment where you are not encouraged to play it safe. In fact, it's just the opposite here.





One adage rarely applied to cancer is, “the bigger they are, the harder they fall”. And yet, this is precisely what the Young lab’s research on super-enhancers in tumor cells indicates. Super-enhancers are comparatively huge sections of DNA with a function similar to enhancers, which have been under study for the past half-century.

Enhancers were thought to be the genome’s key sites of regulation. By binding specific proteins, these ~1000 base pair-long sections of DNA control the transcription of one or more genes. Recently, however, the Young lab identified enormous sections of DNA that serve the same purpose as enhancers, but at a special set of genes. Aptly named, these super-enhancers operate on a much larger scale and interact with the key genes that control cell state and identity.

According to Young’s research, the super-enhancers running embryonic stem cells and other normal cells are about 10 kilobase pairs long. Cancer cell super-enhancers can be much larger—some are a whopping 200 kilobase pairs. Unlike normal cells, cancer cells develop super-enhancers at nefarious oncogenes that support the most aggressive cancer pathologies. The most toxic tumor cells have developed the largest super-enhancers at many important cancer-driving genes.

“Whenever we show cancer biologists where the super-enhancers are located in the cancer they study, they are over the top with excitement,” says Young. “About half of the genes with super-enhancers they know and are already studying. The other half they didn’t know about, and now they are studying.”

These super-enhancers may also point to a new avenue for cancer treatments. As a consequence of building these colossal super-enhancers, the tumor cells are vulnerable to drugs that inhibit transcription. Work in the Young lab indicates that if a drug blocks a transcription protein, the super-enhancers collapse, killing the cell.

Young explains that the activity of super-enhancers in healthy cells is similar to a dimmer switch. If treated with a transcription inhibitor, these super-enhancers have slightly decreased activity, but overall, the cells remain unaffected. The bloated super-enhancers in cancer cells are so large that their activity profile changes to more of an on-off switch. A minor decrease in transcription is a death sentence for a cancer cell. This ultra-sensitivity could open up a whole new class of cancer drugs that target super-enhancers in a broad range of cancers.

Richard Young

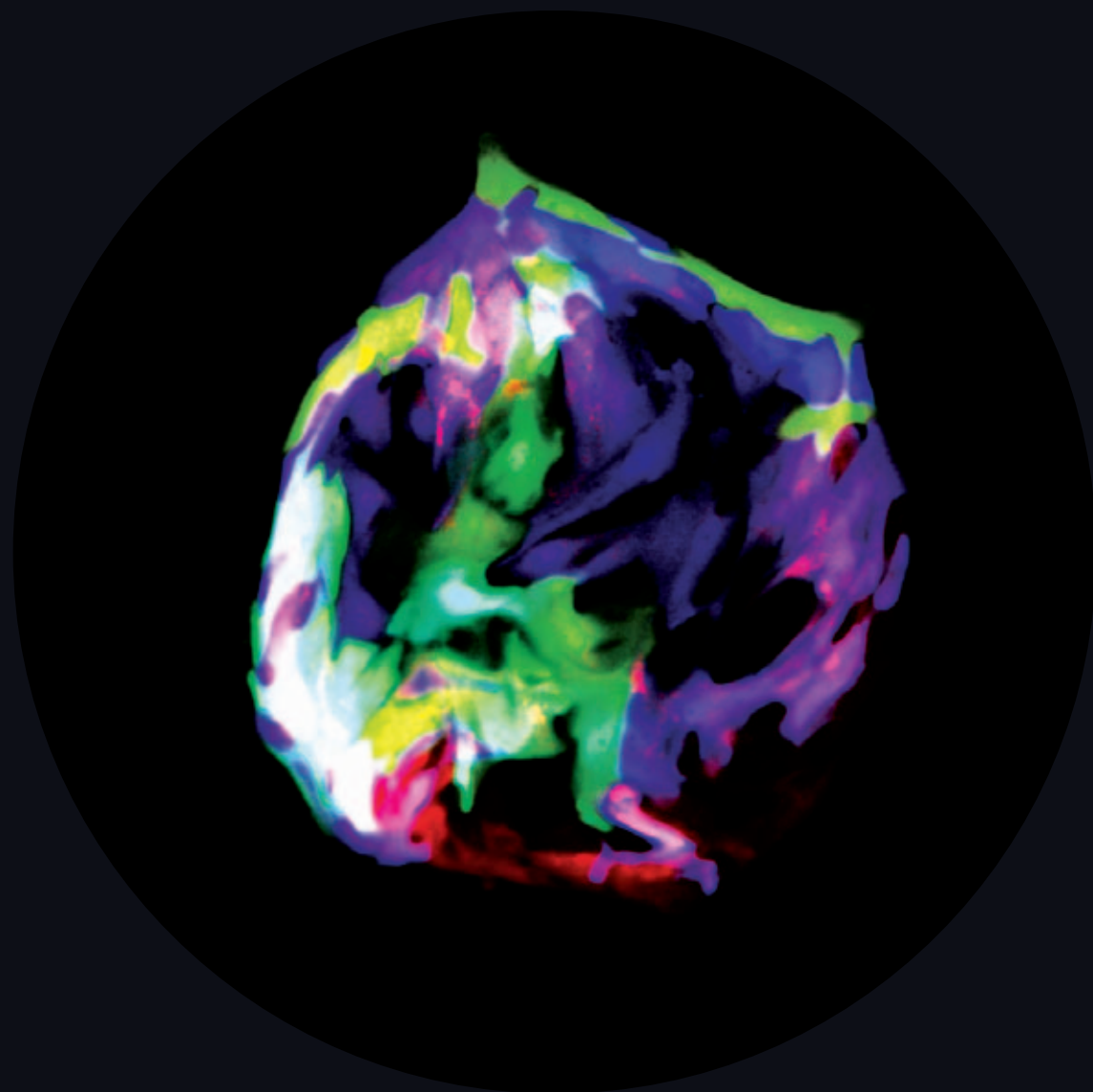
NOT SAFE. NOT SORRY.

As a pilot, I avoid approaching the edge of the flight envelope.


As a scientist, I seek to go beyond the edge of the envelope.

WHITEHEAD FELLOWS

In its 30 years of existence, the renowned Whitehead Fellows program has launched a string of remarkable scientific careers. Here, a small cadre of exceptional young scientists is freed from faculty responsibilities and given lab space, research support, mentorship, and enough latitude to succeed.



Yaniv Erlich

A portrait of Yaniv Erlich, a man with short dark hair and a light beard, wearing a blue button-down shirt and dark trousers. He is sitting on a wooden stool, leaning forward with his arms resting on his knees, smiling at the camera.


In 2013, Yaniv Erlich's lab sent shockwaves through the genomics research community—and beyond—by using simple internet searches of public resources to identify nearly 50 individuals who had submitted personal genetic material as anonymous participants in genomic studies.

The work was as an exercise in “vulnerability research,” a common practice in the information security field. Erlich and his team proved that under certain circumstances, the full names and identities of research participants can be determined, even when their genetic information is held in databases in de-identified form. The outcome showed scientists, the general public, and agencies maintaining genomic databases that the threat of privacy breaches is real.

Erlich had no intention of revealing any names, and prior to his work appearing in the journal *Science*, he alerted officials at the National Human Genome Research Institute (NHGRI) and National Institute of General Medical Sciences (NIGMS) about security gaps in their genetic databases. In response, NIGMS and NHGRI moved certain demographic information from publicly-accessible sectors to help mitigate risk.

“Our aim was to better illuminate the current status of identifiability of genetic data,” Erlich says. “More knowledge empowers participants to weigh the risks and benefits when considering whether to share their own data.”

Sebastian Lourido

A portrait of Sebastian Lourido, a man with dark hair, wearing a white button-down shirt under a dark jacket and olive green trousers. He is standing with his hands in his pockets, smiling at the camera.

Long a fan of the unconventional, Sebastian Lourido arrived at Whitehead to research a puzzling family of single-celled parasites known as apicomplexans. Lourido once described these parasites—which include malaria-causing *Plasmodium* and *Toxoplasma gondii*, responsible for the infection toxoplasmosis—as “under-studied.”

One of the reasons apicomplexans have remained relatively unexplored is that, unlike such well-known model organisms as worms, fish, flies, mice, and yeast, the genomes of these tiny creatures have to date been largely resistant to manipulation. While scientists studying mice or planarian flatworms, for example, have routinely used such techniques as RNA interference to disrupt gene expression and track the effects, parasitologists have had to sit on the sidelines, lacking a method generalizable to the entire parasite genome.

Now Lourido and his lab have devised an elegant solution, modifying the hot new genome editing platform known as CRISPR for use in *Toxoplasma*. To say he's excited about this development would be an understatement.

“This really opens up the parasite genome in unprecedented ways,” he explains. “We can now target any gene of interest in any part of the genome. We can create knockouts or introduce point mutations. The kinds of questions we can now ask have really changed with this technology.”



David Pincus

When first translated from messenger RNAs, proteins are unstructured chains of amino acids. To function properly, proteins must fold into precise three-dimensional shapes. If a protein is folded incorrectly, it cannot fulfill its role in the cell and may even cause damage. Cells have evolved specialized molecular chaperones to ensure that proteins fold properly.

In the brains of patients with neurodegenerative diseases, the levels of molecular chaperones may decline, and the tangles and plaques seen in these patients' brains are the product of protein misfolding and aggregation. On the other end of the spectrum, an overabundance of chaperone proteins, a characteristic of cancer cells, is thought to promote carcinogenesis and malignancy.

Heat shock factor 1 (HSF1) is the control that keeps chaperone protein levels in balance. Yet little is known about how this important master regulator itself is regulated. Once this is known, perhaps subtle alterations in HSF1's activity could be used to treat these and many other diseases.

As a first step to understanding HSF1 regulation, David Pincus is testing the theory that HSF1 is controlled by a process known as phosphorylation, in which phosphate groups are added and removed from a protein. Pincus has comprehensively mutated all of HSF1's possible phosphorylation sites, both separately and jointly, with results that are likely to change our understanding of HSF1 activation.



The adage may be “seeing is believing,” but for Gabriel Victora, “seeing is understanding” is more apt. Victora and his lab have developed an ingenious way to “paint” specific cells in mouse germinal centers and watch how those cells behave. In their latest work, the lab focused on the T follicular helper (Tfh) cells to gain insight into how the immune system produces the best antibodies against each pathogen.

Amid an infection, the lymph nodes are home to germinal centers, which are the proving grounds for antibody-producing B cells. Within these structures, B cells are culled by Tfh cells based on their ability to produce antibodies that tightly bind to a bit of pathogen, called an antigen. The better the B cell's antibodies bind, the more likely that B cell will survive selection.

Victora's research shows that unlike B cells, which are confined to one germinal center, Tfh cells trek from germinal center to germinal center, which may improve the quality of antibodies produced and allow the immune system to deftly adapt to mutating pathogens. According to Victora, his findings may help researchers understand how to make better vaccines, especially for rapidly mutating viruses, such as HIV.

Gabriel Victora

Community Evolution

Another year brings a new face and a novel youth movement to showcase science

INSTITUTE NEWS

In the fall of 2013, Whitehead Institute welcomed Jing-Ke Weng as its 17th faculty Member. Weng earned a BS in biotechnology from Zhejiang University, and a PhD in biochemistry from Purdue University. During his postdoctoral research at the Salk Institute for Biological Studies, Weng performed pioneering work on the chemodiversity

of plants, a burgeoning arena exploring the complex chemical compositions powering primary metabolism of plant species as well as the secondary metabolites that enable plants to adapt to and thrive in variable environments.

Here at Whitehead, Weng is launching an ambitious research program. One of his projects is aimed at deciphering at the molecular level the precise

mechanisms of action of anti-diabetic drugs, such as metformin.

"Whitehead Institute is such a unique place," he says. "The purpose here is to conduct cutting-edge, groundbreaking research. The Institute makes sure you are unburdened in many ways, which frees your imagination and allows you the intellectual freedom to reach your potential."

To learn more about Weng's research, please turn to page 48.

PUBLIC OUTREACH

During the 2012-2013 academic year, Whitehead's Seminar Series for High School Teachers enjoyed another successful year, its 25th. This venerable program attracted more than 60 teachers from the greater Boston area to the Institute on the first Monday of each month between October and June. This season's series, *Neuroscience Now: The Quest for Breakthroughs in the Brain*, included nine lectures on a variety of subjects ranging from brain development and stem cell-derived neuronal development for disease modeling to optogenetics and the use of gene-based approaches for identifying drug targets for Alzheimer's disease. Nearly 30 teacher partners—Whitehead postdocs and grad students who volunteer for the series—supported program participants throughout the year, attending the lectures and dinners that follow, providing scientific background, and, in some cases, visiting a partner's classroom to speak to students directly.

Sadly, during 2013, another mainstay of Whitehead's public offerings had to be canceled. The Spring Lecture Series



Jing-Ke Weng arrived in the fall of 2013 as Whitehead Institute's 17th Member



During Whitehead's first CampBio program, middle school students delved into many aspects of biology, including plant genetics (left) and the structure of DNA (right).

for High School Students is held during the Massachusetts public school spring vacation in April. The three-day program traditionally commences on the day after Patriot's Day, also known in the Boston area as Marathon Monday. The bombings at the 2013 Boston Marathon, and the ensuing hunt for the perpetrators, created enough public safety concerns to warrant cancellation. Fortunately, the program would resume in 2014.

Recognizing the increasing national commitment to STEM (for Science, Technology, Engineering, and Mathematics) education, the Institute has begun to embrace a responsibility to contribute by reaching out to a younger age group.

During the summer of 2013, Whitehead Institute collaborated with the Boston-based science education group *Science from Scientists* to pilot *CampBio*, a week-long program designed to introduce middle school students to the wonders of the life sciences. In all, 26 eager 7th and 8th graders from schools throughout the greater Boston area converged on the Institute for five days of hands-on activities, laboratory demonstrations, classroom instruction, and conversations with scientists.

A host of exercises showcased research from the labs of Whitehead Members Harvey Lodish and Susan Lindquist, both longtime advocates for educational outreach. The students also made their way through multiple scientific modules, one of which explored the inner workings of a cell. During an instructional session at the MIT Museum, the students

learned about the structure of DNA by using LEGOs to assemble an impressively lengthy double-helix strand.

One of the more intriguing aspects of the program was a "career mixer" during which the campers interacted not only with bench scientists but also with those who had pursued alternative careers in the sciences, such as teaching, communications, and even art. This session was designed to show students the breadth of career opportunities to be found in the life sciences.

Based on overwhelmingly positive feedback, the Institute plans to expand its educational offerings aimed at sparking interest in the sciences among younger students.

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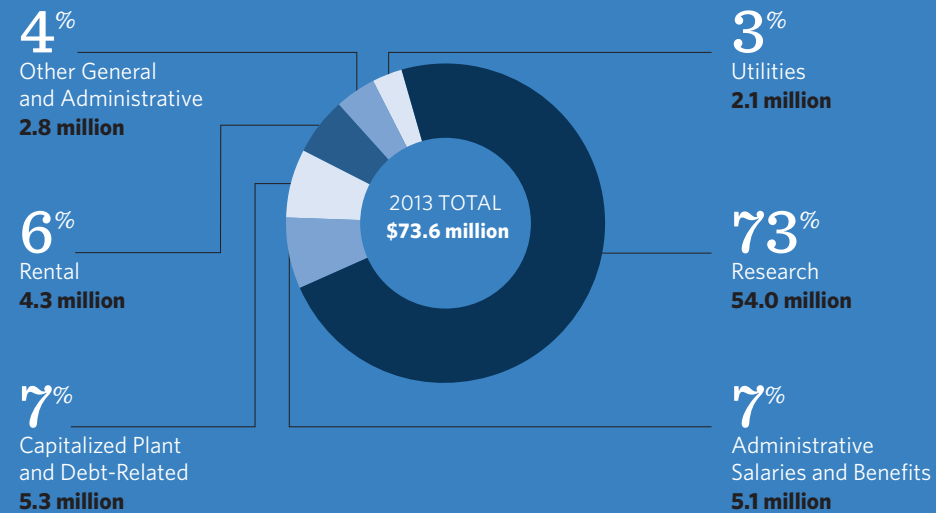
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51.2 million (73%)

Administrative Salaries and Benefits
4.7 million (7%)

Capitalized Plant and Debt-Related
5.3 million (7%)

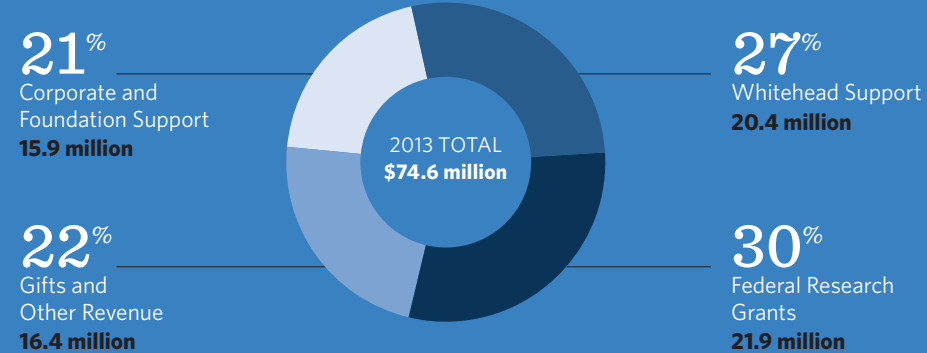
Rental
4.3 million (6%)

Other General and Administrative
2.8 million (4%)

Utilities
2.0 million (3%)

TOTAL
\$70.3 million (100%)

2013 REVENUES & SUPPORT



2012

Corporate and Foundation Support
15.1 million (20%)

Gifts and Other Revenue
17.2 million (23%)

Federal Research Grants
22.8 million (30%)

Whitehead Support
20.9 million (27%)

TOTAL
\$76.0 million (100%)

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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 2013 Breakthrough Prize in Life Sciences (Weinberg), 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), and five Howard Hughes Medical Institute investigators (Bartel, Lindquist, Page, Reddien, and Sabatini).

PAGE 4 / SCIENTIFIC ACHIEVEMENT

In this hyperproliferative human mammary cell line, immunofluorescent markers are used to follow the cells' lineages and various paths to differentiation.

PAGE 16 / PRINCIPAL INVESTIGATORS

Each of the cells in this grouping of heterogeneous mouse breast cancer cells is labeled with a stable color, allowing for the tracking of these cells over extended periods of time. This technique is used to study tumor development, growth, and progression to metastatic disease.

PAGE 52 / WHITEHEAD FELLOWS

Clonal tracking (via color labeling) of human mammary epithelial cells is used to determine how individual cells can give rise to multiple different cell types within the mammary epithelial tissue.

IMAGES

COVER ILLUSTRATION *Craig Frazier*

PRINCIPAL INVESTIGATOR & WHITEHEAD FELLOWS PORTRAITS *Jared Leeds*

PAGE 4 *Dexter Jin/Whitehead Institute* **PAGE 6** *Reprinted from Cell, "Poised Chromatin at the ZEB1 Promoter Enables Breast Cancer Cell Plasticity and Enhances Tumorigenicity," Christine L. Chaffer, et al, Volume 154, Issue 1, 3 July 2013, Pages 61–74, DOI: 10.1016/j.cell.2013.06.005.* **PAGE 7** *Reprinted with permission from AAAS from Nicolas Rohner, et al., "Cryptic Variation in Morphological Evolution: HSP90 as a Capacitor for Loss of Eyes in Cavefish", Science 13 December 2013; Vol. 342 no. 6164 pp. 1372-1375.* **PAGE 8** *Gabriel Victora/Whitehead Institute* **PAGE 9** *Reprinted with permission from AAAS from Tardiff, et al., "Yeast Reveal a 'Druggable' Rsp5/Nedd4 Network that Ameliorates α -Synuclein Toxicity in Neurons", Science, 22 November 2013; Vol. 342 no. 6161 pp. 979-983.* **PAGE 11** *Lawrence Berkeley National Laboratory/Science Photo Library* **PAGE 13 (TOP)** *Reprinted with permission from Macmillan Publishers Ltd: Nature Reviews Genetics, "Gene expression: Super enhancers," Vol. 14, 367, copyright 2013.* **PAGE 13 (BOTTOM)** *zentilia/Shutterstock.com* **PAGE 16** *Julia Fröse/German Cancer Research Center & University of Heidelberg (Fröse now works at Whitehead Institute)* **PAGE 52** *Daniel Miller and Ethan Sokol/Whitehead Institute* **PAGE 58** *Ceal Capistrano/Whitehead Institute* **PAGE 59** *Ceal Capistrano/Whitehead Institute* **PAGE 60** *Lisa Abitbol*

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