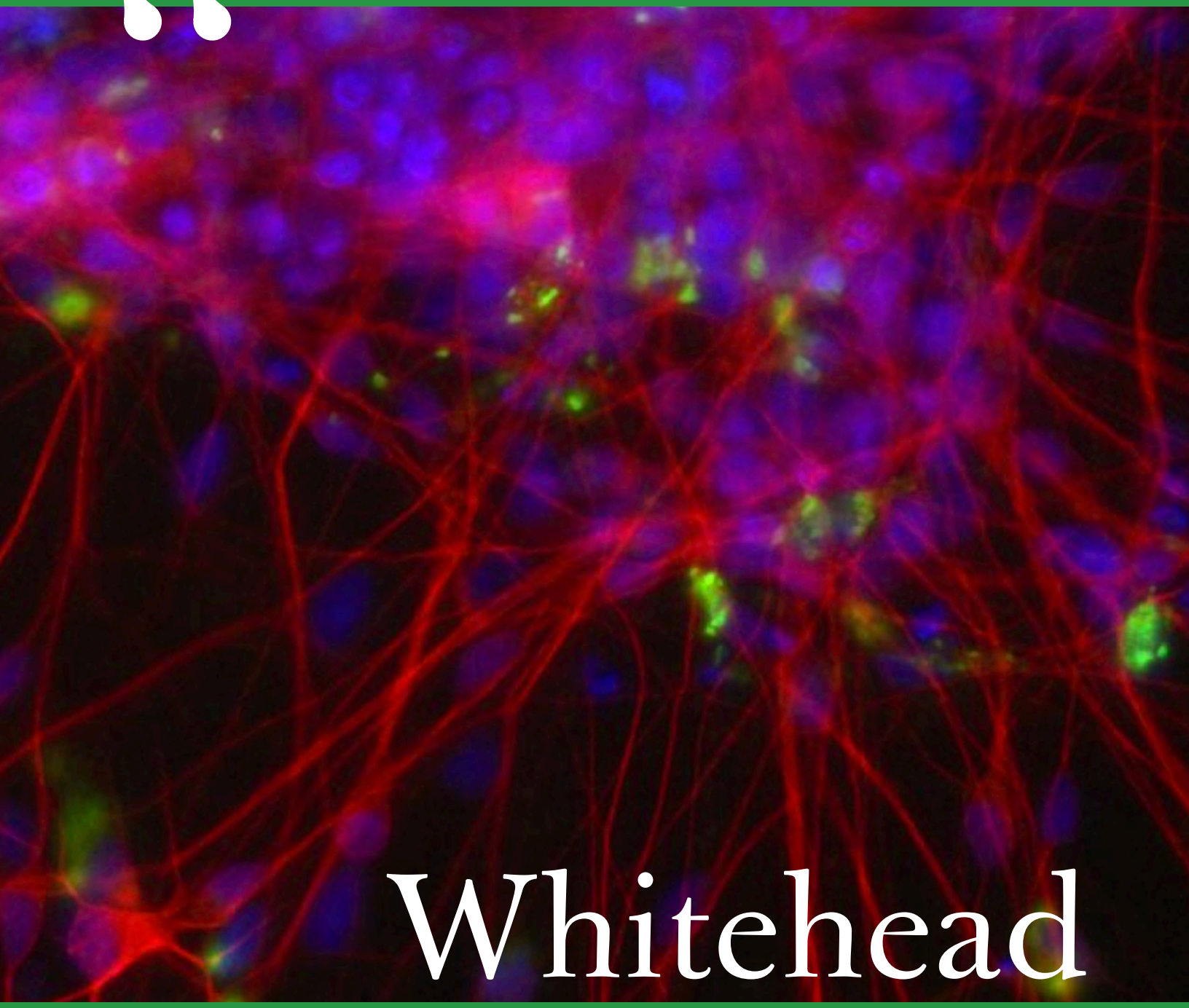


Whitehead Institute

ANNUAL REPORT 2019

Contents

The Changing Face of Discovery

For 37 years, Whitehead Institute has demonstrated an ability to drive scientific discovery and to chart paths into new frontiers of knowledge. Its continuing achievements are due, in substantial part, to the unique capacities and dedication of Members who joined the Institute in the 1980s and '90s — from Founding Members Gerald Fink, Harvey Lodish, Rudolf Jaenisch, and Robert Weinberg to those who followed, including David Bartel, David Sabatini, Hazel Sive, Terry Orr-Weaver, Richard Young, and me. Those long-serving Members continue to do pioneering science and to be committed teachers and mentors. Yet we have begun an inevitable generational transition: In the last two years, Gerry and Terry have closed their labs, and Harvey will do so this coming year.

The exigencies of time mean that, increasingly, Whitehead Institute's ability to maintain its vigorous scientific leadership depends on our next generation of researchers.

As I move toward the conclusion of my term as director, I am particularly proud of the seven current Members and the 14 Whitehead Institute Fellows we recruited during the last 16 years. The newest of those stellar researchers joined us in 2019: Whitehead Institute Member Pulin Li and Whitehead Fellow Kipp Weiskopf. Pulin studies how circuits of interacting genes in individual cells enable multicellular functions, such as self-organizing into complex tissues, and her research brilliantly combines approaches from synthetic biology, developmental and stem cell biology, biophysics, and bioengineering to study these multicellular behaviors. Kipp, a clinician-scientist who trained as an oncologist at Brigham and Women's Hospital and Dana-Farber Cancer Institute, has expertise spanning protein engineering, cell biology, immunology, translational medicine, and clinical oncology. At Whitehead Institute, he will continue studying myeloid immune checkpoints and explore their potential for new cancer immunotherapies.

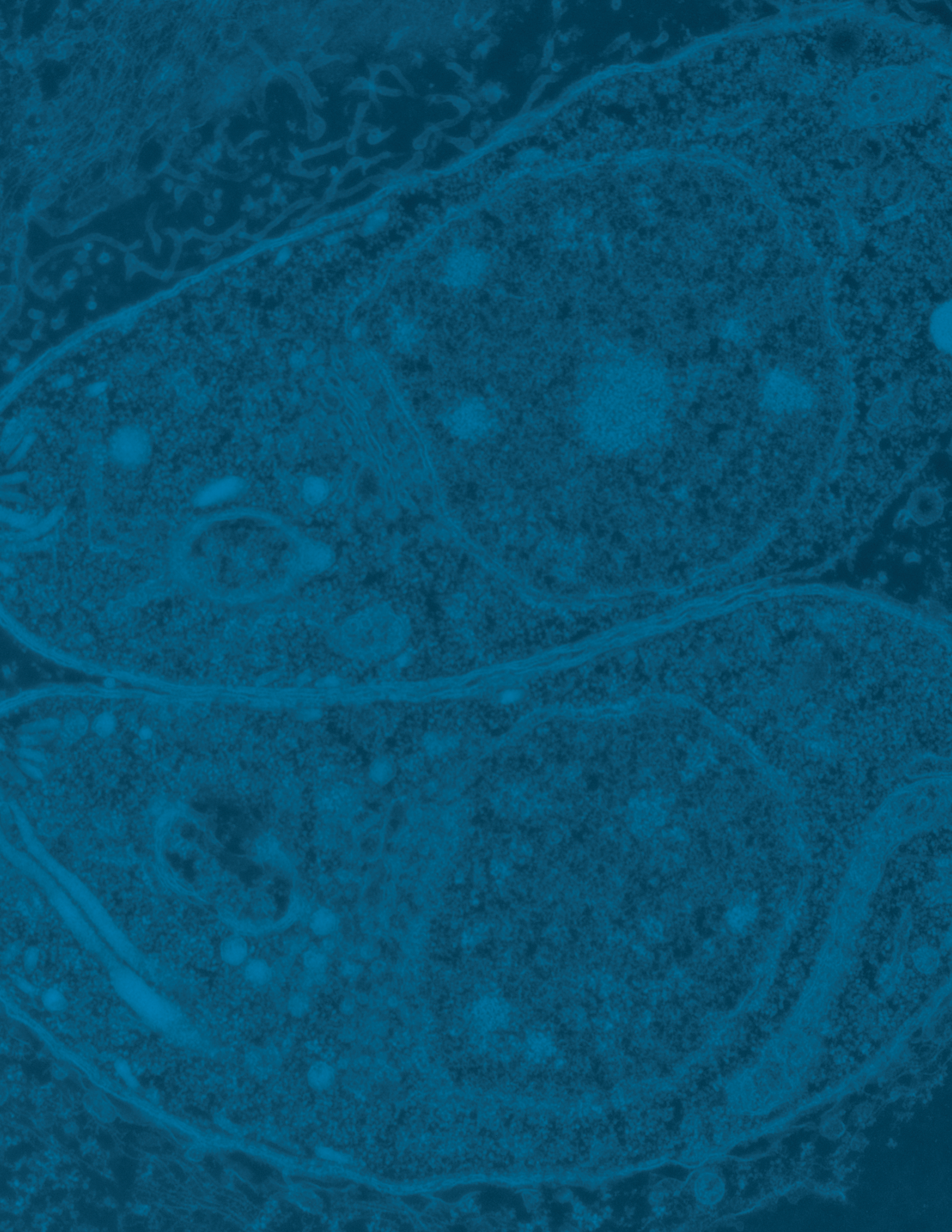
Pulin and Kipp reflect our commitment to deepen and expand our collective expertise — and to reinforce our culture of engaging in courageous science that continuously pushes the boundaries of knowledge. Since 2004, that commitment has led us to recruit early-career researchers who have matured into some of the world's finest scientists: Peter Reddien and Iain Cheeseman, who are renowned for their work on, respectively, tissue regeneration and cell division; Mary Gehring and Jing-Ke Weng, who have growing global reputations for their creative investigations of plant epigenetics and genetics; Sebastian Lourido, who is illuminating the field of parasitology; and Ankur Jain, who is helping to elucidate the role of RNA in disease.

For nearly four decades, Whitehead Institute Members have embodied scientific excellence and helped drive biomedical research forward in meaningful ways. And we are, I believe, well-positioned to carry that record forward for many years to come.

The opportunity and responsibility for defining the Institute's future will soon shift to the extraordinarily well-prepared hands of Ruth Lehmann, the globally respected cell biologist who will become director in July 2020. I am excited to be succeeded by such an accomplished scientist and leader, and I am thrilled to gain another new research collaborator — especially one with such an impressive track record of discovery.

The future is indeed bright for Whitehead Institute.

David Page
Director, Whitehead Institute



Leading Science Forward

Since its inception in 1982, Whitehead Institute has had extraordinary leadership. Founding Director and Nobel laureate David Baltimore was succeeded by a series of pioneering investigators: Gerald Fink, an internationally honored geneticist and science enterprise leader; National Medal of Science winner Susan Lindquist; and, since 2004, David Page — a MacArthur Foundation fellow and Howard Hughes Medical Institute investigator who has led the Institute with skill, insight, and success.

David now wants to devote all of his time and talent to pursuing his breakthrough research on sex differences in health and disease. In July 2020, he will be succeeded by Ruth Lehmann, continuing our line of prestigious and highly accomplished leaders. A globally respected developmental biologist, Dr. Lehmann fits the board of directors' vision for the next director. An eminent scientist and experienced leader, she is deeply committed to the Institute's mission of creative, fundamental research that can transform human health.

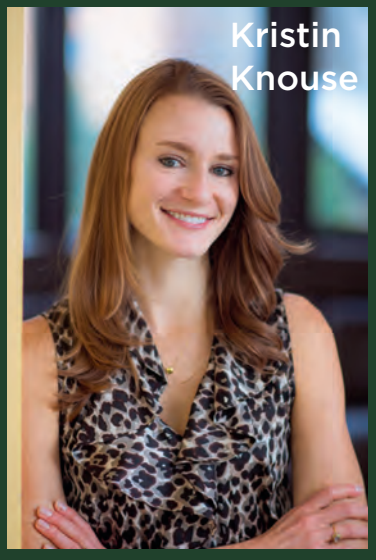
Lehmann's appointment represents a homecoming. She was a Whitehead Member and Massachusetts Institute of Technology faculty member from 1988 to 1996 before she began a distinguished 23-year career at New York University. There she has directed the Skirball Institute of Biomolecular Medicine and the Helen L. and Martin S. Kimmel Center for Stem Cell Biology and chaired the university's Department of Cell Biology.

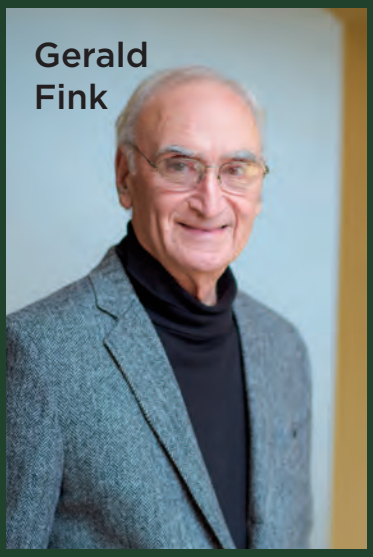
Lehmann is also a global scientific leader. She served as president of the Society of Developmental Biology and of the Drosophila Board, and she will serve as president of the American Society for Cell Biology in 2021. She has been widely honored, having been elected a member of the National Academy of Sciences, a fellow of the American Academy of Arts and Sciences, and a member of the European Molecular Biology Organization. She was awarded the Society of Developmental Biology's Conklin Medal and the Lifetime Achievement Award from the German Society for Developmental Biology.

For 37 years, Whitehead Institute has been one of the world's most influential biomedical research centers — producing a continual stream of significant discoveries and new research tools and approaches. We are confident that, in Ruth Lehmann, Whitehead Institute has a leader who will enable this persistently pioneering community of scientists and educators to extend and augment its legacy of impact for many years.

Charles D. Ellis
Chair
Whitehead Institute Board of Directors

Whitehead Members & Fellows




Gerald
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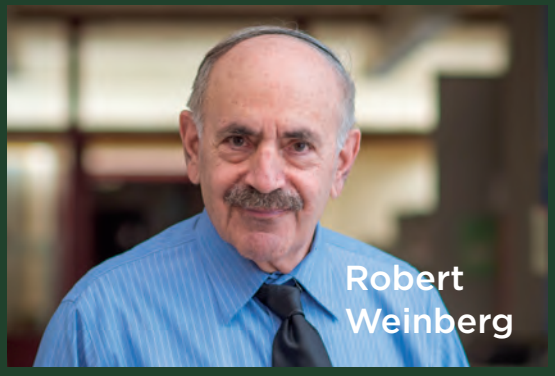
Robert
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Kipp
Weiskopf


Jing-Ke
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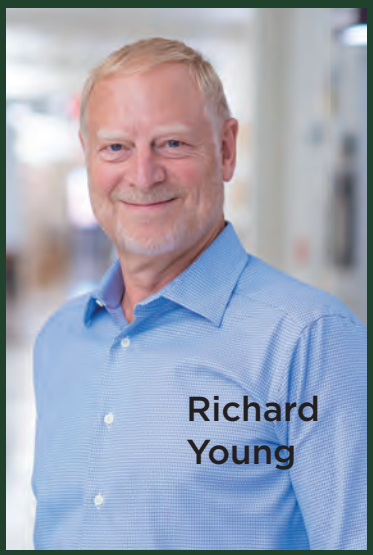

Richard
Young

Whitehead Science

Looking Beyond the GENE

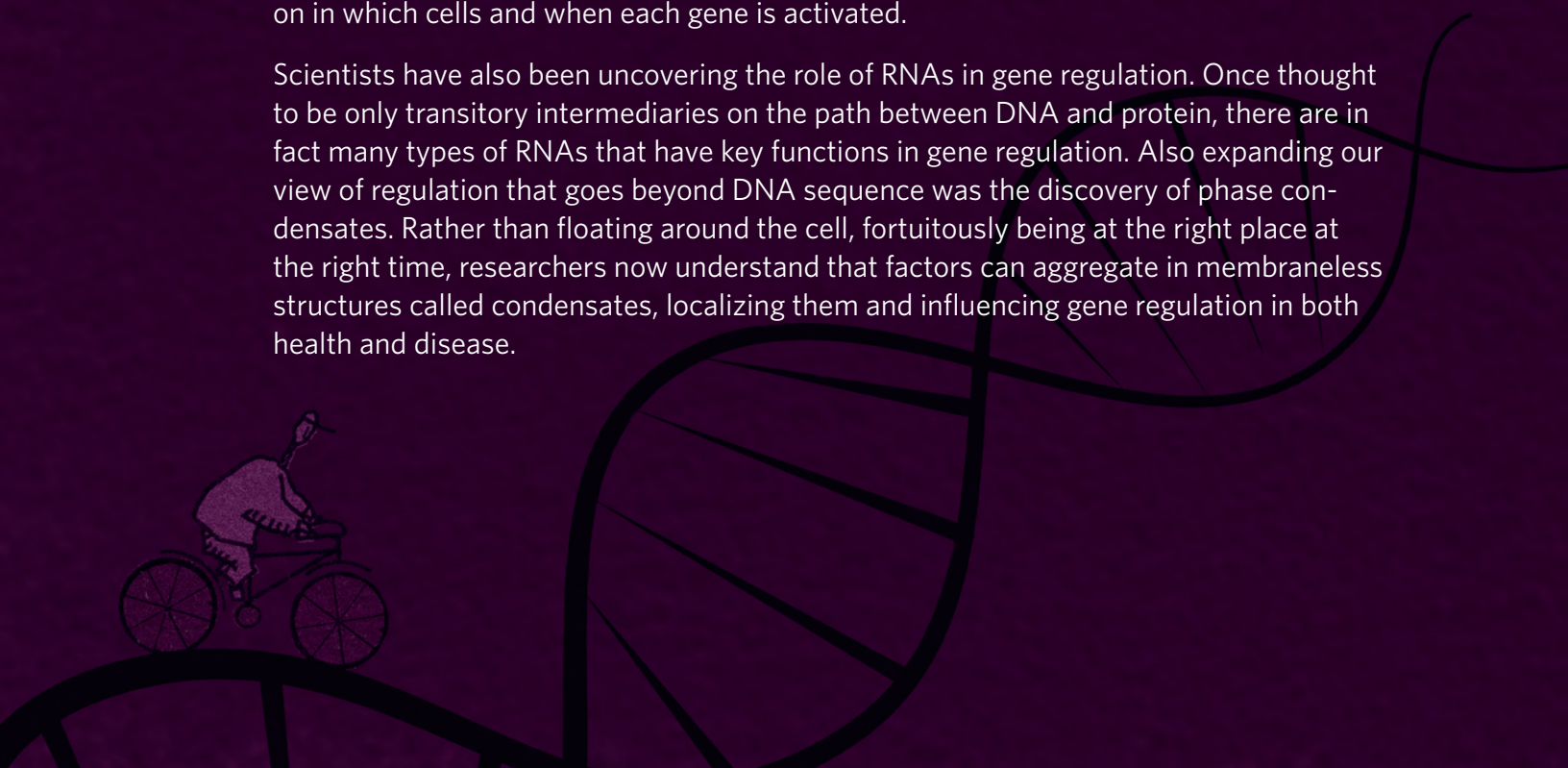
By uncovering new ways that genes are regulated, Whitehead Institute researchers are upending existing paradigms of gene expression and providing important insights into health and disease.

In order for a gene to do its particular job, it first must be read, or transcribed into RNA, and then that RNA must be translated into a functional protein. Myriad regulators influence these steps between gene sequence and final product. These regulators can determine how highly a gene is expressed or whether it is expressed at all. Therefore, in order to more fully understand the genetics underlying biological processes, researchers must identify the regulators involved.

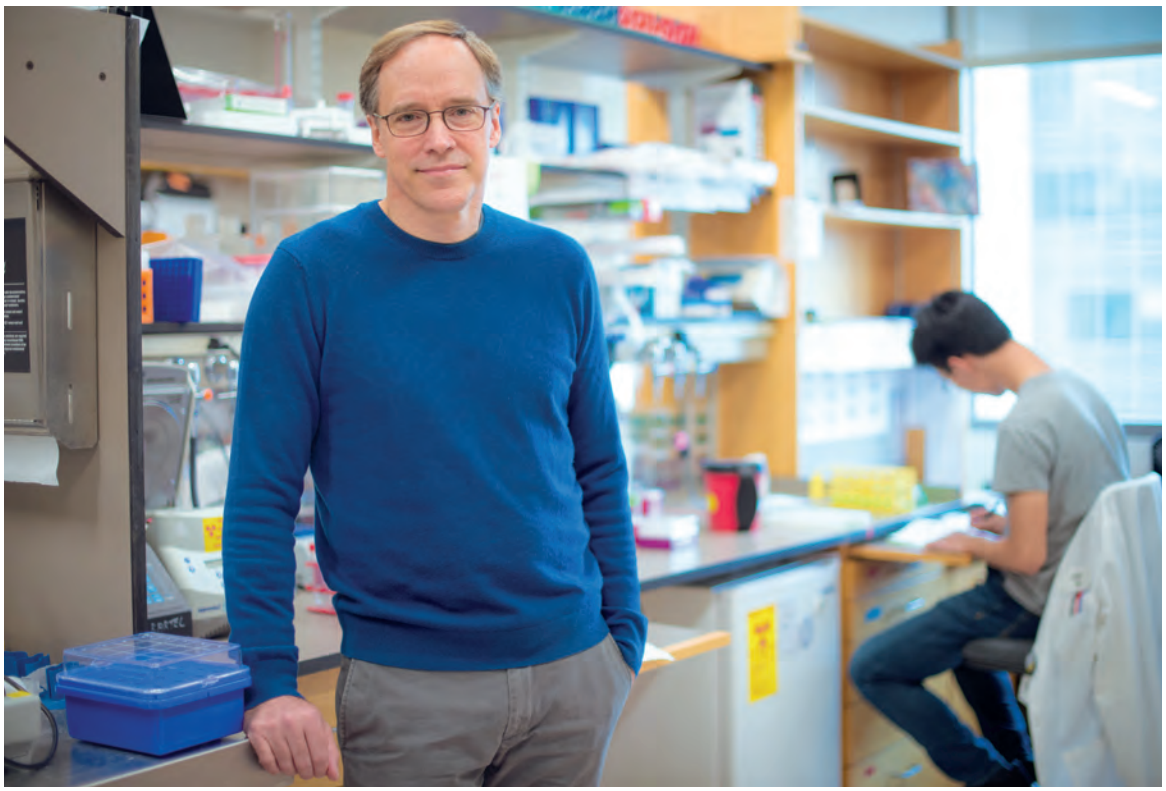
Some of these regulators have been known for a relatively long time, such as enhancers, which are DNA sequences that help increase transcription of certain genes, and transcription factors, proteins that bind to regulatory DNA sequences — including enhancers — and help control transcription rates. However, the full scope of the processes that regulate genes is still being uncovered. To that end, Whitehead researchers are investigating avenues of gene regulation that were previously unknown or not fully understood.

One area of genetic regulation that goes beyond the gene is epigenetics, in which regulatory information, independent of DNA sequence, can be passed down through generations. Mechanisms include DNA methylation — in which small chemical tags attach to DNA and, by so doing, alter the activity of a gene, often silencing it — or alterations of histone proteins, part of the packing material that helps compact DNA in the cell nucleus. Epigenetic mechanisms are necessary for embryonic development. Every cell in a developing organism has identical genes, and it is primarily epigenetic cues that enable the cells to differentiate and form distinct tissues by controlling which genes are turned on in which cells and when each gene is activated.

Scientists have also been uncovering the role of RNAs in gene regulation. Once thought to be only transitory intermediaries on the path between DNA and protein, there are in fact many types of RNAs that have key functions in gene regulation. Also expanding our view of regulation that goes beyond DNA sequence was the discovery of phase condensates. Rather than floating around the cell, fortuitously being at the right place at the right time, researchers now understand that factors can aggregate in membraneless structures called condensates, localizing them and influencing gene regulation in both health and disease.



THE SCULPTORS OF GENE EXPRESSION



As scientists have been able to explore more deeply how our genes are transcribed into RNAs called messenger RNAs (mRNAs) and how those mRNAs are ultimately translated into proteins, scientists at Whitehead Institute and around the world have uncovered hundreds of regulatory RNAs, different types of RNAs that attenuate or enhance gene expression. Collectively, their research shows that frequently it is regulatory RNAs, such as microRNAs (miRNAs), that tune protein production. At only 22 base pairs long, miRNAs may be small, but their effects resonate throughout evolution and development in both plants and animals. Whitehead Institute Member **David Bartel** likens miRNAs to sculptors of the transcriptome, chiseling away at gene expression to such an extent that, in some cases, miRNAs can trigger developmental changes. More often, miRNAs optimize gene expression, tailoring it for many genes in each cell type.

The sum is greater than the parts

Scientists may classify RNAs such as miRNAs and long noncoding RNAs (lncRNAs), another type of regulatory RNA, by length, but noncoding RNAs themselves recognize no such boundaries when they interact with each other. A case in point is a highly conserved network of noncoding RNAs acting in the mammalian brain

that was identified by Ben Kleaveland, a postdoctoral researcher in Bartel's lab. While gene regulatory networks are well described, this was the first documented regulatory network comprised of three types of noncoding RNA: two miRNAs, a lncRNA, and a circular RNA. All four components of the network are conserved throughout mammalian species and enriched in the brain, particularly in neurons, suggesting that the network may be important in brain function.

Introns: "Discarded" RNA regulates a stress response

Nestled between the sections of an mRNA that ultimately encode a protein, introns are excised shortly after transcription. Like footage spliced from a film, introns were thought to end up on the cellular cutting room floor and discarded. But with the help of Whitehead Institute Founding Member **Gerald Fink**, Jeffrey Morgan, a former graduate student in the Bartel lab, identified a group of introns in yeast that are redirected from the dustbin when the yeast population becomes too crowded for its environment. The researchers discovered that these introns constitute a previously unknown branch of the well-studied TORC1 signaling pathway that helps control cell growth during periods of stress. When activated by yeast overgrowth, the branch seems to help the cells cope with more challenging conditions.

When RNA function follows form

Regulation by RNAs is not limited to noncoding RNAs. Whitehead Institute Fellow **Silvia Rouskin** is teasing apart how RNAs fold in cells, how those structures can regulate their own expression in healthy cells, and how misfolded RNAs may be involved in diseases such as neurodegeneration and cancer. Rouskin and her lab study the human immunodeficiency virus (HIV), the virus that causes AIDS. Although many aspects of HIV have been well researched, little is known about how the virus can make all of the proteins in the correct amounts necessary for productive infection from the same starting RNA molecule.

Rouskin's work indicates that the RNA itself may regulate which proteins are produced from it. According to Rouskin, the HIV RNA folds into several distinct shapes. By exposing or hiding certain signals on its surface, it can control how the host's cellular machinery processes the RNA and which of its nine genes are expressed. HIV's success at utilizing one RNA with multiple shapes to create distinct proteins may not be isolated. Related research indicates that a similar mechanism may affect gene expression in the human brain.

A NEW PHASE OF UNDERSTANDING

Biologists once thought that molecules in the cell floated around at random, which failed to explain why these molecules turned up just where they were needed for cell processes to occur. In recent years, scientists have refined the model of cellular organization, showing that molecules form compartments and structures without membranes that are called phase-separated condensates. Whitehead Institute researchers are delving into how these condensates factor into disease and help maintain healthy cells.

Bringing the gene expression machinery together

The presence of molecules in condensates has important implications for the regulation of genes governing cell identity — including cancer-causing oncogenes. Whitehead Institute Member **Richard Young** investigates how biological condensates control vital cell processes like gene transcription. In a study led by postdocs Ben Sabari and Alessandra Dall'Agnese, Young's lab showed that the proteins that transcribe DNA into RNA coalesce into liquid-like, phase-separated condensates with properties like a droplet of oil in vinegar. Forming a condensate allows the proteins to concentrate at key genes that decide a cell's fate. These genes, Young found, are located near DNA sequences called super-enhancer regions, which provide an address for the condensate to form. If condensates develop at the wrong locations, gene regulation can break down, potentially changing the cell's identity and leading to the uncontrolled growth seen in cancer. By identifying which properties of molecules let them join condensates, Young hopes to provide insight into therapies aimed at restoring cells to healthy, regulated states.

Recent work in the Young lab added to the picture of what allows molecules to enter condensates. A study led by postdoc Ann Boija and Isaac Klein showed that transcription factors have a region that is intrinsically disordered — meaning it has a flexible, noodle-like structure — and that this property allows transcription factors to join condensates. This finding clarified a model of condensate formation, providing new ways to explore drugging condensates to control gene transcription. A study led by postdoc Eric Guo and graduate student John Manteiga identified a regulatory switch that decides which condensate a critical protein complex joins. The RNA Polymerase II (Pol II) complex is the main piece of the apparatus that reads DNA and transcribes it into RNA. Young's group showed that when a protein called a kinase chemically modifies this complex, Pol II moves from condensates involved in transcription initiation to condensates involved in processing RNA transcripts. These findings from the Young lab could help cancer researchers understand how cells move into a dysregulated state and illuminate new ways to bring cells under control.

RNA condensates and disease

Whitehead Institute Member **Ankur Jain** is extending the reach of condensate biology by studying RNA. Like DNA, RNA has an alphabet of four nucleotides — adenosine (A), cytosine (C), uracil (U), and guanine (G). Typically, researchers would examine how mutations in DNA cause dysfunctional proteins that lead to disease. Jain takes a different approach, looking at how problems in the intermediate RNAs can help explain what goes wrong in disease. He studies a group of diseases called repeat expansion disorders, which include neurodegenerative disorders such as Huntington's and amyotrophic lateral sclerosis (ALS), also known as Lou Gehrig's disease.

In these disorders, RNA molecules with high levels of Gs and Cs interact with each other through base-pairing between the Gs and Cs. This causes the RNA molecules to clump together in the cell, forming a type of condensate called an RNA aggregate. These aggregates can build up in the cell, and are thought to disrupt vital processes. A better understanding of how RNA aggregates form and change could provide ways to break them up using drugs and restore cells to their normal states.

Jain's lab is developing new techniques to visualize RNA aggregates within cells. The goal is to create methods to identify RNA clumps in tissues collected from patients, letting researchers ask new questions about RNA's role in particular diseases and how the aggregates might change over time. As neurodegenerative diseases are typically age-related, these new techniques could prove essential to figuring out what causes neurons to malfunction. In addition to examining the role of RNA aggregates in repeat expansion disorders, Jain also wants to know how interactions between RNA molecules can aid in healthy cell function. Studying RNA provides Jain with a system to ask fundamental questions about how molecules interact that nonetheless have direct applications to understanding and treating neurodegenerative diseases.

EPIGENETICS: CHEMICAL GUIDEPOSTS FOR GENE EXPRESSION

Methylation controls gene expression by altering how the cell's transcription machinery interacts with the DNA. By affecting which genes are turned on and off, methylation helps cells define which type they are — for example, muscle, liver, or skin cells. Redistributed methylation can even change cell types as they mature. In fact, the list of methylated genes in a cell, called the methylation profile, transforms during development. Appropriate methylation is critical for health as well: Abnormal methylation can contribute to cancer, diabetes, and heart disease.

Whitehead Institute scientists are researching questions that are revealing critical aspects of methylation's roles in gene regulation, such as how methylation is maintained within a cell and how it is passed down through generations.

A troubling inheritance

Altered methylation in animal genomes can persist across generations. In research that could shed light on whether methylation might play a role in how cancer seems to run in some families, Whitehead Institute director and Member **David Page** and former postdoc Bluma Lesch discovered that a mutation in a particular protein in mouse sperm leads to modified methylation of certain portions of the sperm's DNA and DNA-associated proteins and that these changes are linked to an increased frequency of cancer in the offspring produced from the mutated sperm.

In their work, Page and Lesch deleted the *Kdm6a* gene from mouse sperm, whose protein removes some of the methylation from particular histone proteins around which DNA is spooled. With the demethylating KDM6A protein absent, these histone proteins became hypermethylated, and nearby portions of the sperm's DNA are also methylated. Although most methylation in mammalian sperm and eggs is usually reset at fertilization, some of the modified sperm's increased protein and DNA methylation was passed to the offspring, either because the methylation resisted being reset or was reestablished.

The resulting mice, despite inheriting a functional *Kdm6a* gene from their mothers, appeared healthy until they hit middle age, and then showed an increased likelihood of developing a wide variety of cancers compared to mice whose methylation remained untouched. Page and Lesch have not yet investigated whether similar epigenetic inheritance occurs in humans.

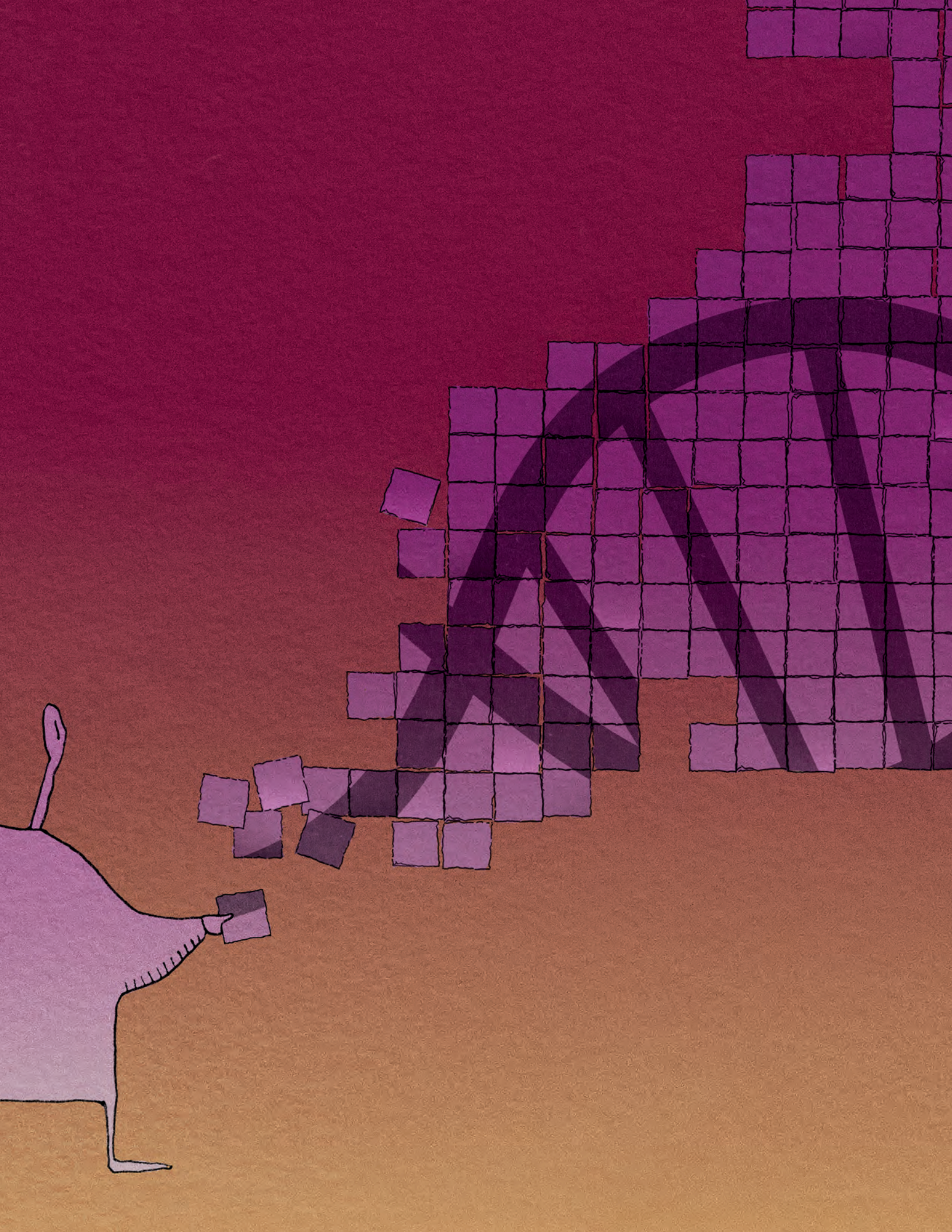
The question is not purely hypothetical. Certain cancer drugs currently in use target epigenetic mechanisms, and there has been no research into how altering these mechanisms could affect the children conceived by people taking the drugs.

Mother and father's methylation creates tug-of-war during development

In plants, many seed characteristics, such as size and number of seeds produced, are both genetically and epigenetically controlled. Understanding how this happens during development could allow scientists to identify novel ways to increase crop yields.

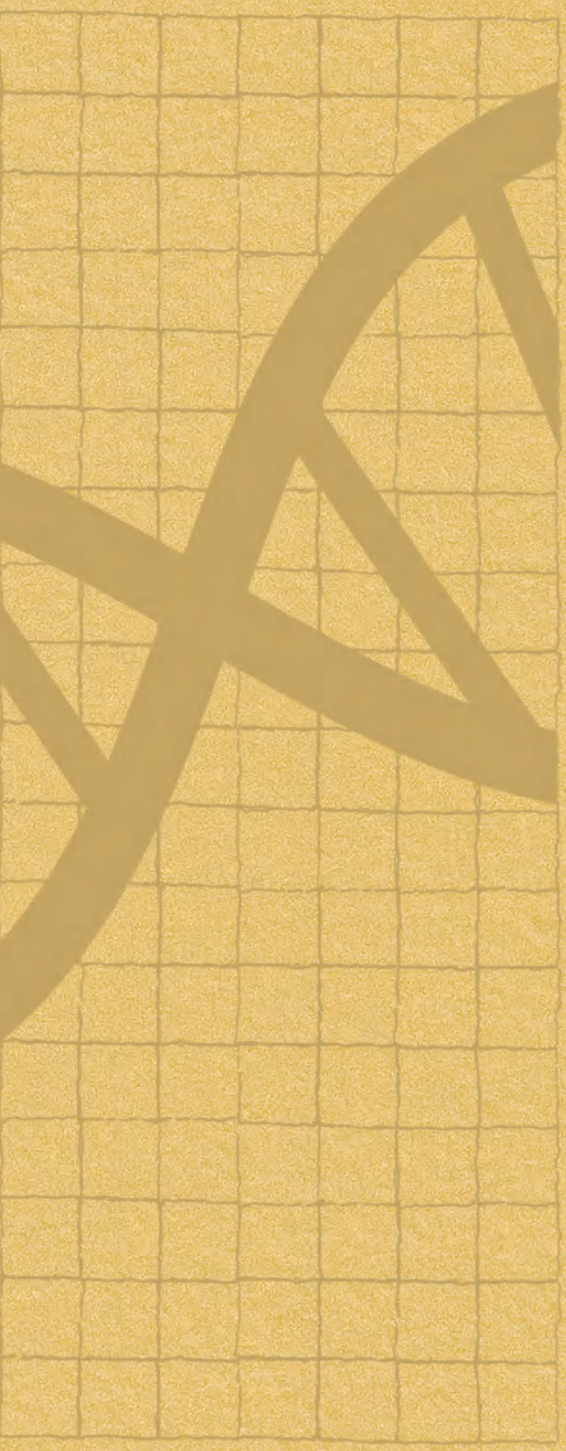
The endosperm is a plant tissue that cradles and nourishes the seed's embryo and provides two-thirds of the calories in a typical human diet in the form of wheat grains, corn kernels, and rice grains. Endosperm development provides a window into a specific type of epigenetic gene control called imprinting. In this type of gene regulation, copies of genes are differentially expressed based on whether they came from the seed's mother or father. This distinct expression is often associated with different DNA methylation patterns on each copy of the gene. Due to imprinting, only the mother's or father's copy is expressed for about 200 genes in the cells of the endosperm.

Imprinting is thought to have evolved because of a genetic tug-of-war between mothers and fathers. It is in the interest of the mother, whose seeds can be fertilized by numerous fathers, to nourish all of the seeds equally, no matter their father. But each father wants its seeds to outperform the seeds from other fathers and pushes the mother to devote more nutrients to his offspring. This parental tension can have significant effects. Work by Daniela Pignatta, Katherine Novitzky — former researchers in **Mary Gehring**'s lab — and Gehring has demonstrated that altering the imprinting of the gene HDG3, a gene that controls the expression of other genes involved in plant patterning and development, is sufficient to affect seed size and the timing of seed development.



Pixels to PICTURES

Whitehead Institute Members are synthesizing individual findings to build a deep, comprehensive understanding of their areas of research.



Individual research projects tend to have a narrow focus. They might ask questions about the role of a specific gene or a small set of genes related to a particular trait or disease. They might seek to understand the expression or function of a particular protein in a specific tissue type or at a certain point in the cell cycle. But over time, Whitehead Institute Members are synthesizing these individual findings to build a deep, comprehensive understanding of their areas of research. Our scientists fill in the picture of how biological processes work, pixel by pixel, until the whole image becomes clear.

BUILDING A BODY MAP

Planarians are next to invincible to injury thanks to their extensive powers of regeneration. If one of these freshwater worms is chopped into many pieces, each piece will regrow its missing parts to become a fully functional worm. Whitehead Institute Member **Peter Reddien** has spent well over a decade working to understand how planarians achieve their remarkable feats of restoration. Over the years, he has used his learnings to build a comprehensive picture of the genes and processes involved in regeneration.

Reddien has illuminated the guidelines that the worms' stem cells, called neoblasts, operate under to ensure accurate regeneration. First, he found that the neoblasts are guided by positional control genes (PCGs), which are expressed in muscle tissue and create a sort of GPS system to direct cells to make the right identity choices and find the right destinations during regeneration and normal cell turnover. Later, he found that cells also rely on their proximity to regenerating organs to determine where to go, which helps avoid errors caused by the temporary discrepancy between the PCG body map and the animal's anatomy after a wound.

Because muscle tissue is so important to regeneration as the source of PCGs, Reddien has been investigating what other roles it plays in planarian biology. Recently, he and graduate student Lauren Cote found that muscle also functions as planarians' connective tissue, the stuff that provides structural support for the body and secretes the extracellular matrix — the material between cells. Based on these findings, Reddien speculates that connective tissue might have a role in regeneration, both in planarians and much more broadly in animals.

Building a more complete picture of a biological process such as regeneration often involves not only adding new discoveries but revising previous assumptions. Recently, Reddien and graduate student Aneesha Tewari discovered that a set of processes that facilitate repair and regeneration near wound sites in planarians and

other animals capable of regeneration, the missing tissue response, is not, as they had expected, essential for regeneration. Their findings suggest that the missing tissue response does not kickstart regeneration but rather accelerates it. This discovery simplifies the list of essential ingredients needed for regeneration.

PRODUCING NATURE'S MEDICINES IN THE LABORATORY

Whitehead Institute Member **Jing-Ke Weng** is studying how plants produce the rich variety of chemicals that help them interact with their environments, many of which have medicinal properties that have made them mainstays of traditional global medicine for hundreds or even thousands of years. Many of these plants are hard to cultivate or would be endangered by overharvesting. In order to harness their useful chemistry sustainably, Weng has developed a scalable system for producing molecules of interest from these plants in the laboratory as well as ways to tweak the molecules to further improve their medicinal properties. First, Weng

determines the pathway that the plant uses to produce the molecule of interest, identifying all of the genes involved. Then he puts copies of these genes into something that grows quickly, like bacteria, yeast, or the tobacco plant, so that they will begin to produce the molecule. These organisms are easy to maintain at scale, allowing for the molecule's mass production. The system also lets Weng produce modifications on the molecule of interest by inserting slightly varied combinations of genes into the tobacco or microbes, so researchers could test and tailor the molecules to create better, safer therapeutics.

Recently, Weng and postdoctoral researcher Tomáš Pluskal used this model to determine how kava, a plant that has been used for thousands of years in Polynesia to make a calming drink of the same name, produces its anti-anxiety and pain relief molecules (called kavalactones). They then demonstrated that the kavalactones could be mass-produced in bacteria and yeast.

Meanwhile, Weng and postdocs Bastien Christ, Chengchao Xu, and Menglong Xu also found the evolutionarily new biochemical pathways that allow Himalayan paris (*Paris polyphylla*), which has wound-healing properties, and fenugreek (*Trigonella foenum-graecum*), which promotes lactation, to synthesize diosgenin, a steroidal natural product serving as the single most important precursor for the world steroid hormone industry. The researchers again applied their findings to create a better production model, engineering yeast and the tobacco plant to produce diosgenin.

Out of these investigations into specific molecules of interest, Weng has built a widely applicable model for drug discovery and development from plants, combined with sustainable mass production, that he hopes will be adopted by others in order to harness the full potential of the plant world's diverse chemistry.

BEYOND X AND Y

A GROWING UNDERSTANDING OF SEX DIFFERENCES IN HEALTH AND DISEASE

For decades, Whitehead Institute Member and Director **David Page** has studied and uncovered insights into the sex chromosomes, the X and Y chromosomes that determine biological sex. However, in recent years he has transformed the focus of his lab to understanding the broader biology of sex differences throughout the body. When most people think of sex differences, they think of the sex chromosomes, sex hormones, and the reproductive tract — but a growing body of evidence is uncovering that sex differences exist on a cellular and molecular basis throughout the body, not just in the gonads.

These differences, despite their likely significance in health and disease, have been poorly understood. Men and women differ in disease risk, prevalence, symptoms, and/or outcomes in a variety of cases. For example, while women are more prone to autoimmune diseases like lupus, men are more likely to suffer from certain forms of heart disease. The biology underlying these sex biases has been largely unknown, but Page suspected that molecular sex differences play a role.

This year, work by Page and graduate student Sahin Naqvi supported that hypothesis. They found that thousands of genes in tissues across the body have sex-biased expression, meaning that while the gene is identical in males and females, its products and effects are more pronounced in one sex than the other. Some of these sex biases are conserved across mammals, while others are specific to a species or lineage (like primates). Page's team then demonstrated that sex-biased gene expression contributes to the average difference in height between men and women, an easy-to-measure test case supporting the idea that such biased expression has functional consequences.

Though the researchers used height as a classic first example, the lab expects that further research into sex-biased gene expression will provide similar insights in cases of health and disease. To that end, they have amassed a database of sex-biased genes in 12 tissue types in five different mammalian species, including humans and animals commonly used in medical research. With this research, Page is uncovering that while scientists have been working with a rather narrow picture of the impacts of sex on biology, in fact there is a complex tapestry of molecular differences throughout the body waiting to be illuminated.

PIECING TOGETHER THE COMPLEX CHOREOGRAPHY OF CELL DIVISION

Cell division is a carefully choreographed dance that all participants must execute faithfully and on time. Chromosomes must be duplicated, aligned, evenly divided into matching sets, and firmly but carefully pulled to opposite sides of the cell before two new daughter cells form around them. Cells rely on complex machinery to carry out the steps of cell division, and if anything goes wrong — if any of the machinery is broken or missing — there can be serious consequences, such as missegregation of chromosomes resulting in cells with the wrong number, which can have implications for development and disease.

Whitehead Institute Member **Iain Cheeseman** studies the machinery of cell division, focusing on the kinetochore, a large complex of proteins that assembles in the center of chromosomes during cell division and connects them to microtubules, hollow protein tubes that pull paired chromosomes apart so one of each pair ends up in each daughter cell. Cheeseman's group has discovered much about the structure, function, and interactions of individual parts of the kinetochore, and from these insights they have developed a deeper understanding of how the machinery of cell division accomplishes its delicate task.

For 12 years, the Cheeseman lab has focused on how cells divide. In recent work, they studied these core processes instead in cells that are not undergoing division. In the human body, cell division is the exception, with most cells existing in a non-dividing state. This made Cheeseman and postdoc Zachary Swartz wonder how cells preserve the ability to divide long-term, especially in cells like human oocytes, egg precursors that may lay dormant for decades before undergoing division.

A key challenge that these cells face is how to preserve the kinetochore and other cell division machinery. The kinetochore assembles at a specific part of the chromosome, a region of DNA in the middle of chromosomes called the centromere. This region is defined by the proteins that assemble there, including a critical protein called CENP-A. Without CENP-A, the centromere won't function correctly during cell division, and chromosomes will not be accurately transported into nascent daughter cells. However, proteins such as CENP-A degrade over time.

The researchers discovered that, whereas CENP-A was thought to be static, in fact cells actively maintain their proliferative capacity by replacing and replenishing their CENP-A over time. However, they found that differentiated cells, cells that have become highly specialized and no longer divide, do lose their CENP-A, which would prevent their further proliferation and possibly explains why some tissues such as muscle only rarely develop cancers. This suggests that CENP-A could be a useful signal to identify which cells are still capable of division. Altogether, these findings paint a richer picture of the centromere as a dynamic entity whose maintenance is crucial for cellular health.

CONSTRUCTING THE FRAMEWORK OF HUMAN REGENERATION

As Whitehead Institute Fellow **Kristin Knouse**'s lab enters its second year, Knouse is asking a number of questions whose answers together should shed light on the regenerative capacity of human organs. Knouse is getting at this bigger picture by investigating the liver, an organ that has the rare ability to regenerate and recover from even serious injuries.

Humans have several tissue types that renew themselves regularly or can heal from wounds, such as skin and the intestinal lining. These tissues rely on stem cells, cells that can proliferate and differentiate into a range of cell types. What Knouse finds fascinating about the liver is that it is the only human organ in which differentiated cells, cells that have become fully specialized to perform specific tasks in a specific tissue type, retain the ability to proliferate. In other organs, once cells become differentiated, they stop being able to divide and proliferate. Without a stem cell reserve or the ability to return to a proliferative state, these tissues have no options for regeneration. This is why if a person suffers injury to part of their heart or brain, the organ can't replace the missing cells. But if a person injures part of their liver, some of the liver cells begin to proliferate, dividing and generating replacement liver.

Using mice, Knouse is working to understand what makes liver cells capable of this sort of regeneration when other cell types are not, with the hope that this research could one day contribute to regenerative therapies for events such as stroke, heart attack, and neurodegeneration.

In order to study these questions, Knouse's lab is tracking individual liver cells to determine whether all liver cells can proliferate and what must happen for them to transition back into a state of proliferation. Her lab is also researching which genes are linked to proliferative capacity and why other cell types — specifically heart cells — do not proliferate when they receive the same stimuli that would activate stem cell or liver cell proliferation. Together, these studies will provide a richer understanding of cell proliferation with the additional potential to inform regenerative medicine.

PUMPING UP RED BLOOD CELL PRODUCTION

Red blood cells are the most plentiful cell type in our blood and play a vital role transporting oxygen around our body and carbon dioxide waste to the lungs. Injuries that cause significant blood loss prod the body to secrete a one-two punch of signals — stress steroids, such as glucocorticoids, and erythropoietin (EPO) — that stimulate red blood cell production in the bone marrow. For over 20 years, Whitehead Institute Founding Member **Harvey Lodish** has investigated the effects of glucocorticoids on red blood cell production. Recently, Lodish and postdocs Hojun Li and Anirudh Natarajan refined their understanding of how stress steroids — glucocorticoids in particular — increase red blood cell production and how early red blood cell progenitors progress to the next stage of maturation toward mature red blood cells.

These findings are especially important for patients with certain types of anemias that do not respond to the clinical use of EPO to stimulate the final stages of red cell formation, such as Diamond-Blackfan anemia (DBA). In this rare genetic disorder, the bone marrow does not produce enough early red blood cell progenitors, called burst-forming unit—erythroids (BFU-Es), that respond to glucocorticoids. In both healthy people and DBA patients, these BFU-Es divide several times and mature before developing into colony-forming unit—erythroids (CFU-Es) that then, stimulated by EPO, repeatedly divide and produce immature red blood cells that are released from the bone marrow into the blood. The lack of BFU-Es in DBA patients means that the glucocorticoid signal has a limited target, and the cascade of cell divisions that should result in plentiful red blood cells is contracted and instead produces an insufficient amount.

One of the standard treatments for DBA is boosting red blood cell production with high doses of synthetic glucocorticoids, such as prednisone. But the mechanisms behind these drugs and their normal counterparts are not well understood. By deciphering the mechanisms by which glucocorticoids stimulate red cell formation, scientists may be able to identify other ways to stoke CFU-E production — and ultimately red blood cell production — without synthetic glucocorticoids and the harsh side effects that their long-term use can cause. Work this year from Lodish, Li, and Natarajan has helped decipher how BFU-Es progress through their maturation process.

By looking at gene expression in individual BFU-Es from normal mice, Li and Natarajan determined that the developmental progression from BFU-E to CFU-E is not a sudden switch, as previously thought, but is instead a smooth continuum. They also found that, in mice, glucocorticoids exert the greatest effect on the BFU-Es at the beginning of the developmental continuum by slowing their developmental progression without affecting their cell division rate. In other words, glucocorticoids are able to effectively compensate for a decreased number of BFU-Es by allowing those that do exist, while still immature, to divide more times.

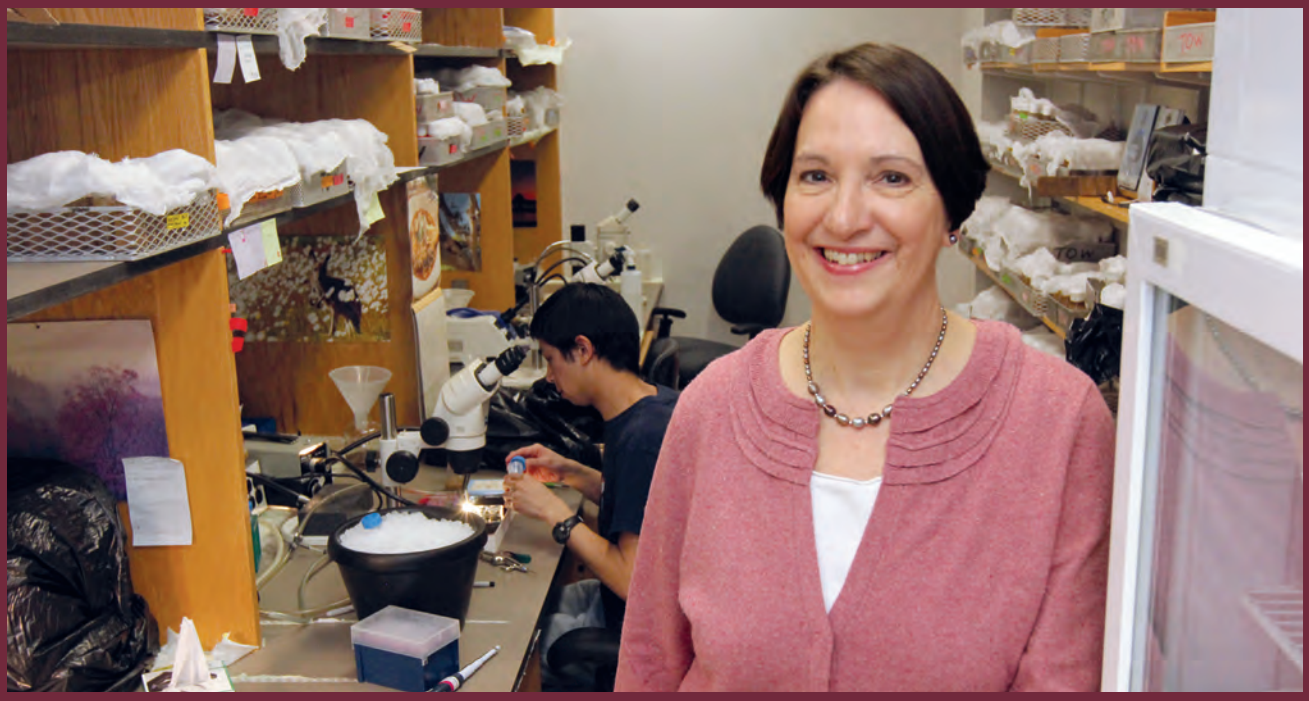
Li and Natarajan's work reveals previously unknown aspects of the mechanism by which glucocorticoids stimulate red blood cell production. With this better understanding, scientists are one step closer to pinpointing more targeted approaches to treat certain anemias such as DBA.

Terry Orr-Weaver: On Fostering Science's New Vanguard

For 32 years, Terry Orr-Weaver was a Member of Whitehead Institute and a professor in the Department of Biology at the Massachusetts Institute of Technology (MIT). Over the course of her career, Orr-Weaver became an internationally respected and honored scientist. Her investigations have illuminated fundamental aspects of the cell cycle and provided insights into diseases caused by breakdowns in cell division, including cancer and certain birth defects. Among many scientific achievements, she discovered two proteins crucial for proper partitioning of chromosomes during meiosis and revealed new players in molecular pathways leading to cancer. She has more than 175 scientific publications to her credit.

Orr-Weaver has been widely recognized for her accomplishments. She is an elected member of the National Academy of Sciences, an elected fellow of both the American Academy of Microbiology and the American Association for the Advancement of Science, and an American Cancer Society research professor. She received the Excellence in Science Award from the Federation of American Societies for Experimental Biology. She also has held major leadership roles, serving as president of both the Genetics Society of America and the National Drosophila Board as well as chair of the Damon Runyon Cancer Research Foundation's Scientific Advisory Committee.

From the outset of her career, in addition to running a highly productive research lab, Orr-Weaver committed substantial time and energy to being an educator and mentor. She is lauded by generations of students and young researchers for the deep engagement she brought to her roles as teacher, lab leader, and mentor to colleagues at all stages of their careers. As part of her commitment to training future scientists, Orr-Weaver also guided the Whitehead Fellows Program — working hard for nearly a decade to broaden the diversity of this prestigious, globally recognized, and highly sought-after program.



Clockwise from top: Terry Orr-Weaver in her lab in 2018 [credit: Allegra Boverman]; with Whitehead Member Hazel Sive in the mid-1990s; and with her lab colleagues, heading to a Whitehead Institute Holiday Party.

This past year, Orr-Weaver retired from Whitehead Institute and from the MIT faculty. Here she shares her experiences and perspectives on fostering the next generation of scientists.

Growing up, I had little interest in science until I was inspired by a wonderful high school chemistry teacher, Mrs. Richardson, who had us do lots of experiments in her class. I went on to study chemistry at the University of California, San Diego, where I did research in two faculty members' labs and really enjoyed the experiences. Those two researchers actively mentored me and helped me see science as a possible career. Ultimately, I was the first person in my family to graduate college — and the first to pursue a science-related career. I went on to receive a Ph.D. in biological chemistry from Harvard University and was the first graduate student advised by Nobel laureate Jack Szostak, who discussed my research in his Nobel biography.

After my postdoctoral research at the Carnegie Institute, I joined Whitehead Institute and the MIT faculty. From a young scientist's perspective, there may have been no better place to be: David Baltimore and the Institute's Founding Members had created a highly effective research organization that had almost immediately jumped to the forefront of bioscience innovation. It also had — and still has — a supportive and collaborative culture for young scientists. Thus, it provided me both a unique opportunity and a personal challenge; I was the first woman appointed to be a Member.

As I built my lab, I had many decisions to make. Among the most consequential were determining the research strategy and how to deploy the graduate student and postdoctoral researchers who joined the lab. The dominant paradigm at the time was to choose a core focus, a single important research question, and break it down into a series of narrow projects that students and postdocs would pursue. But I felt that approach was constraining for those researchers-in-training. I believed then — and even more so now — that it was essential to help them design projects that sparked their imaginations and fed their passions for science.

Further, I thought that our projects must start by addressing fundamental biological questions and problems rather than focusing on using particular approaches and techniques. I wanted each researcher to feel ownership of their project, to recognize and accept the personal responsibility involved in designing and pursuing their own projects. That sense of ownership needed to begin in the choice of questions to address and the freedom to choose the technical approaches they would apply. I feel that the consequence of taking this approach over the years has been a corps of creative and self-directed scientists with the ability to employ whatever technique is optimal and to adapt to the continuing emergence of new approaches and technologies.

Operating on those principles, the lab pursued work on three broad and related initiatives: the biological processes driving, respectively, chromosome segregation, the mechanisms through which replication of DNA is altered for developmental strategies (such as to control cell size or permit rapid development), and the transition from a mature oocyte into a fertilized embryo.

In the lab's early years, more senior colleagues would periodically question the approach, suggesting that it was risky for the advancement of my career. They worried we were spreading our resources too thin and would not be able to invest sufficient time and energy to overcome the inevitable setbacks that littered the road to finding the answers we sought. They also expressed concern that we would advance too slowly and fall behind other researchers who were pursuing similar questions. I suppose that their concerns had a certain validity; our approach did slow the progress of any single project. But the narrow focus that many researchers recommended didn't accord with my own vision of the science. It was also a risk-averse approach that felt at odds with the bold mission of Whitehead Institute. And it certainly would not have let me create as rich and engaging a lab experience for my young researchers as I believed they deserved.

In the end, our approach proved highly productive. Over the years, we made important discoveries about the fundamental biological problems we had chosen to study. For example, we were the first lab to identify MEI-S332 (Sgo), a protein essential for accurate chromosome partitioning in meiosis. We discovered the *pan gu*

gene and elucidated its key role in the oocyte-to-embryo transition. We found the Drosophila DUP protein and the human version (Cdt1), which are the throttle controlling the onset of DNA replication. We discovered how organisms can generate large cells by increasing DNA content. These and many other findings from our lab have been foundational for the field's continuing studies. They have also provided fundamental knowledge of how cancer and birth defects develop and progress; and the human versions of MEI-S332 and DUP have been shown to be associated with cancer when incorrectly regulated.

Perhaps as important as our scientific achievements, the lab helped shape the careers of more than 50 scientists who are conducting research and teaching at institutions such as Dartmouth College and Vanderbilt University, or are working at leading biotech companies.

My own educational experiences helped shape what has become, for me, a continuing emphasis on teaching and mentoring and on supporting the development of young scientists in other ways. I view launching the next generation of scientists as a crucial mission. As an MIT faculty member, I welcomed the opportunity to convey the excitement of science in the classroom. In developing my craft as a teacher, I was guided by my MIT biology department colleagues, especially Whitehead Institute Founding Member Gerald Fink and Robert Horvitz, who is the David H. Koch Professor of Biology at MIT. From Gerry and Bob I learned many things, especially the importance of conveying key concepts in a clear, big-picture way — not getting mired in the details of a given organism or imposing a narrowly focused technical lens as the sole way to understand an idea.

Classroom teaching and direct mentoring of students and postdocs in my lab were essential and important. But I came to understand that they were not sufficient, that there were additional ways I could advance the development of young scientists. In particular, it was — and still is — critical to encourage more young women to enter science, to support their career advancement, and to ensure that they have equitable access to resources and leadership roles when they become senior scientists.

Thus, I accepted the presidencies of the Genetics Society of America and the National Drosophila Board for several reasons. First, to help make the case for strong federal support for basic science, which continues to lag — to our nation's peril. Second, to expand the organizations' mentoring and outreach efforts, helping to increase the number of smart and committed young people choosing careers in life sciences. And third, because I wanted, by my example and through my advocacy, to assert the right and importance of women scientists to be leaders in their academic institutions, fields, and scientific organizations.

That is also a reason why I served on the graduate committee overseeing the MIT Ph.D. program in biology for more than 25 years and co-chaired the program for four years. And it is why I led the Whitehead Fellows Program. The Fellows Program provides the environment and resources to permit talented young scientists to launch their research visions — and has a tremendous track record of producing scientific leaders. During my time as program director, we worked hard to enhance the Fellows' diversity through expanded nationwide outreach efforts. We substantially increased the proportion of women who have been named Fellows; in fact, three of the four current Fellows are highly accomplished women.

Fostering the next generation of scientists is critical. We must inspire more young people to enter science. And it is crucial that we ensure adequate funding for their training, countering national trends of reduced support. As a nation, we must pay forward the tremendous benefit we have received from training previous generations of scientists. It is the only way science will truly flourish. As for myself, I have never forgotten the debt I owe my undergraduate science mentors — professors Percy Russell and Susan Taylor — for recognizing my potential and helping set me on my path to basic science research and a rewarding career as an investigator, educator, and leader. Now, as I consider how to focus the next phase of my career, I am committed to continuing the broader mission that Susan and Percy — and Mrs. Richardson — chose for themselves: guaranteeing that the next generation of scientists is robust and that each budding scientist is able to pursue their full potential for discovery and leadership.

Avid mountain hiker Terry Orr-Weaver above Machu Pichu (right); and (left, top to bottom) hiking the Presidential Traverse in New Hampshire, on Washington State's Mt. Rainier, and with sons Matthew Weaver (left) and Nathaniel Weaver (right) in the Peruvian Andes.

Exposing VULNERABILITIES

Through fundamental discovery, researchers at the Institute are increasing their grasp of how biology ticks and defining fresh paths to potential novel therapies in the future.

Whitehead Institute scientists are uncovering key components of the pathways and processes essential for growth and survival. These same critical components that drive our biology may, at the same time, point to vulnerabilities or Achilles' heels that could be targeted to treat or even prevent disease or infection. Through fundamental discovery, researchers at the Institute are increasing their grasp of how biology ticks and defining fresh paths to potential novel therapies in the future.

MAKING SENSE OF GROWTH AND METABOLISM

Whitehead Institute Member **David Sabatini** is probing the basic mechanisms that regulate growth — the process whereby cells and organisms accumulate mass and increase in size. The pathways that control growth are often hindered in human diseases like diabetes and cancer. Sabatini and his lab are identifying and characterizing these mechanisms in order to understand their roles in normal and diseased mammals. One of the pathways of interest to Sabatini is called the mechanistic target of rapamycin complex 1 (mTORC1) pathway. This pathway coordinates cellular growth with metabolism by sensing levels of amino acids, growth factors, and other elements, and adjusting energy generation, protein production, and other cellular processes. Many of these decisions take place in the mitochondria, where the cell's energy is produced, and in the lysosomes, the cellular recycling bins that break down proteins, fats, and carbohydrates. Sabatini, who first discovered the core mTOR factor as a graduate student, and his lab are figuring out how the mTORC1 pathway senses various elements to effectively regulate growth.

Nora Kory, a postdoc in the Sabatini lab, is studying the role that mitochondria play in a particular aspect of metabolism called one-carbon metabolism. This process is required for the creation of many important fats,

nucleotides that comprise DNA and RNA, and amino acids that are the building blocks of proteins. Because these molecules are crucial for the growth and proliferation of cells, many quickly-dividing cancer cells rely on one-carbon metabolism to support their growth. Transport of the amino acid serine into the mitochondria is a key step for one-carbon metabolism, yet the mitochondrial serine transporter has been unknown. Using a CRISPR-Cas9 mediated genetic screen in human cells, Kory identified the transporter as sideroflexin 1 (SFXN1). The protein is overexpressed in many cancers, including leukemias and lymphomas, which suggests that it could be a point of vulnerability that could one day be targeted by cancer therapies.

Some members of the Sabatini lab are also studying diseases that result when the mitochondria or lysosomes do not function normally. By understanding what goes wrong to cause these diseases, the researchers hope to gain insight into the processes that drive proper function and also potentially highlight therapeutic targets for when these processes go awry. Sabatini lab postdoc Raghu Chivukula is investigating familial pulmonary fibrosis, a genetic disease which affects the lysosomes in lung cells. By analyzing the biochemistry of these lysosomes, Chivukula wants to understand how their malfunction can make lung cells vulnerable to fibrosis and how normal lysosomes should function. Postdoc Jessica Spinelli is probing how mitochondria adapt to nutrient availability. Spinelli is particularly interested in how mitochondria, which usually require oxygen to function and should be vulnerable to inadequate oxygen, are able to adapt to the low oxygen levels that exist in certain portions of the intestine and in some microenvironments within cancerous tumors.

IDENTIFYING GAPS IN THE ARMOR OF RESILIENT CANCER CELLS

While some cancerous tumors remain at the place in the body where they originated, others spread from their primary site to distant parts of the body in a process called metastasis. This process is associated with changes in the cancer cells that can make them a formidable opponent. According to Whitehead Institute Founding Member **Robert Weinberg**, who has studied breast cancer for decades, cancer cells that are able to metastasize have undergone a process called an epithelial-mesenchymal transition (EMT) in which cells with characteristics of epithelial cells, which tightly stick together to form a continuous, smooth, barrier-like tissue, acquire traits of highly mobile mesenchymal cells. The accompanying changes in the cells' gene expression

profile during this transition make them impervious to many therapies and able to survive in parts of the body other than where they originated.

Working to understand exactly how this transition happens, Weinberg and Yun Zhang, a postdoc in the Weinberg lab, recently determined that the EMT is not an on/off switch but rather a gradient, with most cancer cells achieving only a partially mesenchymal state. Defining where particular cancer cells fall on this epithelial-to-mesenchymal spectrum could potentially inform diagnosis and therapy: More epithelial-like cancer cells may be vulnerable to certain therapies, whereas cells in a more mesenchymal state tend to be more aggressive and resistant to those same therapies. Yet cancer cells in a mesenchymal state are not impregnable, and Weinberg and Zhang's work to understand their biology may illuminate novel therapies that exploit these cells' weaknesses.

Recently, Weinberg expanded his research beyond breast cancer to study ovarian cancer as well. Both types of cancer have some common traits and pathology due to their origins as epithelial cells, and Weinberg is applying his expertise and findings from his breast cancer research to improve scientists' grasp of the causes of ovarian cancer and identify potential treatments for this understudied disease. In order to better understand its biology and potential vulnerabilities, Sonia Iyer, a postdoc in the Weinberg lab, has created one of the first mouse models of ovarian cancer. Iyer's work already has shed light on how the EMT program affects ovarian cancer's aggressiveness and spread.

FIRING OFF INSIGHTS INTO BRAIN FUNCTION AND DISORDERS

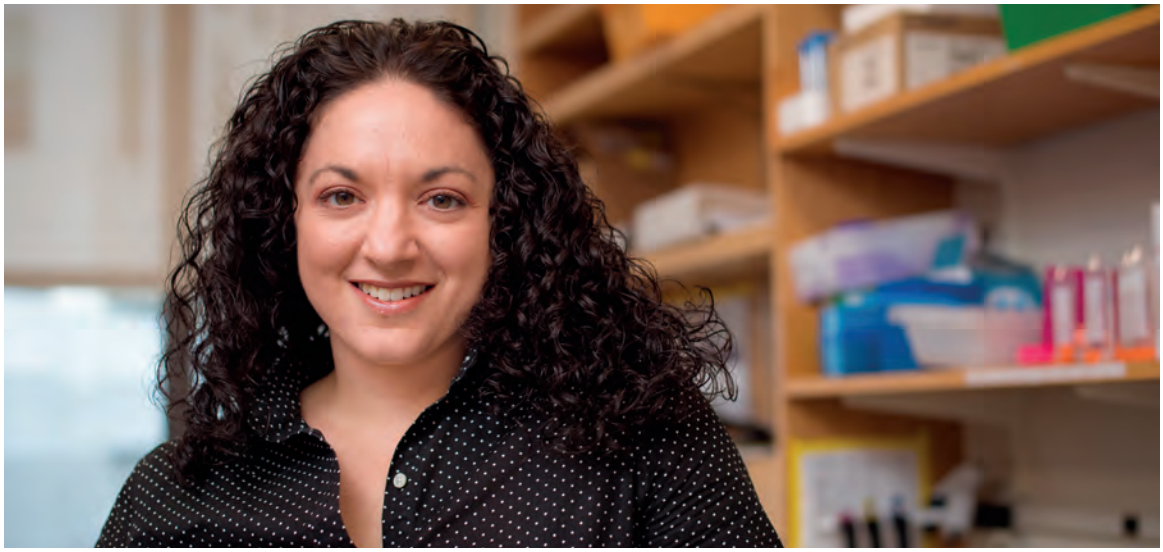
In contrast to mesenchymal-like cancer cells' resilience, neurons in the brain depend on a delicate biochemical balance to properly function and transmit electrical signals between neighboring cells. In order to better understand these highly specialized cells and how certain genetic mutations can cause their dysfunction, Whitehead Institute Member **Hazel Sive** and her lab are investigating how a neurodevelopmental disorder called 16p11.2 deletion syndrome affects the levels of proteins and fats that are essential for neurons to communicate. Associated with autism, ADHD, anxiety, and other conditions, 16p11.2 deletion syndrome is caused by removal of a group of genes within a small section of chromosome 16. The genes in this section appear to affect each other's activity through a complicated web of interactions that is vulnerable to disruption.

This intricate interplay between the genes within the 16p11.2 region is what Sive and Danielle Tomasello, a postdoc in the Sive lab, are investigating in order to find the underlying genetic causes of the disorders associated with 16p11.2 deletion syndrome. Instead of a direct connection between one mutated gene and a specific symptom, as is the case for cystic fibrosis and sickle cell anemia, symptoms arising in 16p11.2 deletion syndrome are caused by a network of genetic interactions. However, there are certain key genes within this network. Sive and Tomasello's research strategy centers around one gene that the lab identified as key to the syndrome: *fam57a*, which is primarily expressed in the brain and thought to maintain the levels of certain fats that are necessary for proper brain function. By tugging on the *fam57a* thread, Tomasello is unraveling the 16p11.2 network to identify the genes with which *fam57a* interacts and that alter brain cell biochemistry (metabolism) when these interactions falter. Early results from this research with zebrafish and human neurons reveal that deletion of the *fam57a* gene changes the levels of important fats and some proteins, resulting in brain cells that produce much weaker electric signals, and also potentially increases the vulnerability of brain cells to the effects of other genetic mutations.

Tomasello is now looking at how *fam57a* interacts with two other genes in the 16p11.2 region, *aldoa* and *cdipt*, that also control cellular biochemistry. By understanding how this trio of genes modulate activity of one another, Sive and Tomasello are establishing a new model for probing the complicated causes underpinning 16p11.2 deletion syndrome. The paradigm of interacting genes that control brain metabolism, identified by the Sive group, goes far beyond this specific syndrome, and a network of metabolic genes is likely to contribute to many brain disorders.

SURVEYING THE COMPLEX GENETIC LANDSCAPE OF MULTIPLE SCLEROSIS

More than 200 risk variants have been linked to multiple sclerosis (MS). These genetic alterations increase a person's likelihood of developing MS. This complex disorder, which destroys the insulating myelin sheath surrounding nerve fibers, is both an autoimmune and neurodegenerative disease. During the course of the disease, many patients experience flare-ups, with increased symptoms caused by autoimmune activity, followed by periods of remission, during which symptoms improve as the brain attempts to heal and recover.



Most researchers investigating MS are focusing on the effects that risk variants have on the autoimmune aspects of the disease, but Whitehead Institute Fellow **Olivia Corradin** is taking a different tack. Using computational approaches to analyze massive amounts of genetic data from people with MS, Corradin is assessing how multiple MS risk variants cooperate to influence expression of target genes and evaluating where in the body these genes are disrupted.

Corradin is also investigating how the brain responds to the injuries that the immune system inflicts. Her research suggests that some people with certain genetic risk factors are less resilient to the disease's autoimmune activity in their brain, and this vulnerability puts them at a greater risk of developing MS. By understanding the genetic risks underlying the brain's reaction to an autoimmune attack, Corradin hopes to identify therapeutic targets that could boost how well the brain is repaired following such an attack. Corradin plans to deploy the same strategy to tackle other human diseases, including opioid and other substance abuse disorders.

UNDERMINING (ALMOST) INVINCIBLE PARASITES

Malaria, cryptosporidiosis, and toxoplasmosis are diseases caused by hardy parasites called apicomplexans. Yet even these tough parasites have vulnerabilities that may one day be used to eliminate them from their hosts. Whitehead Institute Member **Sebastian Lourido** studies *Toxoplasma gondii (T.gondii)*, the apicomplexan parasite that causes toxoplasmosis. Toxoplasmosis infection can be a serious disease in pregnant women,

infants, and immunocompromised people. More closely related to plants than animals, the apicomplexans' foreign biology is unlike our own or that of most other organisms studied in the lab, such as yeast, fruit flies, or mice.

Lourido and his lab have been investigating fundamental aspects of these organisms, including how they maintain their structure and how they produce energy. *T. gondii* and almost all other organisms use a protein complex called ATP synthase to generate energy within their cells. Lourido and postdoc Diego Huet identified a gene encoding a protein that stabilizes *T. gondii*'s version of ATP synthase. The sequence of the gene differs

enough from previously studied stabilizers that its role within the parasite was not immediately apparent. Indeed, the gene's dissimilarity highlights how evolutionarily distant these parasites are from well-studied organisms, including their human hosts.

Lourido's lab has also teased apart a vital aspect of *T. gondii*'s internal architecture. During its lifecycle, this support system must accommodate the organisms' contortions as they twist and turn through various host tissues. Researchers had already identified two aspects of this framework: armor plating-like sacs, called alveoli, that underlie *T. gondii*'s outer membrane, and thick cord-like microtubules that run two-thirds the length of the parasite's body. Lourido and postdoc Clare Harding recently discovered the protein glue that joins the alveoli and microtubules together to make the parasite's flexible structure possible. Lourido's work not only shows how vastly different *T. gondii* and its apicomplexan cousins are from their hosts, but also how these divergences could ultimately be exploited as weak links in these tough parasites' biology. An effective therapy for a parasitic infection ideally targets facets of the parasite's biology that are distinct from that of the host's, and the unique aspects of apicomplexan biology that Lourido is investigating may one day be used to eliminate the pathogens without affecting their human hosts.

CRISPR-BASED MUSICAL CHAIRS REVEALS ZIKA VIRUS KEYS FOR INFECTION

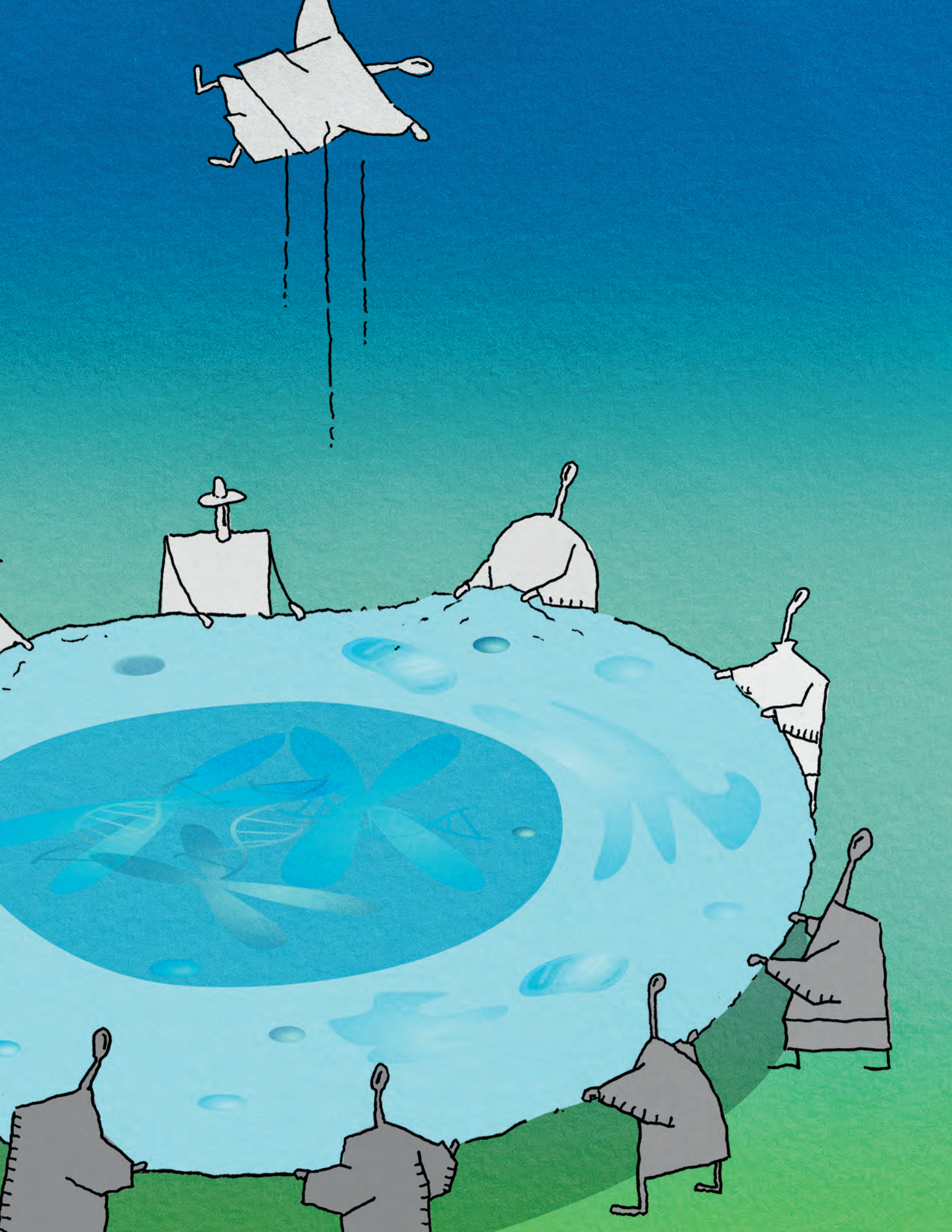
The mosquito-borne Zika virus poses the greatest risk to the fetuses of pregnant women. When the virus invades the developing brain of a fetus, it can cause microcephaly, a brain malformation resulting in a smaller than normal head, as well as potentially severe intellectual disabilities and other cognitive problems. Whitehead Institute Founding Member **Rudolf Jaenisch** has been studying the effects of the Zika virus. Previous work from the Jaenisch lab with brain cells derived from stem cells discovered why neural progenitors, the

cells in fetal brains that will develop into neurons, are particularly vulnerable to Zika virus infection.

In recent work, Jaenisch's lab tackled the question of what the Zika virus requires in a host cell in order to infect it. Understanding this will not only provide researchers with more insight into the virus' biology, but could also potentially identify therapeutic targets — vulnerabilities that could be disrupted to prevent or mitigate infection. Previous research in this area has used human cancer cells, an imperfect model because of the cells' abnormalities and different pattern of gene expression from neurons. Jaenisch, along with former postdocs Yun Li and Julien Muffat, former graduate student Attya Omer Javed, and Heather Keys, the manager of Whitehead Institute's Functional Genomics Platform, instead performed a first-of-its-kind CRISPR screen i n neural progenitor cells to figure out which genes the virus relies on to successfully infect cells. The team created a series of cell lines, each with one gene knocked out, and infected them with Zika virus.

The virus killed most of the cell lines, suggesting that their knocked-out genes were irrelevant to the virus. The surviving cells that thwarted Zika infection implicated genes that the virus needs to do things like enter a host cell and replicate its genome. Next, the researchers treated cells with drugs that target pathways involving the genes identified in the CRISPR screen, hoping to exploit the Zika virus' reliance on these pathways to prevent infection. When they infected the cells with Zika virus, they saw that the drugs did indeed protect the neurons from infection, showing the potential for this approach to identify targets.

Whitehead Community



The Postdoc Experience

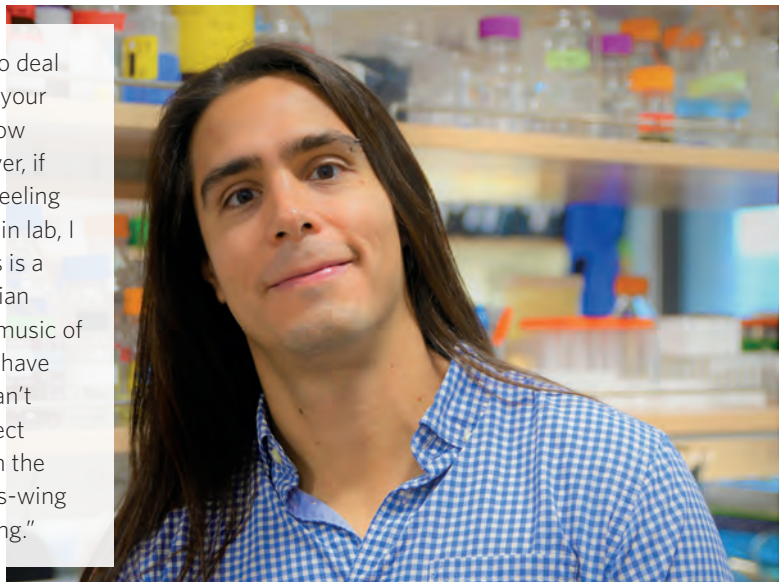
The engine of virtually every laboratory is its postdoctoral researchers – talented investigators at the outset of their careers. Whitehead Institute has long been known for its postdocs' extraordinary talent and skills, and its postdoc "alumni" go on to careers of great accomplishment. Over the past year, for example, 14 scientists completed their Whitehead Institute postdocs and earned faculty positions at academic institutions such as Albert Einstein College of Medicine, University of California, Berkeley, University of Glasgow, and Stanford University or have taken research positions in companies such as AstraZeneca, Codiak Biosciences, and Immunai.

While these early-career scientists are very successful in their work, they are still subject to the vicissitudes of basic science research: the mind-bending complexity of the questions they investigate, the often repetitive tasks and slow pace of progress, the unsuccessful experiments and failed hypotheses that pave the road – one hopes – to eventual success. How do these scientists fuel their persistent efforts, shake off setbacks, and reduce the daily pressure of working in a world-class research organization? Here is how a handful of our postdocs answer that question.

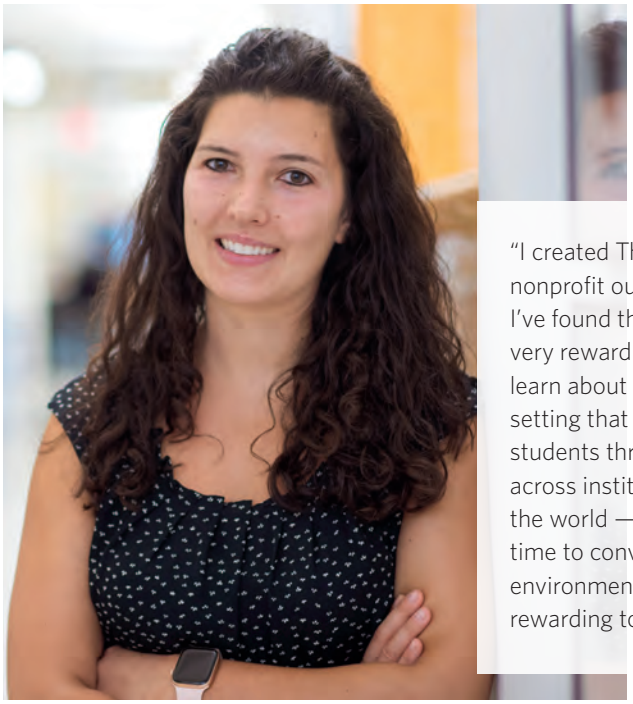
Adrianna San Roman (Page lab) studies the biological differences between females and males and how those differences are manifested in health and disease.

"One of my favorite activities out of the lab is doing experiments with second- and third-grade girls in two local schools. It enables them to hang out with a scientist in a fun environment, sparking their interest in science at an early age and showing them that scientists can look like them. I also participate in the Whitehead Institute teacher-scientist partners program, which pairs postdocs with public school teachers to share ideas and act as a resource. As part of the program, I go to a local high school to talk with students about science careers and my research. They are very interested in the idea of sex differences, and we have interesting conversations. Talking with them and working with their teachers gives me energy."

Diego Huet (Lourido lab) studies the biology of the parasite *Toxoplasma gondii*, which infects one-third of the world's population and is related to the parasite that causes malaria.



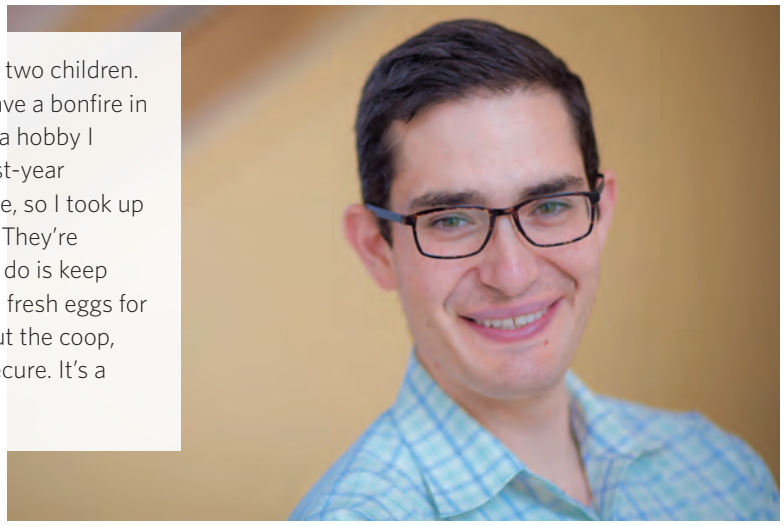
"The hard fact of a research career is that you have to deal with a lot of failure. Sometimes you don't know why your experiment fails, and it doesn't succeed no matter how many times you try to optimize and repeat it. However, if you do manage to make your experiment work, the feeling of achievement makes it all worth it. When I am not in lab, I like to play classical guitar. One of my favorite pieces is a modern classical suite called 'Koyunbaba' by the Italian composer Carlo Domeniconi. It was inspired by the music of Turkey; it's very technical, but I find it relaxing. I also have built on a childhood interest in collecting insects: I can't maintain the physical collection these days, so I collect photos of them on Instagram. Last summer I hiked in the cloud forests of Costa Rica and photographed a glass-wing butterfly, which has transparent wings. It was amazing."



Danielle Tomasello (Sive lab) investigates biochemical changes in neurons that have a deletion of chromosome region 16p11.2, which is associated with a range in neurodevelopmental and mental health disorders.

"I created The Social Scientist (thesocialscientist.org), a volunteer-powered, nonprofit outreach and networking site for scientists and STEM professionals. I've found that building relationships and interacting with other scientists is very rewarding, but many find it challenging to make new connections and to learn about other scientific fields. The Social Scientist offers an informal setting that enables science professionals and enthusiasts from high school students through tenure-track faculty to create and build on new relationships across institutional or disciplinary boundaries. Our volunteers from around the world — including many from Whitehead Institute — are dedicating their time to converse about their journey, including their day-to-day work and environment and why they made the choices they did. It has been immensely rewarding to be helping so many people find their ways in science."

Isaac Klein (Young lab) is also a medical oncologist at the Dana-Farber Cancer Institute; he investigates mechanisms of gene transcription and seeks potential cancer vulnerabilities in phase-separated condensates — membraneless organelles — that form in cells.



"I spend time with my amazing wife, Ellie, and our two children. We have movie nights, cook dinner together, or have a bonfire in the backyard. We also raise chickens out there — a hobby I started when I was seeing cancer patients as a first-year oncology fellow. I needed an outlet for the pressure, so I took up carpentry and built a coop. Then we got chickens. They're actually really easy to take care of. All you have to do is keep them fed and watered, and they produce delicious fresh eggs for you. That's it. Once in a while you have to clean out the coop, and you have to make sure things stay nice and secure. It's a passive but relaxing hobby."

Whitehead Institute Welcomes New Member Pulin Li

"It is a very exciting time to apply quantitative and engineering approaches to developmental biology questions, and Whitehead Institute provides an extraordinary environment for my work," says new Member Pulin Li.

In May 2019, developmental and synthetic biologist **Pulin Li** joined the faculty of Whitehead Institute to establish a research program that could significantly advance the field of regenerative medicine. Li has also been appointed an assistant professor of biology at the Massachusetts Institute of Technology.

"Pulin's insightful work has demonstrated that she is the kind of pathbreaking scientist we prize: brilliant, creative, and passionately dedicated to fundamental biomedical discovery," said Whitehead Institute Director David Page in announcing her appointment. "Her approach to understanding tissue patterning enables scientists to take a pathway apart, rebuild it, and analyze each of its design features' roles in a multicellular patterning process."

During her Ph.D. studies at Harvard University, Li discovered a passion for uncovering fundamental molecular aspects of developmental biology. In particular, she dove into the question of how circuits of interacting genes generate highly dynamic yet choreographed multicellular behavior in zebrafish embryos. Her postdoctoral research in Michael Elowitz's lab at the California Institute of Technology took a bottom-up approach to study tissue patterning, a process fundamental in embryo development and tissue regeneration, and she reconstituted an in vitro system that allows researchers to systematically rewire genetic circuits, finely tune the key parameters, and quantitatively analyze the resulting patterning dynamics. The system bridges biological scales from genetic circuits to single cells to multicellular behavior — and provides a new method for studying developmental and evolutionary questions and, potentially, for advancing tissue engineering. Li's early-career achievements earned her a prestigious National Institutes of Health "Pathway to Independence" (K99) award and an American Cancer Society Postdoctoral Fellowship.

Sarah Keohane Williamson Joins Whitehead Institute Board of Directors

Sarah Keohane Williamson, a longtime financial services executive and deeply experienced leader, has joined the Whitehead Institute Board of Directors.

Sarah Keohane Williamson possesses three decades' experience in investment and corporate management, which has resulted in extensive working relationships with business leaders around the globe. She joined the Whitehead Institute Board of Directors in September 2018.

She currently serves as CEO of FCLTGlobal, a not-for-profit working to increase innovation, economic growth, and savings by encouraging long-term behaviors in business and investing. Previously, Williamson spent more than 20 years at Wellington Management Company LLP — where she served as a partner, director of alternative investments, and chair of the Wellington Trust Company — and held roles with McKinsey & Company Inc., the United States Department of State, and Goldman, Sachs & Co.

Williamson first engaged with Whitehead Institute as a non-director member of the investment committee in 2015 and has now become chair of that committee as well as a member of the finance committee. "But Sarah is far more than just a numbers person," notes board chair Charles Ellis. "She is an experienced leader, and Whitehead Institute will benefit greatly from all that she will bring to the table."

"The work done by Whitehead Institute researchers is essential and exciting," observes Williamson. "It is a privilege and a pleasure to help advance the process of discovery that takes place every day in Whitehead Institute labs."

Celebrating Milestones

Whitehead Founding Member Harvey Lodish celebrates 50 years on the MIT Faculty; Whitehead Member David Bartel marks his lab's 25th anniversary

These days, few people spend 50 years working in one organization. And only a handful of those have had a huge impact on their field. This past year, Harvey Lodish — a powerhouse in cellular and developmental biology — marked five decades as a Massachusetts Institute of Technology (MIT) faculty member and 36 years as a Founding Member of Whitehead Institute. In all, Lodish has had more than 200 trainees and scores of visiting scientists in his lab. Many of them gathered for a weekend-long symposium marking 50 years of discovery, collaboration, and mentorship.

"The symposium was a celebration of Harvey's impact, both as a highly accomplished scientist and as a teacher, mentor, and friend to generations of students, researchers, and health care leaders," says David Nathan, president emeritus of Dana-Farber Cancer Institute, who was a member of the Lodish lab in 1970.

While many of the symposium's speakers took time to celebrate Lodish as a uniquely creative researcher and committed teacher and mentor, the sessions' primary focus was science. For Lodish, one of the most exciting talks was by Nobel Prize winner James Rothman (pictured) — one of Lodish's first postdoctoral fellows — who presented new findings from his Yale School of Medicine lab on mechanisms underlying the near-instantaneous response of individual neurons to stimuli.

In January 1994, then-Whitehead Institute Fellow and now Whitehead Member and professor of biology at MIT David Bartel opened his lab and proceeded, over the next 25 years, to help define the field of RNA biology. Initially studying RNA's ability to catalyze chemical reactions, his lab began to investigate its role in gene silencing; then came early insights into small RNAs' role in gene regulation and the discovery of abundant microRNAs (miRNAs) at work in cells. Since then, the Bartel lab has made a steady stream of discoveries that have helped define how animals, plants, and yeast make and deploy regulatory RNAs.

To celebrate his lab's silver anniversary, Bartel hosted a symposium and reunion for current and former lab members (many of whom are captured in the group photo) as well as collaborators and their families. The two-day event's scientific talks focused on recent findings and new research directions, and participants came from as far as France and Singapore and as near as Boston's Massachusetts General Hospital — where Bartel's graduate advisor, Nobel-prize winner and Harvard University professor Jack Szostak, runs his lab. Observing the scholarly and social celebration, Szostak said that, as a lab leader, joy comes both from seeing biology advance and seeing what the lab's young biologists can do and where they go. In the case of his pioneering protege, Bartel, the geographical distance travelled was small — but the research advances have been huge and continue to grow.

Connecting with Insight and Experience

Richard Foster, former McKinsey & Company, Inc. senior partner, who serves on the boards of the W. M. Keck Foundation and Memorial Sloan Kettering Cancer Center, discussed the concept of creativity and the processes underpinning it.

David Meeker leads the three-year-old biotechnology start-up KSQ Therapeutics, Inc., which was co-founded by Whitehead Institute Member David Sabatini to use proprietary CRISPR-based methods to identify druggable targets for treating cancer and immune system diseases.

The Whitehead Institute's Whitehead Connects program brings renowned business and science leaders to interact with the Institute's scientific, academic, and entrepreneurship community. Two of last year's speakers were drug development industry leader David Meeker and former McKinsey & Company, Inc. senior partner Richard Foster.

Foster, who serves on the boards of the W. M. Keck Foundation and Memorial Sloan Kettering Cancer Center, discussed the concept of creativity and the processes underpinning it.

"Creativity is the way by which we master the art of the near-possible, and it is a primary measure of our humanity," he observed.

Meeker, a pulmonary medicine physician who went on to guide R&D and operations at drug-maker Genzyme, is recognized for his clear-sighted understanding of the issues facing therapeutics developers.

"Big companies have not been very good at getting value for the resources they are investing," Meeker said. "They engage in a lot of wishful thinking rather than pinpointing the few truly effective therapeutics and the patients for whom they will work. Ultimately, you make money by making people better — and you do that by following the science."

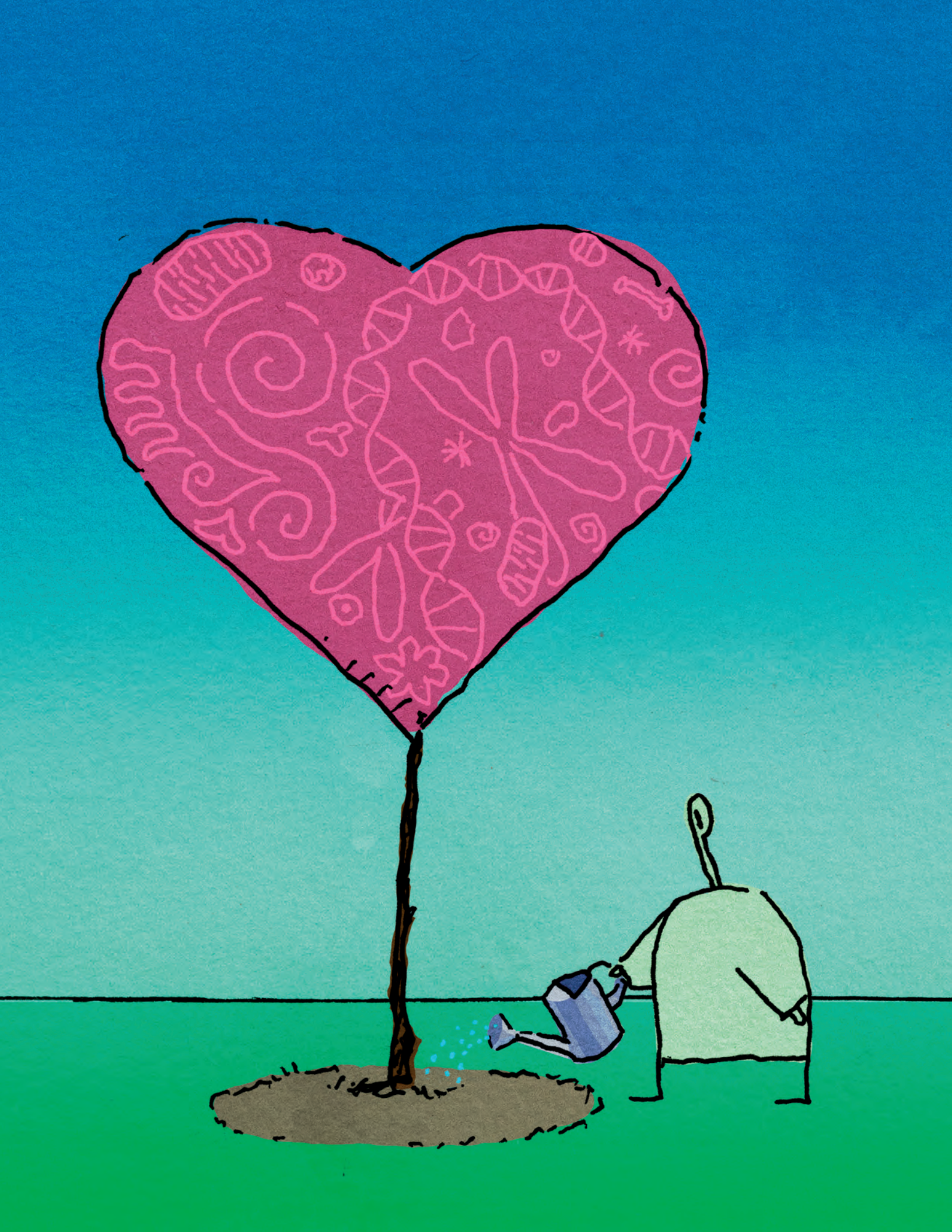
Whitehead Institute Public Program Offerings Continue to Evolve

As part of its mission, Whitehead Institute maintains a strong commitment to science education and outreach through initiatives designed to enhance science teaching and learning for the larger community. These programs are crucial for developing critically thinking young adults, cultivating the next generation of scientists, and contributing to the creation of a scientifically literate population.

With a variety of programs such as lectures and workshops for teachers, special events for the general public, and fully immersive science courses for middle and high school students, Whitehead Institute strives to inspire, educate, and empower its participants about biomedical research.

The 2018-19 season explored the field of neuroscience during Whitehead Institute's high school teacher and high school student programs. In the Institute's fully immersive summer science program, Expedition: Bio, middle school students delved into the amazing biology that thrives in the world around us.

New this year, Whitehead Institute reached out to the community with Spring into Science, a lecture series featuring the latest in biomedical research. Speakers included Whitehead Institute scientists Robert Weinberg, Jing-Ke Weng, Kristin Knouse, and David Page, who shared their research in cancer metastasis, the chemistry and genomics of traditional global medicine, liver cell regeneration, and sex differences in human health and disease.



Whitehead Philanthropy

Endowing Scientific Creativity

In my role, I meet with philanthropists around the country who want to advance biomedical research and, through it, improve medical care for this and future generations. The reason for their giving goes beyond altruism into the realm of purposeful investment. They seek out the organizations that are best positioned to create new scientific knowledge and help drive medical solutions. So I am frequently asked, why invest in Whitehead Institute?

The answer, quite simply, is that the Whitehead Institute scientists are very good at what they do. But their capabilities go beyond world-class scientific knowledge and technical prowess. They are recognized — indeed, lauded — for their vision and creativity; their pioneering, entrepreneurial spirit; and their willingness to take risks. This capacity for creative, courageous science has changed the course of scientific investigation.

It is, for example, what has enabled Gerry Fink to fundamentally change the way scientists approach biological problems. It is what has enabled David Sabatini to leverage his discovery of the mTOR protein into a continuing string of seminal discoveries about metabolism, cell nutrition, and cancer. It is what has enabled Hazel Sive to recently develop a potentially path-breaking research program on how metabolic changes in brain cells may drive a range of mental health disorders and be key to new treatments. And it is what has enabled Mary Gehring to use plant biology to uncover epigenetic changes that alter how DNA is read, affecting reproduction and the health of future generations of individual plant lines.

Indeed, the desire and ability to pursue courageous science is characteristic of all Whitehead Institute Members. They chose to join the Institute, in large part, because it provides the strong, supportive environment — the collaborative culture, leading-edge technical facilities, and access to pan-disciplinary expertise — that is a *sine qua non* for vision, creativity, and risk-taking to flourish.

There is one more essential factor: independent funding that specifically supports intellectually risky, boundary-breaking bioscience research. That is why we have made it a priority to establish named endowed chairs for Whitehead Faculty, providing direct support for our investigators' most challenging and important work. We now have four such chairs, including the Margaret and Herman Sokol Chair in Biomedical Research held by Fink and the Landon T. Clay Career Development Chair recently awarded to Gehring. Our strategic goal is to work with philanthropists to establish at least a dozen more.

Achieving this long-term goal is important because, unfortunately, most of the dollars provided by relatively risk-averse federal agencies and independent foundations are being directed to support mainstream projects that pursue tried-and-true investigative paths. But that is not the Whitehead Institute way.

So why invest in Whitehead Institute? Why establish a named chair for one of our pioneering researchers? Because this is the Whitehead way: advancing knowledge that shapes the future of medicine and health care through scientific risk-taking — by bridging boundaries, creating new tools, leap-frogging assumptions, and cutting new intellectual paths to solve the most important questions.

Since 1982, Whitehead Institute has helped open new realms of biomedical knowledge and has had outsized impact on some of the most pressing challenges in science.

I invite you to invest in a group of extraordinary researchers who are shaping the future of biomedicine. Enable them to continue Whitehead Institute's pursuit of courageous, risk-taking science with impact.

Sharon J. Stanczak
Vice President, Institutional Advancement

Jono Goldstein and Kaia Miller Goldstein: Catalyzing Science, Health, and Prosperity

As longtime supporters of Whitehead Institute, Jono Goldstein and Kaia Miller Goldstein have watched what they see as one of the more remarkable stories in biomedical research unfold: the growth of a wholly new kind of research organization into a globally recognized engine of discovery. Indeed, beyond observing, they've become catalysts for the Institute's science-shaping research.

Shortly after Whitehead Institute was launched, Jono was a Massachusetts Institute of Technology (MIT) undergraduate researcher in the lab of Whitehead Institute Founding Director and MIT professor David Baltimore. "I was like a fly on the wall, observing the formation of the Institute, its extraordinary faculty, and its research program," he recalls. Over the following decade — first as a graduate student, then as a private equity investor — Jono continued to have a front-row seat as the Institute building's construction sparked the physical transformation of Kendall Square, then as its scientific achievements spurred the growth of the Kendall Square life sciences research and innovation community.

In 1998, Jono enthusiastically accepted an invitation to join the Whitehead Institute Board of Associates, and, in 2008, he joined the Institute's governing board of directors. "I'm fascinated by basic biomedical research," he says, "and the exposure to researchers doing such incredible, innovative science — and driving such important discoveries — reinforced my desire to help move science forward in a practical way."

It was a desire shared by his spouse, Kaia. A consultant on international economic development, she has worked in dozens of countries, advising government and business leaders in Latin America, Asia, the Middle East, and Africa — where she is an advisor to the president of Rwanda. She and Jono share a belief in the power of education, the importance of preparing young people to take on society's challenges, and the role of science in guiding choices. These beliefs are reflected in their philanthropy. They are both deeply engaged in a number of organizations that advance the health, education, and future opportunities for children and that promote a sustainable, just, and prosperous world.

"Whitehead Institute fits into our philanthropic strategy perfectly," Kaia says. "The research being pursued at Whitehead Institute is essential; it creates fundamental knowledge that can have concrete impact by enhancing the quality of people's lives and contributing to the development of communities." For that reason, she explains, "Jono and I actively engage with the labs, we go to hear Members' talks, we work hard to understand how their work can have impact."

Their support helps ensure that Whitehead Institute investigators have the most supportive environment possible for pursuing their research. In addition, Jono chairs the board's development committee, introducing Whitehead Institute's work to other philanthropists and inspiring their involvement. "Philanthropy is critical to the organization's capacity to drive discovery, tackle new challenges and blaze new scientific paths, and train the next generation of scientists," Jono explains. "Yes, Whitehead Institute continues to produce impactful discoveries and technical advancements. But today, its endowment covers less than a third of its budget, and federal and corporate support for pioneering basic science research has declined significantly in recent years. Supporting Whitehead Institute represents a unique opportunity for donors to learn about great science, meet phenomenal researchers, and truly make a difference.

"We're proud to be connected with this organization, which both needs and deserves our support," he emphasizes.

"That's a message we really want other donors to hear," Kaia says. "Because we believe that Whitehead Institute's research is helping shape the future of health care — and, in that way, creating opportunities for people throughout the world to prosper."

Whitehead Leadership

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FACULTY AND FELLOWS
Whitehead Institute principal investigators are world-class scientists dedicated to improving human health through fundamental biomedical research. Under the Institute's close affiliation with the Massachusetts Institute of Technology (MIT(, Whitehead Institute Members also are members of MIT's biology department or other MIT departments.

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

FACULTY ACHIEVEMENTS
Whitehead Institute's world-renowned faculty include the recipient of the 2011 National Medal of Science (Rudolf Jaenisch); the recipient of the 1997 National Medal of Science (Robert A Weinberg); nine Members of the National Academy of Sciences (David Bartel, Gerald R. Fink, Jaenisch, Harvey F. Lodish, David Sabatini, David C. Page, Weinberg, and Richard Young); four members of the Institute of Medicine (Fink, Jaenisch, Page, and Weinberg); and five Fellows of the American Academy of Arts and Sciences (Fink, Jaenisch, Lodish, Page, and Weinberg).
All Whitehead Institute faculty are also professors at MIT.

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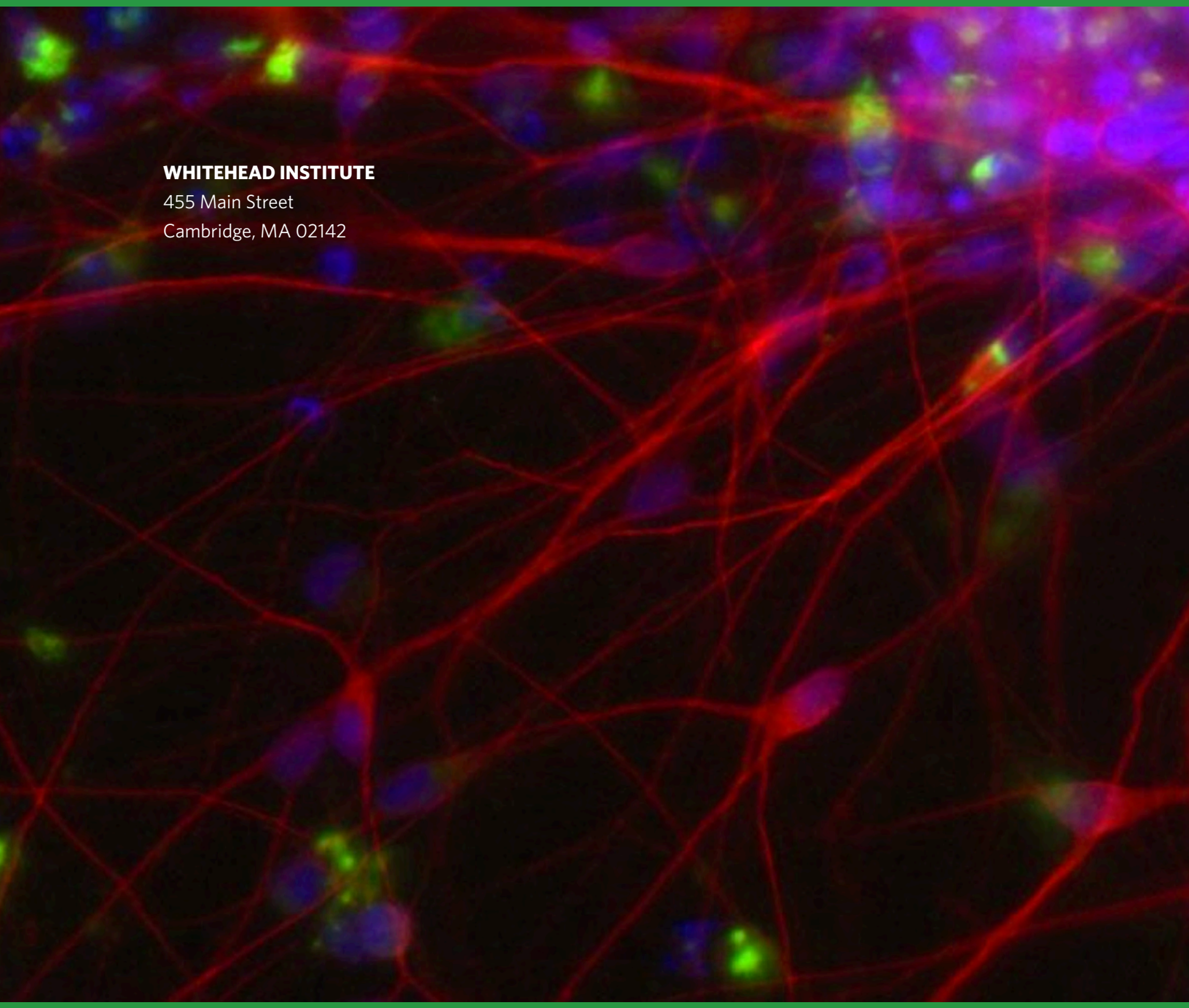

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