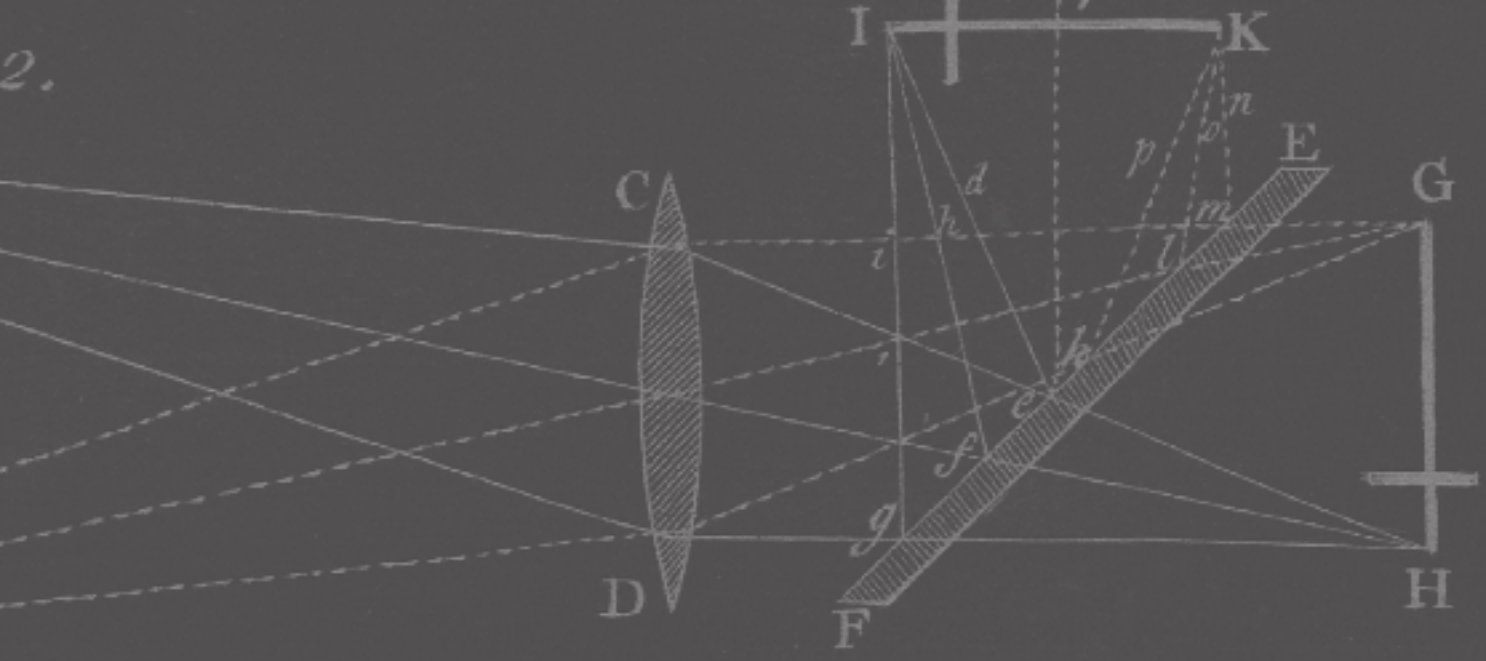

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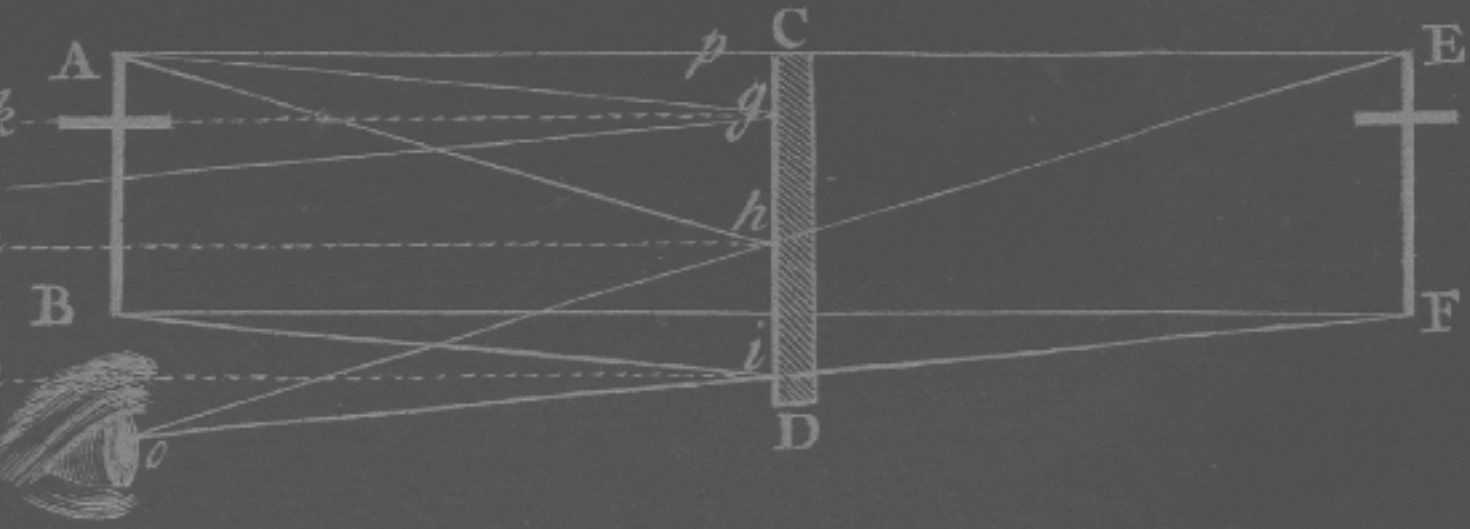
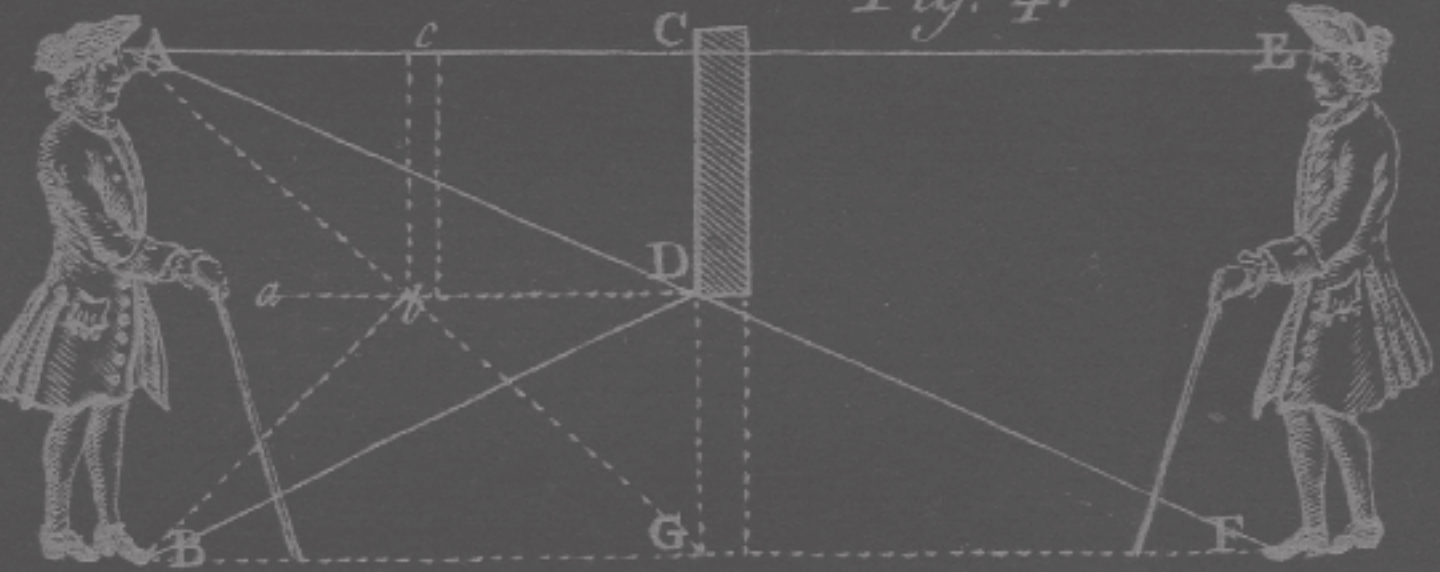


Fig. 4.



another angle

Solving the most vexing problems demands persistence and dedication. It also requires creativity, flexibility, and a willingness to change perspectives—to look at things differently. At Whitehead Institute, the world's best biomedical researchers are tackling science's biggest challenges, but the collisions are seldom of the blunt, head-on variety. Rather, these talented individuals have come to realize that progress is far more likely when they approach from another angle.

contents

from the director

In praise—and pursuit—of unlearning

From time to time, it bears remembering that as scientists, we never actually prove anything. Rather, we are in the business of disproving. We don't gather facts. We construct models that explain how the universe works, and, if we're honest with ourselves, once we construct a model, we must begin to destroy it.

It's a messy process but an essential one. We can too easily become attached to our models, putting scientific progress at risk. Had we not challenged some of the most seemingly compelling models of our recent history, we might still believe that the vast majority of the human genome is composed of "junk DNA" that's merely along for the ride. It turns out the so-called non-coding elements comprising that "junk" are pretty important. We might also simply have accepted the longstanding dogma that cell differentiation—the journey of embryonic stem cell to specialized adult cell—is strictly a one-way street. Such acquiescence might have prevented the discovery that is induced pluripotency. The reprogramming that sends adult cells back to an embryonic-like pluripotent state is one of the most significant breakthroughs in modern biology.

At the core of this constructive deconstruction is unlearning, that relatively rare ability to dismiss willingly and completely that which we have held to be true. For many, it is an unnatural action, one that almost always requires abandoning considerable investments of time and energy. As renowned science fiction author and biochemistry professor Isaac Asimov famously stated: "It's not so much what you have to learn if you accept weird theories, it's what you have to unlearn."

At Whitehead Institute, we willingly embrace the weird theories because we are a faculty of accomplished unlearners. We select for people who have the interest and ability to systematically unlearn, and this approach invariably pays off. During 2014, for example, the National Academy of Sciences (NAS) honored Whitehead Member David Sabatini with the NAS Award in Molecular Biology. David became the fifth of our Members to earn this prestigious award, which recognizes a recent notable discovery in molecular biology by a young scientist. Another of our young scientists, Jing-Ke Weng, was named a 2014 Pew Scholar in the Biomedical Sciences. It's a wonderful accolade for Jing-Ke and further validation of our eye for emerging talent. If form holds, Silvi Rouskin, a new Whitehead Fellow we recruited to the Institute at the close of 2014, is facing a very bright future.

We will encourage Silvi to revel in unlearning because, when faced with a vexing problem, we here at Whitehead Institute approach it from—as is the theme of this report—another angle. We do so because scientific leadership demands it. The pages that follow capture the many different angles our scientists took over the past year as well as the advances and accolades that ensued. It's an inspiring collection made possible by the creativity of our researchers and the enormous support of staff, faculty, and friends—all of whom I'm grateful to say believe in the power of unlearning.

David Page
Director

scientific achievement

At Whitehead Institute, research and discovery are more than buzzwords. They are institutional currency, driving—and distinguishing—a potent scientific enterprise. Each year, the body of life sciences knowledge expands in significant ways, and those engineering the expansion are recognized accordingly.

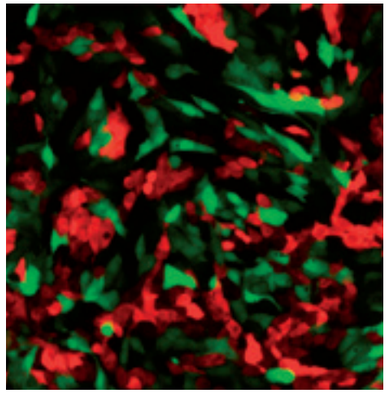
In Search of Vulnerabilities

One of the elusive goals in the treatment of cancer is to halt its spread. Yet, metastatic cancer cells, which can migrate from primary tumors to seed new malignancies, have thus far been resistant to the current arsenal of anticancer drugs.

Recently, however, researchers in the lab of Whitehead Member **Piyush Gupta** identified a critical weakness that actually exploits one of these cells' apparent strengths—their ability to move and invade tissues. Cancer cells acquire invasive and stem cell-like traits by undergoing a process called an epithelial-to-mesenchymal transition (EMT), which transforms cube-like, immobile cells into elongated, mobile ones. Once mobile, cancer cells use the blood stream as an expressway to migrate to distant sites in the body to establish new tumors. Moreover, cancer cells that undergo an EMT also resist radiation and most chemotherapy.

Gupta and his colleagues had previously identified two compounds that were selectively toxic against invasive, post-EMT cancer cells, leaving their non-invasive counterparts unscathed. Seeking to understand what distinguished these compounds, the scientists discovered that they kill by stressing the endoplasmic reticulum (ER) of EMT cells. Non-EMT cells are unharmed because their ER is unaffected by these compounds.

It turns out that EMT cells gain their motility by secreting massive amounts of scaffolding proteins in a process highly stressful to their ER. Additional, chemically-induced stress proves lethal. A pathway known as PERK helps cells survive the stress of protein secretion, and in EMT cells, is always active. In studying roughly 800 patient tumors (both primary and metastatic) across a range of cancer types, Gupta's lab found that expression of EMT genes is tightly correlated with PERK pathway activity.



The finding suggests that the pathway may represent both a therapeutic target and a potential marker to guide treatment.

Notes Gupta: "This is the first vulnerability of invasive cancer cells that we really understand."

In other work focused on cancer drug resistance, scientists in the lab of Whitehead Member **Susan Lindquist** showed that the molecular chaperone heat-shock protein 90 (HSP90), long known to help organisms adapt to environmentally stressful conditions, also enables estrogen receptor-positive (ER+) breast cancers to become resistant to hormonal therapy. This mechanism of drug resistance provides a strong rationale for combining HSP90 inhibition with other interventions in the treatment of ER+ breast cancers. In fact, this hypothesis is being tested in an ongoing clinical trial of an HSP90 inhibitor plus an estrogen blocker.

The image above shows cancer stem cells (stained green) and non-cancer stem cells (stained red) cultured together in normal media. Cancer stem cells tend to be resistant to conventional therapy.

Unexpected Mechanisms at Work

In any animal's lifecycle, the shift from egg cell to embryo is a critical juncture. This transition represents the formal initiation of development—a remarkably dynamic process that ultimately transforms a differentiated, committed oocyte to a totipotent cell capable of giving rise to any cell type in the body.

Induction of totipotency requires dramatic changes in gene expression. Most studies of such changes have largely focused on transcription, when DNA strands are copied into the messenger RNA (mRNA) that is subsequently translated to produce the proteins essential for cellular function. However, Whitehead Member **Terry Orr-Weaver** recently showed that translation is also vital at this stage of the lifecycle.

In a nearly four-year undertaking, her lab conducted perhaps the most comprehensive look yet at changes in translation and protein synthesis during a developmental change, using the oocyte-to-embryo transition in Drosophila as a model system. The lab employed global polysome profiling, ribosome footprint profiling, and quantitative mass spectrometry to reveal a surprisingly large number of mRNAs that are translationally regulated. Approximately 1,000 mRNAs were found to be upregulated, with several hundred more downregulated during this transition. The scientists also discovered a set of roughly 60 mRNAs whose translation was upregulated without a corresponding increase in the levels of protein produced. This apparent paradox suggests that at the oocyte-to-embryo transition, protein degradation is occurring simultaneously with translational activation.

Orr-Weaver believes this work has opened new research avenues, including trying to determine whether previously unidentified proteins are regulating the switch from meiosis to mitosis at this key transitional moment.

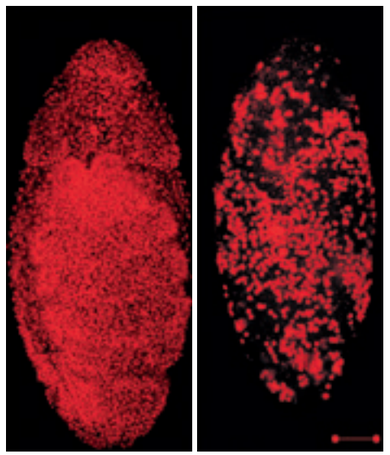
"We found new proteins whose function has been unknown," she says. "But from the changes in their level, they may be responsible for flipping that switch."

In the meantime, researchers in the lab of Whitehead Member **Hazel Sive** found another developmental surprise, discovering that a signaling pathway once thought to have little if any role during embryogenesis is actually a key player in the formation of the front-most portion of developing vertebrate embryos. Moreover, signals emanating from this region—referred to as the "extreme anterior domain" (EAD)—orchestrate the complex choreography that gives rise to proper facial structure.

Using the frog *Xenopus* as a model, the lab found that the Kinin-Kallikrein signaling pathway, best known in humans for its roles in regulating blood pressure, inflammation, and kidney function, is a key player in craniofacial development.

Says Sive: "We had no inkling that this pathway was active in the embryo."

Gastrulating Drosophila embryos with red-stained DNA. At left is a normal embryo. At right is an embryo produced by a mother improperly expressing the Lid gene, which encodes a factor whose levels increase at egg activation.



Yeast and Stem Cell Modeling to the Rescue

Several years ago, Whitehead Member **Susan Lindquist** pioneered the use of yeast to model the pathologies of neurological disorders and screen for potentially beneficial compounds. In 2014, her lab did it again, discovering a drug that reduces levels of the toxic protein fragment amyloid-β (Aβ), preventing at least some of the cellular damage caused when Aβ accumulates in the brains of Alzheimer's disease patients.

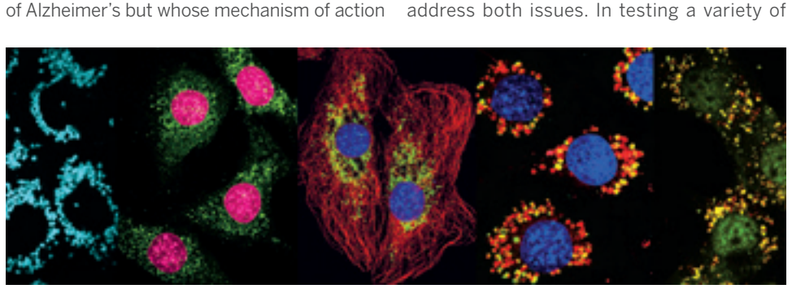
In the most recent work, a team of scientists in Lindquist's lab used the yeast model to screen approximately 140,000 compounds in search of chemicals that rescue the cells from Aβ toxicity. The screens homed in on the drug clioquinol, which had shown some promise in animal models of Alzheimer's but whose mechanism of action was unclear. The yeast studies point to the drug's ability to bind and remove copper, which is found in higher concentrations in diseased brain tissue.

"Our work in the yeast model shows that clioquinol decreases the amount of Aβ in the cells by 90%," says Daniel Tardiff, a scientist in Lindquist's lab. "I've tested a lot of compounds before, and I've never seen anything as dramatic."

The findings have prompted additional searches for compounds with similar structures and properties that can be tested in animal models and, eventually, in humans.

Also in 2014, researchers in the lab of Whitehead Member **Rudolf Jaenisch** advanced our understanding of Niemann-Pick Type C1 (NPC1) disease, a rare but devastating genetic disorder characterized by abnormal accumulation of cholesterol in liver and nerve cells, leading to liver failure, neurodegeneration, and—ultimately—death, often before age 10. By studying nerve and liver cells grown from patient-derived induced pluripotent stem cells (iPSCs), Jaenisch lab scientists determined that NPC1 disease is caused not only by defects in cholesterol processing but also in autophagy—a key cellular degradation pathway that malfunctions in many neurodegenerative diseases.

Based on that finding, the scientists theorized that targeting both the cholesterol accumulation and stalled autophagy found in NPC1 might represent a viable treatment strategy, and they set about screening for compounds that could address both issues. In testing a variety of agents in the patient-derived iPSCs, they discovered that the drug carbamazepine, which is prescribed for epilepsy and bipolar disorders, jumpstarts autophagy in liver and nerve cells. Carbamazepine, combined with low doses of the cholesterol-lowering drug cyclodextrin, rescued both the cholesterol accumulation and autophagy defects in the NPC-mutated cells. This drug combination is expected to advance to animal and clinical testing.



Cells displaying patterns of cholesterol accumulation and impaired autophagy in NPC1 mutant mice. (L to R): Cholesterol (cyan) in vesicles, Autophagic cargo (green) surrounding nuclei (magenta); Late endosomes (green) outside nuclei (blue); Co-localization of Dextran (yellow) in lysosomes (red); Collection of immature autophagosomes (yellow dots).

Benchtop Mixologists Build Better Cocktails

Scientists and patients have long hoped that embryonic stem cells (ESCs)—capable of forming nearly any cell type in the body—could provide insight into numerous diseases and perhaps even be used to treat them. Progress, however, has been slowed by an inability to transfer research and tools from mouse ESC studies to their human counterparts.

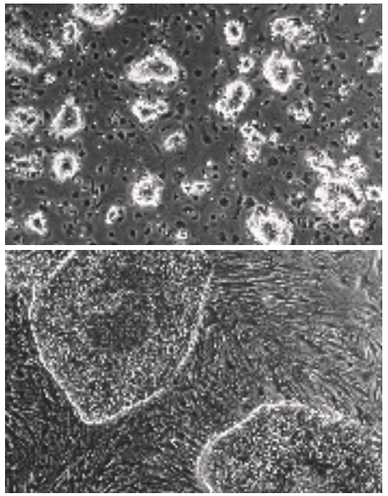
The function and differentiation of mouse ESCs into more specialized cells are well understood, but this understanding has been of surprisingly limited use in human ESC research, as the human cells behave differently. A challenge for scientists is that human ESCs exist in a state that is just slightly more advanced (a state referred to as "primed") than mouse ESCs, which are found in a more fundamental, purely pluripotent, "naïve" condition.

Achieving this naïve state in human ESCs has been an elusive goal in the field, as the state is thought to be essential for creating cells with potential therapeutic applications. In an important advance, researchers in the lab of Whitehead Founding Member **Rudolf Jaenisch** recently discovered a method to manipulate and maintain human ESCs in a base pluripotent state similar to that of mouse ESCs. And they did it without the use of reprogramming factors that could potentially alter subsequent generations of cells.

Says Jaenisch: "We have discovered a new pathway to generate something we believe is a totally different state of pluripotency in human ESCs that is very close to the mouse naïve state. These cells may be essential for ESC technology."

The lab achieved this new level of ESC naïveté by exposing the cells to a cocktail of small molecules. In another form of biological mixology, a separate group of Jaenisch lab scientists devised a cocktail that enhances the quality of induced pluripotent stem cells (iPSCs)—adult cells reprogrammed back to an embryonic stem cell-like state. The advent of the iPSC era generated enormous enthusiasm that diminished when researchers found that the genetic factors used in the original reprogramming process can cause serious genetic and epigenetic abnormalities that lower the cells' quality and limit their therapeutic usefulness.

To overcome this, Jaenisch scientists recently used bioinformatics to study the genetic effects of alternative factors during reprogramming. They eventually discovered a combination of four transcription factors whose use led to cell colonies in which 80% of reprogrammed cells were of sufficient quality to meet stringent pluripotency criteria. By comparison, only an estimated 20% of cells reprogrammed with the original cocktail passed muster.



A cocktail of five kinase inhibitors (5i) can convert conventional "primed" human embryonic stem cells (hESCs; bottom) to a "naive" state (top) similar to that of mouse ESCs. Conversely, naive cells generated in 5i can return to the primed state in the presence of serum and fibroblast growth factor.

honors and awards

Mary Gehring
In May, the journal *Cell* included Whitehead Member Mary Gehring among its featured "40 under 40." To mark its 40th anniversary, editorial staff at the journal interviewed a select group of promising young scientists about the current state of research in general, their careers, and the challenges they face. The Institute was well represented within this cohort, which also included former Jaenisch lab postdoc Jacob Hanna and former Cheeseman lab postdoc Tomomi Kiyomitsu.

Rudolf Jaenisch
In March, the German Society for Biochemistry and Molecular Biology (GBM) presented the 2014 Otto Warburg Medal to Whitehead Founding Member Rudolf Jaenisch. Given annually since 1963, the award is meant to encourage and recognize pioneering achievements in fundamental biochemical and molecular biological research. According to the GBM, Jaenisch was honored for "his groundbreaking work in the field of epigenetic regulation of gene expression in mammalian development and disease. He is known worldwide for his research on embryonic stem cell biology." Named in honor of German biochemist Otto Heinrich Warburg, recipient of the 1931 Nobel Prize for Medicine, the Warburg Medal is regarded as the highest award for biochemists and molecular biologists in Germany. In addition to the medal, Jaenisch received a prize of 25,000 euros. Jaenisch is now the third Whitehead Member awarded the Warburg Medal. Robert Weinberg was the 2007 recipient, while Member Susan Lindquist was so honored in 2008.

Susan Lindquist
In September, the Diana Helis Henry Medical Research Foundation and the Adrienne Helis Malvin Medical Research Foundation selected Whitehead Member Susan Lindquist as their 2014 Distinguished Lecturer. The foundations recognized Lindquist for her groundbreaking accomplishments in neurodegenerative disease research, including her innovative role in analyzing protein folding and using yeast cells as a platform to address Parkinson's disease. The foundations, which were established to engage directly in medical research in the fields of Parkinson's disease and cancer, created the Distinguished Lecturer award in conjunction with Johns Hopkins Institute for Cell Engineering to celebrate distinguished achievement and scholarship in the field of Parkinson's disease research. The annual recipient spends a day as a visiting professor conferring with students, postdoctoral fellows, and principal investigators for the foundations and Johns Hopkins University School of Medicine. The honor included a scientific presentation, a commemorative statue, and a cash award of $50,000.

In December, Lindquist was named recipient of the 2014 Vanderbilt Prize in Biomedical Science. Established by the Vanderbilt University School of Medicine, the Prize honors women scientists with a stellar record of research accomplishments who have made significant contributions to mentoring other women in science. In announcing the Prize, Lawrence Marnett, Ph.D., associate vice chancellor for Research and senior associate dean for Biomedical Sciences stated: "The selection of Dr. Lindquist as our 2014 Vanderbilt Prize in Biomedical Science winner underscores the importance we place on research innovation and mentorship at Vanderbilt University. Her groundbreaking science and commitment to mentoring women scientists embody the purpose of the Prize."

David Sabatini
In January, the National Academy of Sciences (NAS) announced that Whitehead Member David Sabatini is the recipient of the 2014 NAS Award in Molecular Biology. The award recognizes a recent notable discovery in molecular biology by a young scientist (defined as no older than 45) who is a citizen of the United States. Sabatini was honored "For his discovery of components and regulators of the mTOR kinase pathway and his elucidation of the important roles of this signaling pathway in nutrient sensing, cell physiology, and cancer." Sabatini received a medal and a prize of $25,000. Sabatini is the fifth Whitehead Member to receive the award. Gerald Fink, Robert Weinberg, Peter Kim, and David Bartel were honored in 1981, 1984, 1993, and 2005 respectively. Whitehead Founding Director David Baltimore was the 1974 recipient, while former Whitehead Fellows James Berger and Angelika Amon were so honored in 2011 and 2008. In addition, several past Whitehead trainees have won the award, including former Jaenisch lab postdoc Jeannie Lee in 2010, Kim lab grad student Erin O'Shea in 2001, and Weinberg lab grad student Clifford Tabin in 1999.

In July, Sabatini received the 2014 Colin Thomson Memorial Medal from the Association for International Cancer Research (AICR). The Medal, named for AICR founder Colin Thomson, has been presented annually since 2007 to a scientist regarded as having made a notable contribution to research in cancer.

Robert Weinberg
In October, the Massachusetts Society for Medical Research recognized Whitehead Founding Member Robert Weinberg as one of its 2014 Biomedical Research Leaders. Coinciding with Massachusetts Biomedical Research Day, the awards were bestowed upon those who have made significant contributions to biomedical research and education. Weinberg was cited specifically for "Groundbreaking discoveries in the mechanisms and treatment of cancer and his mentorship of three generations of MIT researchers."

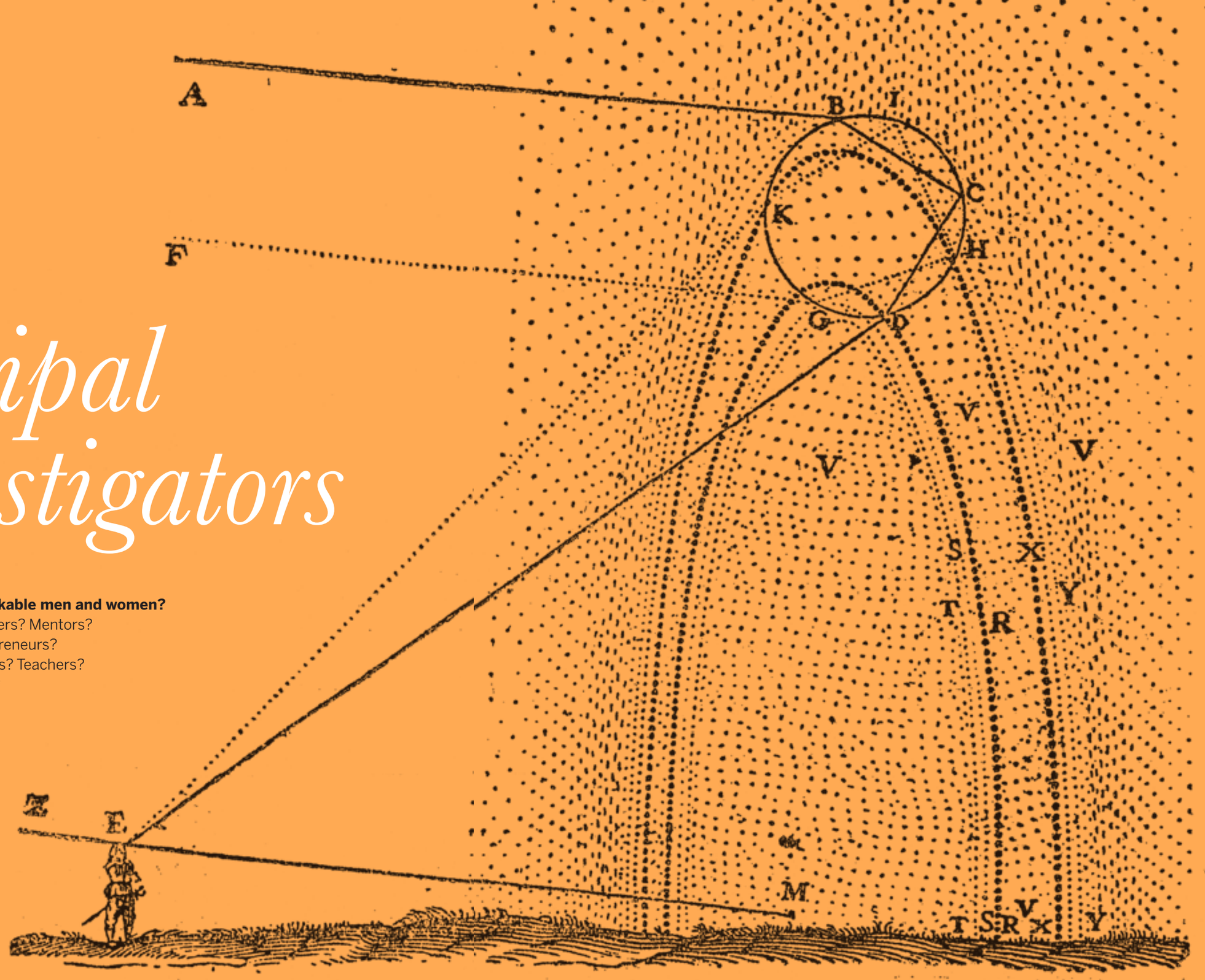
Jing-Ke Weng
In February, the New Phytologist Trust named Whitehead Member Jing-Ke Weng a winner of a Tansley Medal for Excellence in Plant Science. The New Phytologist Trust, an independent charity dedicated to the promotion of plant science, publishes original research in its online journal, *New Phytologist*. The *New Phytologist* Tansley Medal is awarded annually in recognition of an outstanding contribution to research in plant science by an individual in the early stages of his or her career. Shortlisted Tansley Medal applicants are invited to write a single-authored mini-review on the subject area to which their publications have contributed. Weng was one of two Tansley Medal recipients chosen. In addition to having his winning mini-review, entitled "The evolutionary paths towards complexity: A metabolic perspective," published in *New Phytologist*, he received £2,000 in prize money.

In June, the Pew Charitable Trusts named Weng a 2014 Pew Scholar in the Biomedical Sciences. Weng, who joined the Whitehead faculty in the fall of 2013, was one of 22 promising young scientists selected for this year's honor. Weng, who is studying how certain plant-derived products can be effective in treating human disease, will receive $60,000 in research support annually for four years. Launched in 1985, Pew's scholars program supports top U.S. scientists at the assistant professor level and has, since inception, provided more than 500 young investigators with more than $130 million in research funding for projects that, though seemingly risky, have the potential to benefit human health. Weng is the third Whitehead Member to be named a Pew Scholar. Mary Gehring became a Pew Scholar in 2010, while David Sabatini earned the same honor in 2003. Former Whitehead Fellow Fernando Camargo, now an investigator at Children's Hospital Boston, became a Pew Scholar in 2010.

Also in June, the American Society of Plant Biologists bestowed its 2014 Early Career Award on Weng. The award acknowledges outstanding research by a scientist generally not more than seven years post-PhD. The Society formally recognized Weng for his "extraordinary record of achievement, creativity, and future promise as a leader in understanding the evolution of biochemical diversity in plants."

principal investigators

Who are these 17 remarkable men and women?
Are they scientists? Leaders? Mentors?
Experimentalists? Entrepreneurs?
Colleagues? Collaborators? Teachers?
Enthusiasts? Visionaries?
Yes.
Yes they are.



david bartel

Over the past 15 years, much has been learned about microRNAs and the regulating effects that these 20-25 nucleotide-long pieces of RNA have on gene expression. Now researchers know that microRNAs have been conserved through millennia of evolution and are abundant throughout the plant and animal kingdoms. Hundreds of microRNAs are thought to target at least 60% of the human genome and play critical roles in normal development and cell function. Abnormal microRNA activity is linked to cancer, heart disease, neurological disorders, and other diseases.

To attenuate gene expression, a microRNA pairs with potentially hundreds of messenger RNAs (mRNAs) that contain sequences corresponding to the microRNA's seven-nucleotide-long "seed region". With a microRNA bound to it, an mRNA is either degraded or blocked from being translated into a protein.

To better understand microRNAs and their importance, scientists need to know which mRNAs they target. David Bartel is at the forefront of providing tools for this endeavor, and in 2004, helped create TargetScan, an online tool that predicts microRNA targets. Since its debut, TargetScan has been updated to reflect advances in our understanding of microRNAs.

Over the past five years, however, several labs have produced data indicating that microRNAs are even more promiscuous in their mRNA interactions than had been thought. If true, TargetScan's predictions might be woefully incomplete.

After analyzing experimental data, Vikram Agarwal, a graduate student in Bartel's lab, confirmed that microRNAs are in fact interacting with far more mRNAs than predicted by TargetScan. However, these newly recognized interactions are not important, as the microRNAs do not repress these so-called non-canonical targets. Agarwal went on to expand TargetScan's statistical model designed to predict which interactions will be most effective, and the current version is more accurate than ever. In fact, TargetScan now reflects microRNA activity as accurately as any experiment that directly identifies the targeting interactions, but is far faster, more convenient, and costs the user nothing.

"This is an important improvement. The new version of TargetScan should be a useful starting point for any biologist who wants to consider the set of mRNAs targeted by a microRNA," says Bartel. "We hope it is a resource people continue to use."

Another angle **"There's been excitement in the field about the prospect of many additional microRNA target sites. But we're providing a counterpoint to those studies, saying, yes, those additional sites are being recognized in the cell, but they don't seem to be consequential, as they are not imparting detectable regulation."**

iain cheeseman

When paired chromosomes are separated and allocated during cell division, the centromere is a hub of activity. It is where the chromosomes are joined and where the kinetochore protein complex links the DNA to microtubule proteins that winch the chromosomes apart. Correct placement and function of the centromere and kinetochore are key to proper cell division and cell survival—anomalies in either may lead to cancer or cell death.

Contrary to popular understanding, the centromere is not a specific DNA sequence. Rather it is located where multiple copies of the histone protein CENP-A attach to the DNA.

"Every single cell in your body has to mark that same site," Cheeseman says. "That site is the same in your mom, and the same in your grandmom, and the same in your great-grandmom, and so on. The fact that the marking of this site is so unbelievably strong—not just in every cell of your body but through generations—is incredibly powerful."

Each time the cell copies its DNA in preparation for cell division, it must ensure that the centromeres of the new and old DNA strands are replenished with CENP-A. How this precise process is controlled had been a fundamental question in cell division research. Kara McKinley, a graduate student in Cheeseman's lab, recently determined that two kinases, CDK and Plk1, work in tandem to regulate CENP-A's replenishment.

The Cheeseman lab also recently gained important insight into the kinetochore's role in cancer cells. Previously, some researchers thought that specific kinetochore genes were up-regulated in cancer cells such that this change in their levels was critical to cancer cells' flourishing.

Cheeseman and his lab were skeptical. Instead of heading to the lab, Cheeseman began something akin to a journal club. Lab members argued and discussed how to assess kinetochore gene expression. Then Cheeseman brought in Whitehead's Bioinformatics and Research Computing core facility to analyze vast amounts of public data from tumor samples, cancer cell lines, and transcriptional profiling of normal human tissues. According to the results, all kinetochore genes are ramped up to the same degree, indicating that kinetochore proteins are overexpressed in cancer cells as part of a general cell division program.

After sifting through the data, the team determined that FoxM1—a transcription factor previously implicated to be important in cancer—likely coordinates the kinetochore genes' expression. Although cancer cells do not overexpress individual kinetochore proteins, their activation of this broad-based cell division program, which includes the kinetochore genes, may provide a way to target the strong proliferative capacity of these cells.

Another angle **"People have been interested in finding a molecular basis for the chromosomal instability that is present in many cancer cells but have been myopically focused on expression levels of key genes because of how easy it is to look at this. Our work says that these levels have no relevance whatsoever to cancer. This has allowed us to refocus on the mutational basis for cancer rather than the expression basis for it."**

gerald fink

For geneticist Gerald Fink, fighting the pathogenic fungus *Candida albicans* has long been both a passion and a frustration. He has sought to find the vulnerabilities of this yeast, which in immunocompromised patients is associated with mortality rates as high as 40%. But he has been thwarted because *Candida*'s peculiar biology has made it refractory to genetic manipulation: it lacks a sexual cycle, has two copies of every gene, and doesn't have any plasmids, the small DNA molecules that make it possible to shuttle genes in and out of an organism. These obstacles to genetic engineering have made *C. albicans* largely resistant to drug discovery efforts that seek to identify gene-based therapeutic targets.

"It's been difficult to discover effective antifungal agents because we've been unable to explore the *Candida* genome for functions that are vital to its growth," says Fink. "We need to target *Candida*'s vital functions to discover something that will kill the organism but not the patient. It's been virtually impossible to explore that hidden realm of its genome, but we've changed all that."

How? Fink and his lab turned to the novel genome editing system known as CRISPR, modifying its components specifically to overcome the challenges *C. albicans* poses to genetic engineering. The modifications allowed the system to target any gene, and in one shot eliminate both copies in laboratory strains of *C. albicans* with remarkable precision and efficiency. In fact, the system proved so effective, that scientists in the Fink lab were able to knock out both copies of three genes in a single experiment—a feat that previously was considered unachievable.

The lab then tested its modified CRISPR knockout system on a highly drug-resistant strain isolated from a clinical setting. With several genes knocked out, the formerly resistant strain was now rendered susceptible to exposure to the major class of antifungal drugs. Fink estimates that the modified CRISPR system should successfully target roughly 98% of *C. albicans'* more than 6,000 genes, which means scientists should now be able to identify all of the genes essential for the organism's growth and to analyze those associated with the many mechanisms of drug resistance *C. albicans* employs.

Notes Valmik Vyas, a Fink lab postdoctoral scientist who spearheaded the *C. albicans* CRISPR work: "It's an exciting time to be working on *Candida*."

Another angle **"I've spent my life as a scientist studying sex, focused on how chromosomes and genes are apportioned to subsequent generations. Sex is a critical step in the evolution of organisms, combining favorable genes from both parents in new combinations that permit the next generation to survive. But now I'm faced with an organism that doesn't have sex yet has survived for hundreds of millions of years. So, I encounter another angle: sexless evolution. How do sexless organisms maintain diversity over hundreds of millions of years? It's a longstanding question in population biology and may hold the answers to the resilience of this fungal pathogen."**

mary gehring

Pluck a daisy and look at it closely. The cells in the stem, leaves, and petals all tap into the same genome for their design. Yet genes activated in the stem are not necessarily active in the leaves or petals. A cell's gene expression profile is determined by which genes are suppressed and which are activated.

Adding methyl (CH3) groups to the DNA of a gene's promoter is one epigenetic method—meaning no alteration occurs to the DNA sequence itself—of regulating gene expression. According to current scientific thought, this type of methylation suppresses the gene by denying a cell's transcriptional apparatus access to the gene's promoter or by recruiting proteins that ultimately bind and repress the DNA. Conversely, demethylation frees the DNA to be expressed and serve as a template for protein production.

But according to Mary Gehring's work in the plant *Arabidopsis*, the gene *ROS1* plays by different rules: methylation promotes the gene's expression while demethylation silences it. The arrangement is especially interesting because the protein encoded by *ROS1* is the plant's primary demethylase—the enzyme that removes methyl groups from DNA. In fact, the protein targets the promoter for its own gene, creating a negative feedback loop.

Gehring describes this mechanism as an epigenetic rheostat that constantly adjusts the level of methylation and demethylation activity in the genome, which must be carefully maintained. If too many regions are methylated and suppressed, the cell is unable to produce the proteins it needs to survive. By contrast, if too many regions of the genome are demethylated and activated, the cell risks expressing potentially harmful DNA segments, such as transposable elements, which comprise about a quarter of the *Arabidopsis* genome.

Such deleterious DNA is not unique to *Arabidopsis*; approximately 85% of the maize genome is transposable elements. Although maize and *Arabidopsis* are separated by about 165 million years of evolution, maize also has versions of *ROS1* that seem to play similar rheostatic roles in the plant. That two plants so distantly related conserved the same mechanism suggests to Gehring that the epigenetic rheostat may be adaptive.

What puzzles Gehring is what's actually controlling *ROS1*'s behavior—how methylation activates it rather than suppressing it. By teasing apart the pathway and genes upstream of *ROS1*, Gehring hopes to shed some light on *ROS1*'s epigenetic regulation.

Another angle **"It's been dogma in the field that methylation inhibits expression when it's found in promoter regions of genes. I'd say we're looking at things from a different angle than most people are in the field right now. We're finding examples of methylation that promotes gene expression in plants, and I don't think this is going to be an extremely rare phenomenon."**

piyush gupta

For decades, scientists studying breast cancer have relied on mouse models created by implanting human tumor cells into immunodeficient mice or by inserting human cancer mutations into mice. But fundamental differences between mammary gland development in humans and mice cause these models to fall short when researchers want to study the development of human breast tissue and the cancers that afflict it.

After puberty, human female breasts contain numerous terminal ductal lobular units that are tree-like structures with balloons at the ends of the branches. During lactation, milk produced in the balloon-like lobules flows through the ducts toward the nipple. Female mice lack these units—they have only the main trunk and branches and develop a simplified version of the remaining structures during pregnancy or lactation. Such stark physiological differences have suggested that mouse mammary glands may not be an adequate model of human mammary development or breast cancer.

One solution to this problem would be to study breast cancer in a three-dimensional (3D) version of mammary tissue cultured in a matrix that supports the tissue's growth and development. Scientists do have such models of human intestinal tissue, but similar mammary models have proven elusive. Researchers had thought that human breast tissue resisted the creation of 3D models because research in mice suggest that fibroblasts and other support cells are required to direct the organization of mammary tissue.

Gupta noticed that in human tissue types amenable to 3D modeling, cells organize themselves and don't require additional support cells. Gupta also knew that unlike mouse mammary tissue, which is mostly fat, human breast tissue is quite fibrous. He began to wonder whether construction of a scaffold more similar to human breast tissue might encourage growth. Scientists in his lab fabricated a "hydrogel" that included four different matrix components found in human breast tissue; the original matrix had one component. The resulting matrix more faithfully mimics the physiological context of human mammary glands.

"We seeded the matrix with normal breast epithelial cells that had never been cultured before, and to our surprise and delight, we saw these massive, truly massive, tissue outgrowths," Gupta says. "They were beautifully complex, with ducts sprouting lobules, and they even responded to many of the same hormones that regulate mammary glands in humans."

Gupta's lab is now using this 3D hydrogel system to dissect the genetics driving the growth of both normal and cancerous breast tissue.

Another angle "We were initially focused on seeding patient-derived cells with the right nutrients in a rigid scaffold. When this failed, we eventually realized that it was far better to seed the cells into flexible scaffolds that were anything but rigid. This way the cells were able to remodel the scaffolds themselves to provide the structural conditions that they needed to grow. Without this crucial shift in perspective, we could never have succeeded."

rudolf jaenisch

Leveraging the latest technological advances in genetics and molecular biology—many of which have either originated or been refined in his lab—Rudolf Jaenisch is bolstering our understanding of the etiology and pathophysiology of a range of neurological disorders.

For nearly a decade, the Jaenisch lab has focused considerable attention on Parkinson's disease (PD), probing its genetic underpinnings and striving to create realistic models of the disorder (the elusive "disease-in-a-dish" paradigm) to study its progression. Although the work has been productive—Jaenisch was the first to show that neurons derived from induced pluripotent stem (iPS) cells could improve symptoms in a rodent model of the disease—progress has been slowed by PD's complexity and the large number of potentially relevant genetic variants that have been identified by broad genome-wide association studies (GWAS).

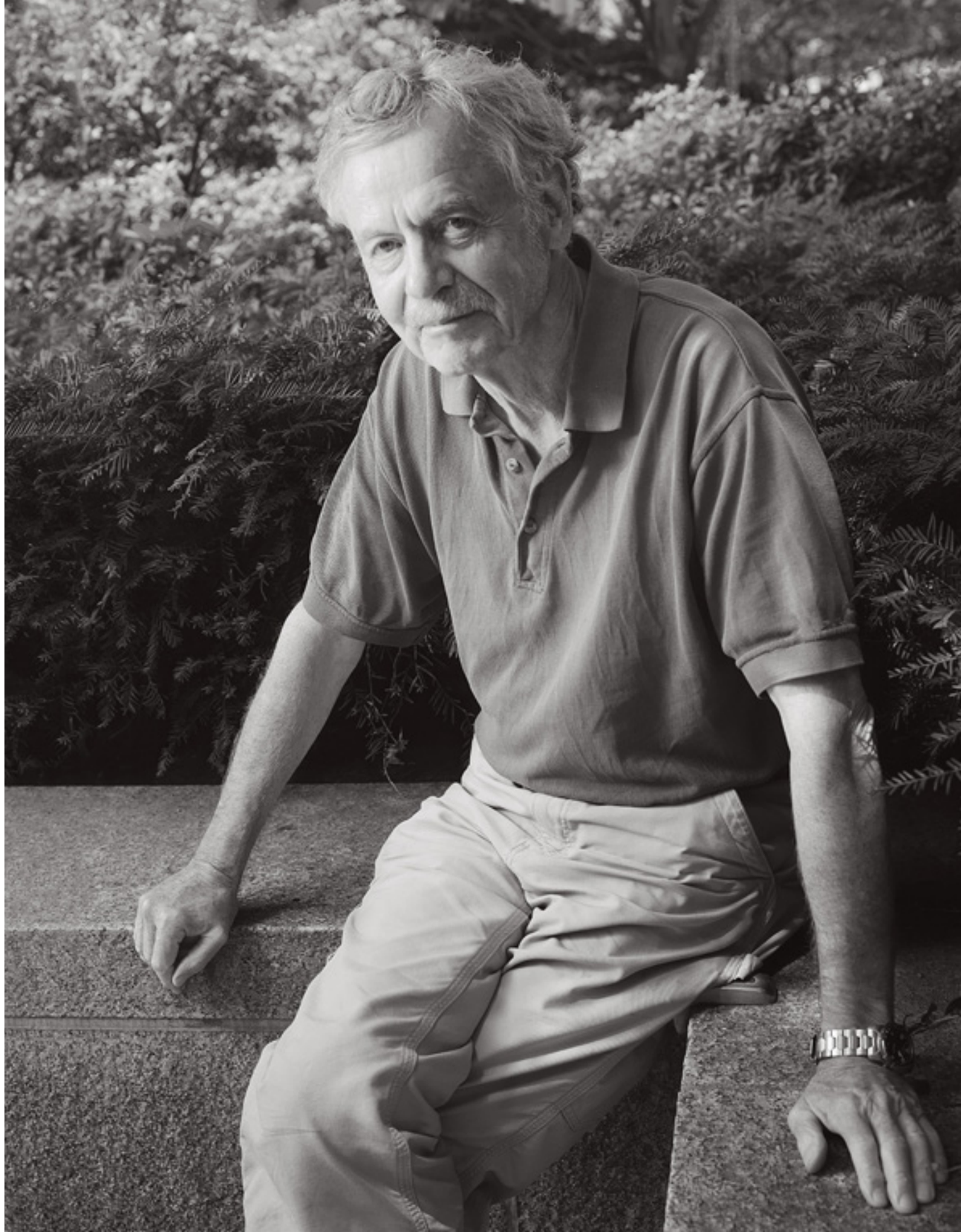
To date, it has been virtually impossible to establish any connection between genetic variants associated with increased risk for PD and actual biological manifestations of disease. Further complicating matters, studies identifying potential disease-causing genes have examined relatively rare familial forms of PD, yet an estimated 90% of PD cases are of the sporadic variety, suggesting that a combination of genetic and environmental factors are causing the disease.

Now the Jaenisch lab is overcoming these hurdles with systematic analyses of the effects that genetic variants identified by GWAS have on gene regulatory elements (such as enhancers) that in turn alter the expression of PD-associated genes. With this genome-wide epigenetic information in hand, the lab then uses the CRISPR/cas genome editing system to create embryonic and iPS cells that are isogenic—that is, cells whose only genomic modification is the single desired genetic variant introduced during editing. By differentiating these isogenic cells into dopamine-producing neurons (the cell type destroyed in PD), the lab is able to study whether and how the variants affect gene expression in the neurons.

The approach is beginning to bear fruit. In new research about to be published, Jaenisch and his lab report the discovery of a PD-associated variant in a non-coding enhancer that regulates the expression of *alpha-synuclein*, a notorious gene long ago implicated in the development of PD.

"This has never been done before," says Jaenisch. "The isogenic cells allow us to exclude outside risk factors, such as the environment, and focus solely on gene expression. We had no molecular insight before into how genetic variants actually contribute to the disease."

Another angle "I've long been interested in methylation (an epigenetic phenomenon during which a chemical group binds to DNA and alters gene expression), but it's difficult to study in mammals. It's a very dynamic process, so we needed to look at it differently. We needed to establish a new approach, so we developed a real-time reporter system that captures the methylation of a gene at single-cell resolution. We can now study it in any cell of the mouse and this can also be done in human cells."



susan lindquist

Over the past several years, researchers in Susan Lindquist's lab have been investigating the ancient cellular survival response regulated by the transcription factor Heat-Shock Factor 1 (HSF1) and the role it plays in supporting malignancy. In normal cells, stressful conditions, including those caused by heat, hypoxia, and toxins activate HSF1, which serves to maintain protein homeostasis and helps the cells endure tough times. Cancer cells, however, can hijack this heat-shock response to their own benefit. A few years ago, Lindquist's lab implicated HSF1 in this corruption, showing that it activates a set of genes in cancer cells distinct from those up-regulated in normal cells during heat-shock.

Building upon that research, the lab recently discovered that HSF1 operates not only on the cancer cells in a tumor, but also on the cells of the tumor microenvironment, or stroma. Here HSF1 drives a transcriptional program different from that operating in adjacent cancer cells. HSF1 activation in cancer cells and stromal cells is a powerful, complementary combination that fuels malignancy. In a series of experiments, scientists found HSF1 activation in stromal cells known as cancer-associated fibroblasts, or CAFs, in a variety of human tumors, including breast, lung, skin, esophageal, colon, and prostate cancers. Moreover, they discovered that not only does HSF1 activation in CAFs up-regulate genes supporting malignancy, it also suppresses genes that would ordinarily trigger a protective, anti-cancer immune response in surrounding tissue.

Although such a synergistic dynamic may seem daunting to overcome, it may actually present an opportunity for therapeutic intervention. While transcription factors such as HSF1 are notoriously difficult to drug directly, these findings suggest that targeting the effects HSF1 has on the underlying tumor biology could change how a cancer responds to therapeutic interventions, perhaps making it less able to cope with other therapies.

Researchers also believe that stromal HSF1 activation has the potential to serve as a diagnostic and prognostic biomarker. In analysis of tumor samples from breast cancer patients, the scientists found that HSF1 activation in the stroma was associated with poor patient outcomes. Further, the researchers found that stromal HSF1 activation in samples from patients with early-stage non-small cell lung cancer was also associated with poor outcomes.

In theory, an HSF1-based biomarker could help predict which patient tumors are most likely to progress and might benefit from more aggressive therapy. Conversely, such information could prevent patients with less aggressive cancers from suffering the ill effects of "over-treatment" with highly toxic therapies.

Another angle **"Attacking cancer by going after its support system in the stroma certainly represents an approach to a major problem from another angle. It's truly exciting to do this. To develop new techniques and new ways of thinking is something I love and have always been passionate about"**

harvey lodish

Red blood cells (RBCs) are an ideal vehicle for introducing a wide array of antibodies, therapeutic proteins, and small molecules into the human body. They survive for three months in the circulatory system, while antibodies and other therapeutic proteins generally last only a few hours or days. The progenitor cells in the bone marrow, like all body cells, have a nucleus, but as the precursors mature, they jettison their nucleus; this eliminates all DNA and the possibility of lab-created mutations causing disease.

"After I came up with that idea three years ago, it became so obvious and the potential so enormous!" Harvey Lodish recalls. Lodish has studied RBCs and erythropoiesis—the formation of RBCs—for more than five decades. Fifteen years ago, fellows in his lab discovered how to encourage mouse red blood progenitor cells to divide and differentiate in culture to make large numbers of normal RBCs. Using this system, his lab teased apart the roles of dozens of important genes, proteins, and RNAs involved in red cell formation. Four years ago, they created a culture system that starts with human bone marrow stem cells—the same cells used in bone marrow transplants—and over the course of three weeks produces several hundred thousand normal RBCs.

This fundamental research, coupled with work by Whitehead Member Hidde Ploegh, spurred Lodish to transform RBCs into cargo-laden vessels. First, he alters the genome of RBC precursor cells to produce a modified version of a normal RBC surface protein. Then using Ploegh's protein-labeling technique known as sortagging, Lodish is able to attach drug molecules, antibodies, or virtually any other molecule permanently to the RBCs' surface.

In one promising experiment, antibodies to botulinum toxin attached to the surface of mouse and human RBCs were able to neutralize the toxin and protect mice against a highly lethal dose of the toxin.

"In principle, any antibody or receptor you put on the surface that binds to a foreign toxin or a virus can be used to remove these nasty molecules and provide protection for many weeks," Lodish says.

In another intriguing experiment, a joint Lodish and Ploegh graduate student linked foreign protein to RBCs and injected them into mice. Remarkably, the altered RBCs did not invoke an immune response and even prevented further induction of a response. According to Lodish, this technique holds enormous potential in treating autoimmune diseases.

Another angle "Working on fundamental biological problems can lead to applied results. Basic science on the one hand gives you the technology, and on the other hand, the insights for how you might actually build a novel platform for therapeutics."

terry orr-weaver

Recently, Terry Orr-Weaver has been investigating train wrecks. However, her inquiries into the causes of such mishaps focus not on the mechanics of locomotives or railroad track switch gear, but rather on the DNA inside fruit fly ovarian follicle cells.

Cells depend on their DNA to provide the blueprints for everything they need to survive, grow, and divide. To pass down proper instructions to their offspring, cells strive to replicate their DNA verbatim. An omission or alteration could result in dysfunction, disease, or death.

During DNA replication, the protein helicase zips along the double-stranded DNA, breaking the hydrogen bonds holding the strands together. A cast of proteins swoops in to add nucleotides to the two single strands, which act as templates during replication. Orr-Weaver likens this apparatus, known as a replication fork, to a train that chugs down a track. But the train does not always arrive at the end of the line. Occasionally, it runs into regions of the genome that can cause it to derail, leading to regions of DNA that are unreplicated and prone to breakage.

To understand fork progression control, Orr-Weaver and her lab have taken another angle: exploiting a developmental event that permits direct analysis of replication forks. Most cells initiate one round of DNA replication per cell cycle, but to amplify certain genes, fruit fly ovarian follicle cells undergo re-replication, during which DNA replication launches again on a replicating DNA section. The precise developmental timing of these events allows forks to be visualized, revealing the consequences of multiple replication forks. Re-replication is also thought to occur in cancer cells and has been proposed to destabilize the DNA, thus the follicle cells provide the opportunity to explore the basis of such defects in cancer cells.

Orr-Weaver and her lab have found two causes of replication fork derailment. One is the protein SUUR, produced by the *SuUR* gene (for "Suppressor of Under-Replication"), which controls gene copy number by acting as a brakeman. As SUUR rides along with the replication fork train, it either stalls or derails the train, producing under-replicated sections of the genome and chromosomal fragility.

Another cause of DNA disasters is akin to an actual trainwreck. When one replication fork collides with another in front of it, the DNA breaks. This source of genome instability in cancer cells enables investigation of DNA repair mechanisms. Cells use two methods to repair the DNA rails: non-homologous end-joining (NHEJ), which is quick but error-prone; and homologous recombination (HR), which is slower but more accurate. To her surprise, Orr-Weaver has found that after replication fork collisions, cells opt for repair by speedier, albeit less faithful, NHEJ.

Another angle "Exceptional strategies used in biology provide new opportunities to decipher fundamental insights through exploitation of their unique experimental advantages."

david page

Having assembled an estimable body of work, David Page is poised to take perhaps the biggest leap of his career.

Over the past 30 years, the Page lab has revealed more about the history and the workings of mammalian sex chromosomes (the X and Y) than virtually any other research group in the world. Throughout, Page's painstaking sequencing efforts and cross-species comparisons of the sex chromosomes have been pushing him toward an intriguing hypothesis: that these chromosomes and their genetic content affect our bodies in ways that reach far beyond the reproductive tract. If the hypothesis is correct—and Page is increasingly convinced it is—it could be a game-changer.

"It's a vision of a human female biology and a human male biology, and we need to approach this systematically," he says. "I'm envisioning a world in which the differences between males and females in health and disease are at the core of how medicine and human biology are taught."

Page's hypothesis stands on two fundamental observations, one from his lab, the other occurring in nature. Not long ago, Page reported on a set of roughly a dozen genes on the human Y chromosome that survived over the course of millions of years of evolution. Moreover, these genes are expressed widely throughout the body and appear to have little if any role in sex determination or sperm production. That these genes were selected for survival suggests their function is critically important.

The second observation comes from the world of reptiles; turtles in particular. The comparative anatomies of male and female turtles are as different as those of men and women. Turtles, however, have no sex chromosomes, meaning that the genomes of male and female turtles are identical. Sex determination in turtles depends on the temperature at which a fertilized egg incubates and is, therefore, an epigenetic phenomenon. What this means, says Page, is that male and female turtles read their genomes differently—the same genes in each sex perform differently, leading to different outcomes.

Because such alternate readings predate the emergence of the sex chromosomes by as much as 300 million years, Page believes the mechanisms for unique male and female genomic interpretations remain in place in humans.

"We're much more like turtles than we are different from them," he says. "Some discoveries have made it clear that the human genome is read differently by males and females. We have to pursue this idea."

Another angle "The lab is certainly coming at the biology of the sexes from another angle. It's been all about the sex chromosomes and now it might not be about them at all. We have to unlearn the role of the sex chromosomes in all of this. The sex chromosomes may cue male and female readings, but they're a hack of a highly evolved system of reading the genome in two different ways."

hidde ploegh

Over the years, Hidde Ploegh's lab has distinguished itself as a workshop of innovation, devising tools and techniques with which to probe the workings of the immune system and its response to antigens, including those from invading pathogens and cancer cells.

Among Ploegh's most recent advances is a novel approach that allows real-time imaging of the immune system's response to the presence of tumors without the need for blood draws or invasive biopsies. The method, which harnesses the imaging power of positron emission tomography (PET), offers a potential breakthrough both in diagnostics and in the ability to monitor efficacy of cancer therapies.

In developing this improved method of monitoring, Ploegh leveraged two research tools that have become staples in his lab. The first exploits so-called single-domain antibodies known as VHHs, derived from the heavy chain-only antibodies made by the immune systems of animals in the camelid family. Ploegh's lab immunizes alpacas—his camelid of choice—to generate VHHs specific to immune cells of interest. The second tool, known as sortagging, labels the VHHs in site-specific fashion to enable the tracking of the VHHs and their targets in a living animal.

Knowing that the tissue around tumors often contains immune cells such as neutrophils and macrophages, Ploegh and his lab members hypothesized that appropriately labeled VHHs might allow them to pinpoint tumor locations by finding the tumor-associated immune cells. Ploegh notes that VHHs' extremely small size—approximately one-tenth that of conventional antibodies—is likely responsible for their superior tissue penetration and thus makes them particularly well suited for such use. In proof-of-principle work, the lab generated VHHs that recognize mouse immune cells, then labeled the VHHs with radioisotopes and injected them into tumor-bearing mice. Subsequent PET imaging detected the location of immune cells around the tumor quickly and accurately. In fact, researchers were able to detect tumors as small as one-millimeter in size within days of their emergence.

With further refinement, Ploegh believes the method could be used to monitor and perhaps tailor cancer immunotherapy, which, though promising, has met with great success in some cases but failed in others.

"PET imaging should allow a much more comprehensive look at the entire tumor in its environment," he says. "Then we can ask, 'Did the tumor grow? Did immune cells invade? What has happened to the tumor?' And to be able to see this without going in invasively is a significant achievement."

Another angle **"We are always trying to design new tools to help solve existing problems. It's a forte of the lab. Single-domain antibodies and sortagging, which can improve protein quality control, are two key examples. We're continually looking for a new angle from which to approach challenges in the field."**

peter reddien

For more than a century, scientists have studied the planarian's ability to regrow almost any part of its body: slice off its head or tail, and the small flatworm will recreate the missing part in a matter of weeks. But the mechanisms underlying regeneration in planarians have remained a puzzle. Although evolutionarily separated from us by millennia, these mechanisms in planarians may provide insights into regeneration and wound healing in humans.

Over the past two years, Peter Reddien and his lab have made two significant contributions to the field. In 2013, his lab determined that muscle cells provide positional control that informs the worm's stem cells which tissues to grow at a wound site. In 2014, the team determined that these stem cells, called neoblasts, are a varied population of pluripotent cells and lineage-committed progenitors.

"We're at an inflection point for the field with regard to our understanding of how stem cells are driving regeneration," says Reddien. "When I look back at the major transition points in our work and in the field, defining the composition of the neoblast population is one of three or four big ones that have happened in the past decade."

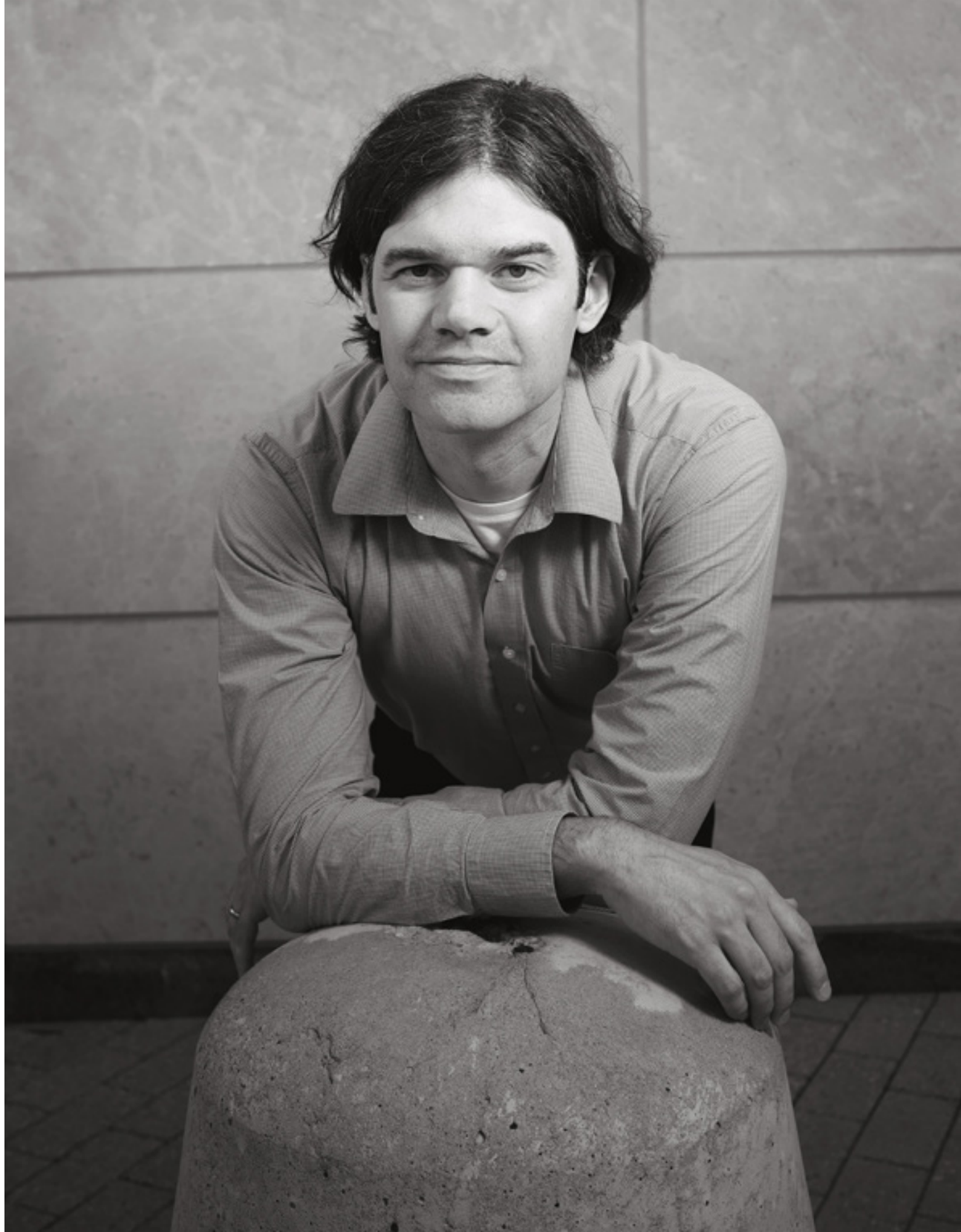
When an animal loses a head, tail, or any other body part, neoblasts migrate to the injury and produce a mass of cells at the wound site. Previously, these neoblasts were thought to be a largely homogeneous population of pluripotent cells. In fact, some of Reddien's research, which shows that a single founding neoblast can maintain an entire planarian, supports this hypothesis.

But further work tipped off Reddien that a wound outgrowth is more like a patchwork of committed progenitor cells. These specialized neoblasts predetermine what tissue that outgrowth will become. This new hypothesis—that pluripotent stem cells produce a heterogeneous population of specialized neoblasts—points to neoblast specialization as a key regulative step in regeneration.

Reddien's lab also recently established a new model organism for studying regeneration—the three-banded panther worm (*Hofstenia miamia*). Planarians and *Hofstenia* may have diverged about 550 million years ago, but research in the Reddien lab has indicated that they share certain basic mechanisms—mechanisms that could be the foundation of regeneration in all species that evolved later, including humans.

"We're in a very important and very exciting era right now," says Reddien. "We're starting to figure out some central pieces of the puzzle, and they are shining a light on what the next important questions are."

Another angle **"We developed—from scratch—a novel model system (the three-banded panther worm) to complement our work with planarians and enable our ability to discover general principles of regeneration."**



david sabatini

Known as much for its complexity as its vital role in regulating cellular and organismal growth, the mechanistic target of rapamycin complex 1 (mTORC1) pathway has seemingly been acting in mysterious ways—ways that have fascinated David Sabatini for years.

Through a variety of interactions, mTORC1 interprets cues in the cellular environment, including the availability of nutrients, and signals the organism to act accordingly. mTORC1 is apt to trigger growth during times of abundance and dial back metabolism when food is scarce. Owing to years of intense scrutiny in Sabatini's lab, the key players of this pathway—whose deregulation is associated with diseases ranging from diabetes to cancer to epilepsy—have gradually been brought to light. Yet, one essential question remained unanswered: how exactly does mTORC1 actually detect the presence of nutrients?

Scientists in Sabatini's lab have been closing in on the answer. Recently, they described for the first time a transmembrane protein known as SLC38A9 that appears to sense the amino acid arginine.

"No one doubts that this is an important pathway, with implications for aging, cancer, and diabetes, and we had figured out the core machinery of the pathway," says Sabatini. "But the mystery has been what are the sensors? Now we've found what is likely the first nutrient sensor. This is what connects that core machinery to the world around it."

The finding suggests a model in which mTORC1, located at the surface of cellular components known as lysosomes, receives "go/no-go" signals from a family of enzymes dubbed Rag GTPases. It had been known that the Rags convey information about nutritional status to mTORC1, but it wasn't clear how the Rags came by this information. Through a series of experiments, researchers found that SLC38A9 is capable of transporting and directly interacting with amino acids, the building blocks of proteins.

Zhi-Yang Tsun, a graduate student who participated in the research, says of SLC38A9's activity: "It's like a relay race and this protein is what starts the race."

Although the discovery of the first putative nutrient sensor in this pathway represents an important advance, Sabatini knows that much work lies ahead. SLC38A9's specificity for arginine suggests that many more such sensors—for other amino acids and glucose, for example—interact either directly or indirectly with mTORC1. Identifying them will thus remain a focus of the lab for years to come.

Another angle **"Our work has shown that all of our cells care about individual nutrients, but this wasn't always the case. There was a belief that humans are too complex, too advanced to be affected at that basic level, and that this was only relevant in lower organisms, like bacteria. So most of the focus was on how cytokines and hormones tell us if we're fed or not. But we took another approach and looked at something more primitive. It led us to uncover this major growth pathway that has implications in cancer, obesity, and diabetes."**

hazel sive

In ongoing studies of vertebrate brain development, Hazel Sive and her lab have recently trained their focus on cerebrospinal fluid (CSF)—a vital player in embryonic brain formation whose precise role in the process has been poorly understood.

The vertebrate brain arises from a cylindrical structure referred to as the neural tube. As an embryo develops, cavities known as brain ventricles form within the center of the tube and fill with CSF. The process is critical, as ventricular malformation and CSF absence are associated with a host of devastating birth defects, including anencephaly—in which the forebrain fails to form. Conversely, hydrocephalus is characterized by abnormal accumulation of CSF and is associated with symptoms ranging from seizures to cognitive impairment.

Determined to understand what makes CSF essential during embryonic brain development, researchers have turned to the zebrafish, a Sive lab workhorse whose genetics and physical attributes have long yielded important insights applicable to mammalian biology, human included. Scientists in the lab developed an approach to drain CSF systematically from zebrafish embryos and assess the effects *in vivo*. To their surprise, Sive lab investigators found that CSF drainage causes extensive brain cell death.

Although it's been known that CSF provides pressure necessary to keep brain ventricles inflated, the fluid itself is packed with hundreds of proteins, nearly 60% of which are found across species, including mice, rats, chickens, and humans. Such protein conservation suggests their importance in CSF function. The lab quickly confirmed this, finding that replacing drained CSF with saline failed to prevent the brain cell death triggered by the initial drainage. Demonstrating similarity between CSF of all species, replacement with mouse CSF kept the brain cells from dying.

These findings led the researchers on a hunt for proteins necessary for cell survival. They zeroed in on retinol binding protein 4 (Rbp4), which transports retinol, a precursor to retinoic acid (RA), a key player in a signaling pathway critical for proper growth and development. They found that inhibiting Rbp4 or RA synthesis led to increased brain cell death. Injection of a human form of RBP4 with retinol, or injection of RA alone, prevented cell death after CSF drainage.

The research is the first demonstration that a factor (Rbp4) in the CSF is necessary for brain cell survival while also describing a novel role for RA signaling via the CSF to promote brain health. Follow-on work seeks to identify which cells are targets for embryonic Rbp4 and to determine whether retinoic acid signaling supports survival of adult neurons.

Another angle **"The CSF work is a good example of how we look at other angles. When we started the project, the field was interested in how the neural tube formed, but we asked why a tube formed? It seemed a more important question, and that different angle led us down a new and important road."**

robert weinberg

Each year, roughly 350 patients with rhabdomyosarcomas—cancers of the skeletal or heart muscles—are diagnosed in the United States. That represents just 0.02% of the 1.6 million new cancer cases that the National Cancer Institute estimates will be diagnosed in 2015. So why is cancer in muscle so rare, especially when compared with common sites such as the breast, lung, or prostate?

That question piqued the interest of one of Robert Weinberg's postdoctoral researchers, who has investigated the topic as something of a side project. To say that Weinberg was initially only modestly supportive is being generous.

"I thought this was a totally silly project, because there could be hundreds of things that keep muscle cells from proliferating, none of which may have anything to do with cancer," recalls Weinberg. "The chances of teasing out the mechanisms that hold muscle cells in a quiet state were astronomically small. But I learned a long time ago to the extent that really original or novel things happen in my lab, they happen not because of me, but in spite of me!"

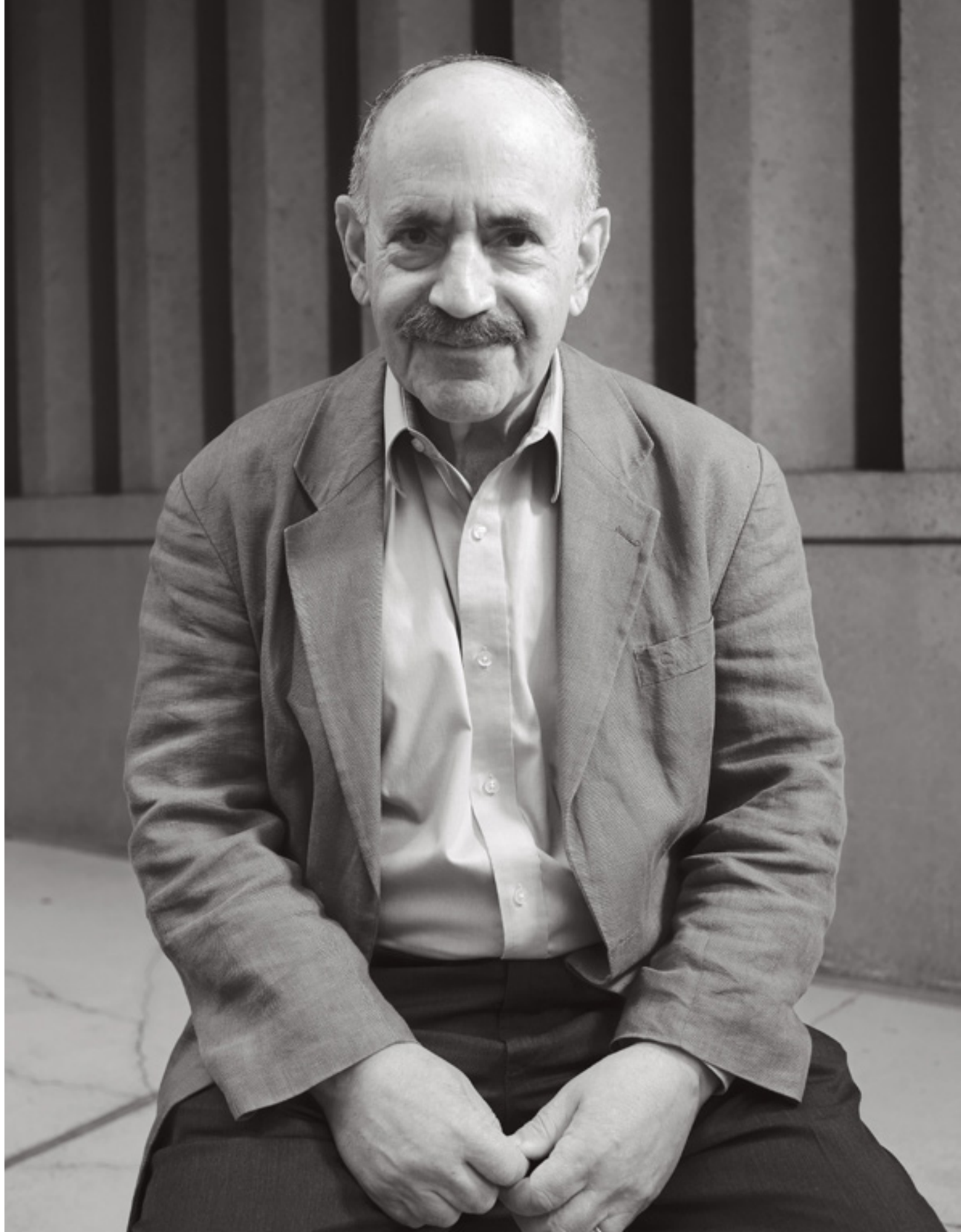
Studying muscle cells is a departure for the lab, which is focused on how cancer, breast cancer in particular, develops, taps into surrounding tissues as it grows, and metastasizes. Previously, the lab determined that an event called an EMT, for epithelial-mesenchymal transition, endows cancer cells with invasive ability and stem cell-like traits that enable them to seed new tumors at distant sites in the body.

Muscle cells are the polar opposites of cancer stem cells. Not only do they not support metastasis, they are unable to initiate tumors. The biochemical characteristics of muscles hint at the reasons why. Once mature, muscle cells express cell cycle inhibitors to prevent further cell division. This trait is incompatible with the biology of cancer cells, which divide freely.

To pin down which molecules endow muscle cells with anticancer properties, Weinberg's postdoc screened for factors active in muscle cells that might have negative effects on the proliferation of cancer cells. She reduced a long list to a handful of candidates, one of which induces cancer cells to differentiate and thus lose their stem cell properties. This factor operates in the energy-producing factories within cells—unlikely and actually unprecedented sites of action for a tumor-suppressing factor. The precise mechanisms that allow it to do its work remain unclear. Still, it represents an entirely novel means by which the formation of cancer cells is inhibited.

Notes Weinberg: "We don't know why this hits cancer so hard, but it is a stunning discovery from research that came from outside-the-box thinking."

Another angle **"Studying muscle cells that rarely become cancerous to gain insight into cancer cells is totally out of left field. And the results of this work are not like any other tumor suppressor gene we've worked with."**



jing-ke weng

Caenorhabditis elegans worms, mice, *Xenopus* frogs, and *Arabadopsis* plants are all model species—organisms that were chosen to represent the diversity of nature in the lab.

"We've learned so much from the model species, but we've also cultivated our knowledge and techniques around these systems, so much so that now we've become trapped," says Jing-Ke Weng.

Weng is breaking out of this model rut to look at the characteristics that make specific species notable. "We're taking an alternative approach and developing an ability and capacity to study all of the amazing features in nature," he says. "Hopefully, we'll uncover something interesting and even potentially useful for society."

Considering the plants he has chosen to study, odds are that Weng will indeed find that interesting something. Take kava kava (*Piper methysticum*). In Polynesian cultures, kava kava tea's soporific effects were reserved for chiefs and priests. Made by squeezing kava kava roots through hibiscus stems, the muddy beverage quiets tempers and increases relaxation—effects that come in handy when negotiating peace in an archipelago. A suite of specialized metabolites, called kavalactones, are found only in kava kava, and hibiscus extracts help extend the release of the metabolites from one hour to as many as six.

Weng wants to know how and why the plant makes these metabolites. In the case of kava kava, a remarkable 17% of the roots' dry weight consists of active compounds. Yet, closely related plants in the same genus, including black pepper, have no kavalactones whatsoever.

Weng plans to harness the chemical diversity in nature to understand how these special compounds are made. Because the kavalactone genes are so enriched in kava but not in black pepper, comparing the two should highlight the genes responsible for kavalactone biosynthesis. Weng plans to apply this strategy to various suites of closely related plants to identify other specialized metabolites that are beneficial to humans.

Beyond facilitating peace treaties, kava kava has been used to alleviate anxiety and depression. To understand why kavalactones have such potent effects, Weng plans to fractionate kava kava root extract and test it on neurons. By monitoring the neurons' response to each of the fractions, he hopes to understand how neurons perceive these molecules and determine the biochemical basis for the feelings of happiness that kavalactones elicit.

Another angle "Currently, it's hard to study non-model organisms because we don't have the genetic tools available. We are developing a new platform that will allow us to study these species by correlating the genes with the traits that we find interesting."

richard young

For the past several years, Richard Young and his lab have been obsessed with the fundamentals of gene regulation; specifically, how the proper expression of genes in a cell results in normal cellular function and good health, while aberrant gene expression—or misregulation—causes disease processes, including malignancy.

Young's studies of gene regulatory elements known as super-enhancers, which set up residence alongside harmful oncogenes and boost their expression, have been exposing vulnerabilities across a range of the most aggressive cancer cells. Young has found that although the super-enhancers drive cancer cell growth and proliferation, they also render the cells exquisitely sensitive to disruptions in transcription. He and colleagues have since been identifying chemical compounds that target key components of cancer cells' transcriptional apparatus, discovering several that appear to tame many of the most treatment-refractory cancer types.

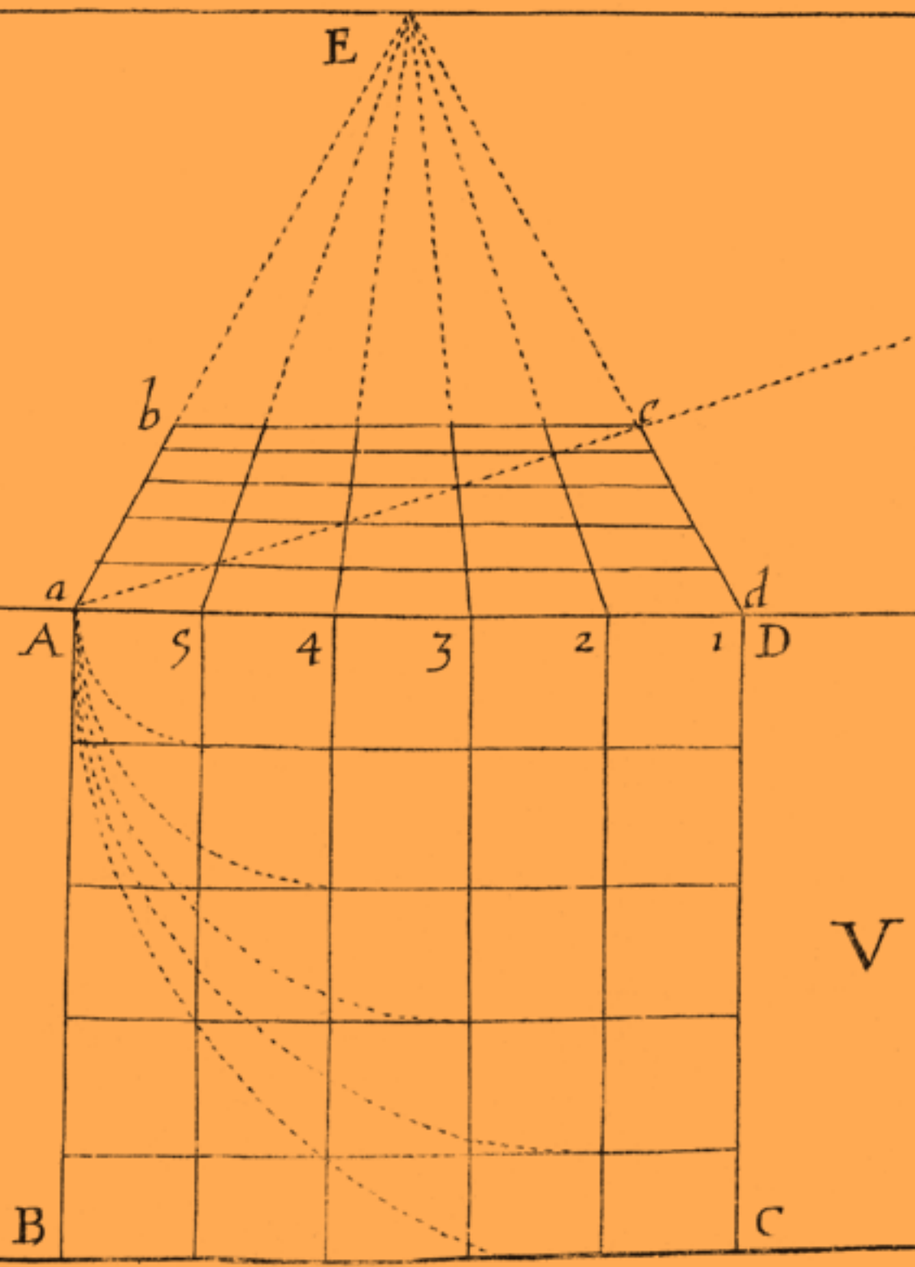
In related work, Young's lab recently uncovered a fascinating relationship between genome structure and the regulation of gene expression. By probing the genome's three-dimensional (3D) conformation, researchers found that key genes controlling cell state and identity occur in loop-like, chromosomal DNA structures dubbed "insulated neighborhoods." It turns out that all essential gene regulation—including control of proper expression and repression—takes place within these enclosed neighborhoods,

"This resolves a 40 year-old enigma," says Young. "We've known that gene regulatory elements can operate at long distances in either direction, but we didn't know how they find the right genes over these distances. Now we know that the proteins cohesin and CTCF form these loops that confine all the regulatory elements within a specific space. Inside these loops is where all the action occurs."

Now armed with the knowledge that gene function follows genome form—and the understanding that normal cellular function requires that the structural integrity of these chromosomal loops be maintained—Young has been exploring whether breaches in the insulated neighborhoods might lead to activation of oncogenes in malignant cells. His lab has been mapping 3D chromosome structure in a variety of cancers, pinpointing the locations of insulated neighborhoods and the sites of enhancer-gene interactions. It now appears that in cancer cell genomes, tiny deletions act to disrupt the boundaries of the insulated neighborhoods, effectively creating an opening for enhancers to enter, activate oncogenes, and fuel aggressive tumor growth.

Young and his lab are now investigating the specific mechanisms by which cancer cells disrupt insulated neighborhoods, confident that such work will point toward novel therapeutic approaches.

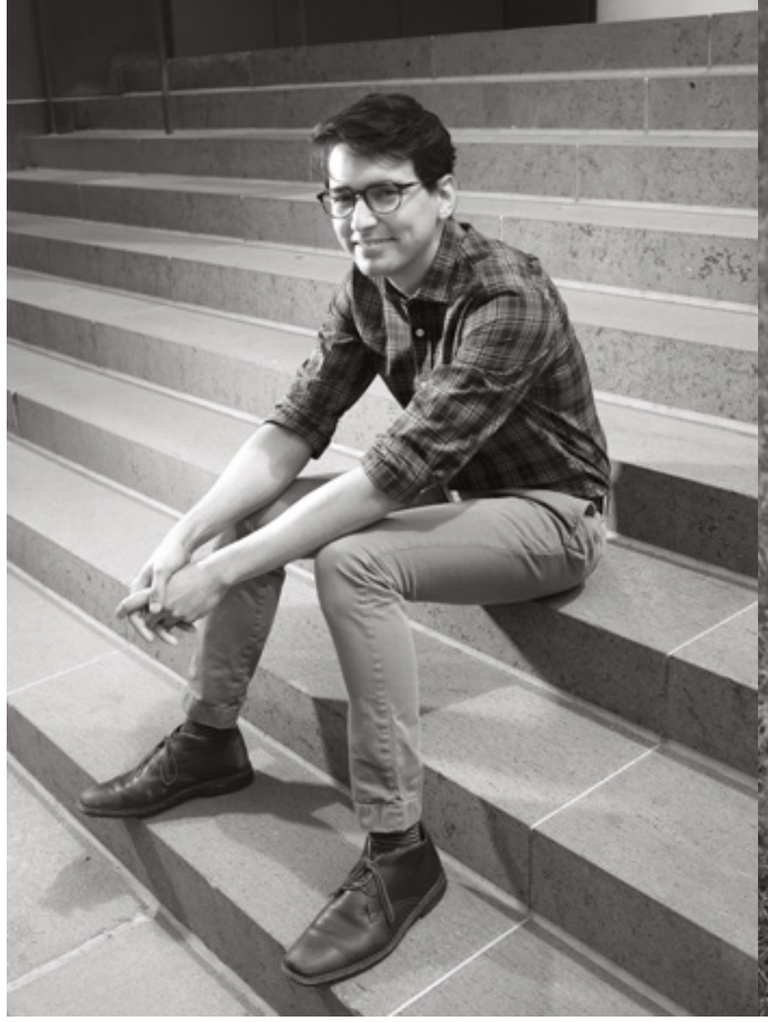
Another angle **"Historically, we've viewed the genome as a linear polymer with genes aligned along that polymer. Understanding how it's structured, and how that structure affects gene control, gives us a new angle on cancer and other diseases."**



whitehead fellows

The renowned Whitehead Fellows program is often imitated but seldom, if ever, duplicated. The concept sounds simple enough: hand pick a small group of extraordinarily promising young scientists fresh out of graduate school and allow each to establish a laboratory in which to pursue an independent research program. Fellows benefit from mentorship and broad-based support while being freed from typical faculty responsibilities, such as teaching. Other organizations have borrowed this template, but none has eclipsed the success of the original.

sebastian lourido



Whitehead Fellow Sebastian Lourido's organisms of choice have long been known as genomic secret-keepers. Lourido studies apicomplexans, single-cell parasites that include malaria-causing *Plasmodium* and *Toxoplasma gondii*, which causes the infection toxoplasmosis. Scientists have lacked the tools to analyze *Toxoplasma* gene function at a genomic scale, so Lourido recently rolled the dice on modifying the genome editing system known as CRISPR for use in apicomplexans.

The results, he says, have been astonishing. His lab has created a genome-scale screening platform that has enabled him to knock out each of *Toxoplasma*'s 8,200 genes and track the outcomes in the population over time. With CRISPR, his lab can determine which genes are necessary for the parasite's survival as well as those that might play a role in the development and maintenance of drug resistance.

Says Lourido: "Before this, you would have had to do 8,200 experiments to look at the function of 8,200 genes. Now we can look at it in the context of a single experiment in which we knock out each gene and determine the full set that are important for the fitness of the parasite in its lifecycle. In the past, it might have taken us three to six months to manipulate a single gene."

david pincus

In diseases associated with protein misfolding—including cancer and neurodegenerative disorders—the master regulator Heat-Shock Factor 1 (HSF1) is a central figure. HSF1 is part of an ancient survival response that maintains protein homeostasis, enabling cells to survive stressful environments. As cellular proteins assemble into amino acid chains, HSF1 controls chaperone proteins that help fold the chains into their proper forms and prevent dangerous aggregation. Cancer cells can hijack HSF1 to form mutated proteins that support malignancy. In neurodegenerative disease, HSF1's activity seems to be suppressed, allowing for toxic accumulations of misfolded proteins.

"Ideally, we would love to tune HSF1 up or down according to need—down in cancer cells to prevent them from using its pro-survival functions and up in neurodegenerative disease to exploit those functions," Pincus says.

Pincus is determined to understand how cells regulate HSF1, believing there may be "molecular handles" that could be exploited to dial HSF1 up or down. He had suspected that phosphorylation—in which phosphate groups are added to specific sites on HSF1—might represent a potential handle with which to regulate HSF1. Recently, however, he experimentally blocked phosphorylation, only to find HSF1 unaffected.

"So now we're pivoting to figure out what actually does regulate HSF1," says Pincus.

silvi rouskin

gabriel victora

Arriving at the close of 2014 as the latest Andria and Paul Heafy Fellow of Whitehead Institute, Silvi Rouskin set out to structure her lab to perform structural research—specifically, using deep sequencing technology to probe messenger RNA (mRNA) structure and its relationship to rates of protein translation and its effects on gene expression.

In addition to carrying genetic information, the linear sequence of RNA can fold into higher order structures capable of interacting with other molecules and directly catalyzing biochemical reactions. Decades of research in model organisms have shown that specific messenger RNA (mRNA) structures are critical for embryonic development and that altered mRNA structures are sufficient to cause a variety of pathologies. Yet, despite the known importance of RNA structures in regulating gene expression, the catalog of functional RNA structures is limited.

Rouskin's lab plans to expand that catalog by using the fruit fly *Drosophila melanogaster* to determine the distribution and changes of mRNA structures during oogenesis and embryogenesis and to investigate how functional RNA structures regulate mRNA localization and translation. The ultimate goal of her research is to understand the principles of RNA folding *in vivo*, how RNA structure regulates gene expression in normal cells, and what aspects go awry in the onset of disease states such as neurodegeneration and cancer.

Within the lymph nodes, cellular gladiators fight for survival. Their arena is the germinal center, and the prize is to attack invaders. As they are presented with antigens—pieces of a virus or another foreign invader—B cells are pitted against one another. The B cells that bind better to the antigens advance, and the losers are destroyed. The antibodies produced by the ultimate winner will tag their targets for destruction.

Although B cells have the potential to create an almost unlimited variety of antibodies, they may be no match for viruses, including hepatitis C, HIV, and influenza, that quickly morph their outer protein armor. Yet even these recalcitrant invaders have segments of their protein coats that must remain stable, as alterations to those segments would impair their ability to infect a host cell or maintain normal function.

"But the virus can make other parts of itself more attractive to the B cells than those necessarily stable parts," says Gabriel Victora. "Why are the B cells fooled? It has to do with how they are selected."

By studying the B cells' battle for supremacy, Victora hopes to determine the rules of engagement within the germinal centers and how to manipulate them.

community evolution

Although the mission remains the same, how it is pursued—and by whom—may change. Such was the case in 2014.

Institute News

At the close of 2014, Whitehead Fellow Yaniv Erlich left the Institute for the final time, bound for Manhattan to take on the dual roles of Assistant Professor of Computer Science at Columbia University and Core Member of the New York Genome Center (NYGC).

As the first Andria and Paul Heafy Fellow of Whitehead Institute, Erlich brought with him an unconventional research program that included developing novel algorithms with which to analyze enormous sets of genetic and genomic data. In 2013, Erlich sent shockwaves through the genomic research community when he published research showing how he was able to use simple internet searches of public resources to identify nearly 50 individuals who had submitted personal genetic material as anonymous participants in genomic studies.

Erlich, whose time at Whitehead spanned more than four years, now spends four days of each week at NYGC and the fifth at Columbia, but he's still working with familiar faces. Two members of his Whitehead laboratory moved to New York with him, while three others participate remotely. He knows his experience as a Whitehead Fellow prepared him well for this next step in his career, even if it brings with it its own challenge.

During "Get a Clue," students learned about fingerprinting from members of the Cambridge Police Department.

"Out in the world, when you're speaking at a big conference, if you're a Whitehead Fellow, you're held to a higher standard," Erlich says. "They treat you like a principal investigator. Nobody cuts you any slack!"

Public Outreach

After the bombings at the 2013 Boston Marathon forced the cancellation of Whitehead's Spring Lecture Series for High School Students, this long-running program returned in April 2014 for another successful installment.

The 2014 program, *Picture This: Neuroimaging and the Brain*, focused on the use of cutting-edge imaging techniques to explore brain function and help develop new strategies to treat a host of neurological disorders. More than 100 students from across Massachusetts arrived at the Institute for three days of presentations from some of the world's most prominent neuroscientists, tours and demonstrations in laboratories at Whitehead Institute and nearby research facilities, lunches with young Whitehead scientists, and a panel discussion on the impact of brain injuries on behavior and disease.

During the 2013-2014 academic year, Whitehead's Seminar Series for High School Teachers drew more than 60 teachers from the greater Boston area to monthly lectures as part of *Deciphering Disease in the Genomic Age*, an exploration of the inner workings of the human genome with an eye toward implications for the diagnosis, prevention, and treatment of human disease. As always, many of the participating teachers were paired with a Whitehead partner—a postdoc or grad student who volunteers to support his or her teacher throughout the year by answering questions, providing occasional supplies for classroom experiments, and perhaps visiting schools to speak with students directly.

In 2013, Whitehead Institute established a partnership with the Boston-based science education group Science from Scientists to pilot

Whitehead's CampBio program immersed dozens of middle schoolers in life sciences lessons. Here, students learn about raptors, identifying bones and bone fragments found in owl pellets.

CampBio, a week-long program designed to introduce middle school students to the wonders of the life sciences. Based on overwhelming success of the inaugural program, Whitehead expanded its offerings for middle schoolers in 2014.

One of the more exciting additions occurred during the February school vacation week, when the Institute, in collaboration with Science from Scientists, hosted *Get a Clue: CSI and the Science of Forensics*. Nearly 20 seventh and eighth graders attended the four-day session, during which they were introduced to the techniques behind crime scene investigation and discovered how forensic science works in the real world. The workshop centered on solving a mock crime, allowing the students to apply the forensic techniques they learned each day, including a lesson on fingerprinting from members of the Cambridge Police Department's Identification unit.

The summer of 2014 included two more week-long *CampBio* sessions in an effort to meet a pent-up demand for stimulating science experiences for boys and girls in the middle school demographic. At the end of the year, the Institute was delighted to secure two grants from biotechnology companies—a grant from Genzyme, a Sanofi company, to fund scholarships for student participants demonstrating financial need, and a grant from the Amgen foundation in support of scholarships and overall program enhancements. Both grants would be used to bolster Whitehead's middle school educational offerings in 2015.

honor roll of donors

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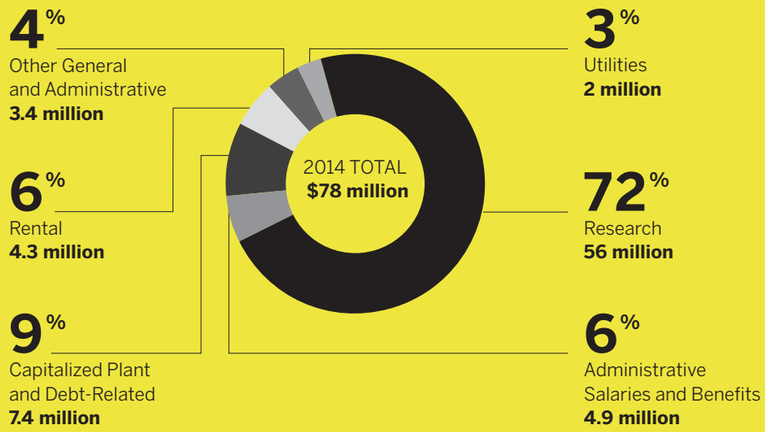


2013

Research
55.8 million (76%)

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

Administrative Salaries and Benefits
5.1 million (7%)

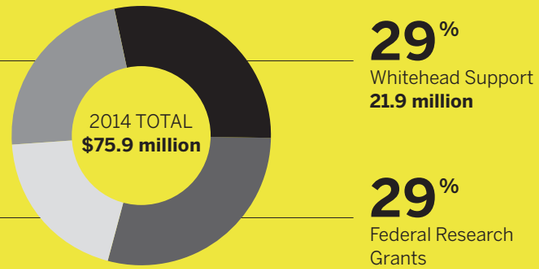
Rental
4.3 million (6%)

Other General and Administrative
2.8 million (3%)

Utilities
0.3 million (1%)

TOTAL
$73.6 million (100%)

2014 Revenues & Support



2013

Corporate and Foundation Support
15.9 million (21%)

Gifts and Other Revenue
16.4 million (22%)

Federal Research Grants
21.9 million (30%)

Whitehead Support
20.4 million (27%)

TOTAL
$74.6 million (100%)

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Whitehead principal investigators are world-class scientists dedicated to improving human health through fundamental biomedical 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).

images

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Principal Investigator & Whitehead Fellows Portraits John Goodman

Page 4 Antique Diagram (copper engraving) depicting the Eye and Optical Principles, 1798/Fotosearch **Page 6** Yuxiong Feng/Whitehead Institute **Page 7** Reprinted from *Cell Reports*, Volume 7/Issue 5, Iva Kronja, Bingbing Yuan, Stephen W. Eichhorn, Kristina Dzeyk, Jeroen Krijgsveld, David P. Bartel, Terry L. Orr-Weaver, "Widespread Changes in the Posttranscriptional Landscape at the Drosophila Oocyte-to-Embryo Transition", Pages No. 1495–1508, Copyright (2014), with permission from Elsevier. **Page 8** Sovan Sarkar/Whitehead Institute **Page 9** Theunissen TW, Powell BE, Wang H, et al. Systematic Identification of Culture Conditions for Induction and Maintenance of Naive Human Pluripotency. *Cell Stem Cell*. 2014;15(4):471-487. doi:10.1016/j.stem.2014.07.002. Licensed under CC BY 3.0. **Page 12** René Descartes, *Discours de la Méthode* (1637)/Wikipedia Commons **Page 48** Middle Temple Library/Science Source **Page 54** Ceal Capistrano/Whitehead Institute **Page 55** Ceal Capistrano/Whitehead Institute **Page 56** Ceal Capistrano/Whitehead Institute **Page 59** Ceal Capistrano/Whitehead Institute

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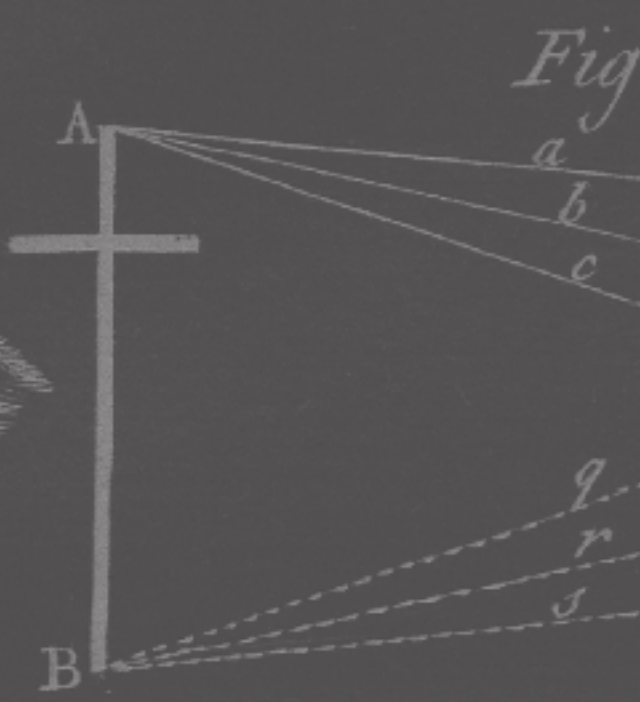

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