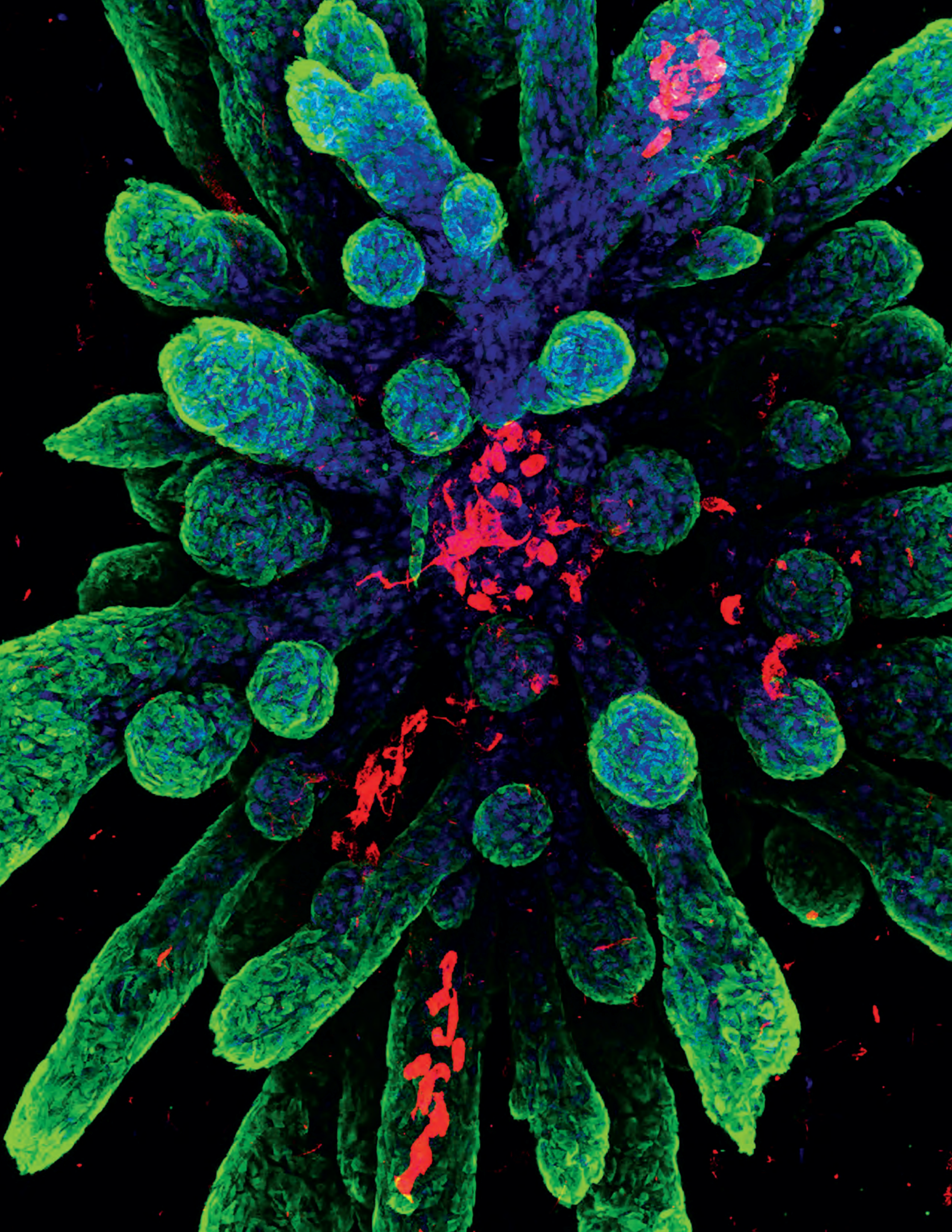
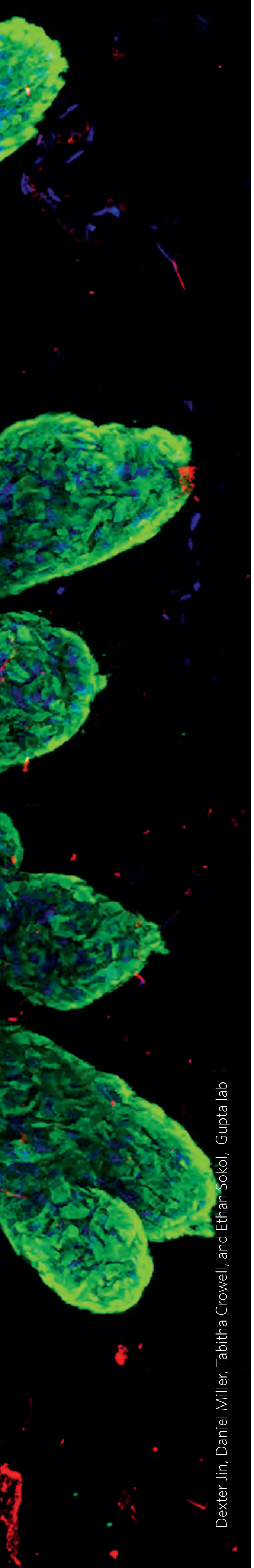
Whitehead Institute

ANNUAL REPORT 2017





Dexter Jin, Daniel Miller, Tabitha Crowell, and Ethan Sokol, Gupta lab

The founding vision was bold, the experiment grand:

Amass a peerless concentration of scientific talent under one roof and catalyze it with the resources and freedom to blaze new trails.

Contents

Envisioning the Future

Whitehead Institute is one of the world's premier independent biomedical research institutions. Our faculty Members are widely acclaimed as scientific pioneers in cancer, cell biology, metabolism, embryonic development, genomics, and plant biology, and the Whitehead Fellows Program is renowned for fostering generations of scientific leaders. The Institute has more than fulfilled the promise that Edwin C. "Jack" Whitehead envisioned when he and David Baltimore founded the organization in 1982. Indeed, many trace the thriving biotechnology industry in Cambridge's Kendall Square back to the moment Whitehead Institute was born, declaring a new era in biology.

Today, Whitehead Institute is preparing to address the challenges of our next 35 years, through our plans to hire six to eight new faculty members and to renew the scientific facilities that will support our continuing preeminence in biomedical research. We are taking the steps necessary to ensure our long-term capacity to imagine, discover, create, and catalyze—in short, we're preparing to lead biomedical research deep into the "Bio-Century."

What will the future of biomedical research look like? It will be increasingly collaborative, computational, and automated. Vast and intersecting data sets will challenge researchers' ability to meaningfully interrogate data, but there will be untold intellectual riches and scientific advancement for those who meet that challenge. At the same time, the "medical" part of biomedical research will flourish as steadily growing technical capabilities will enable us to look at the entire body—from organs to cells to molecules and back up again—providing a deep, nuanced understanding of both health and disease.

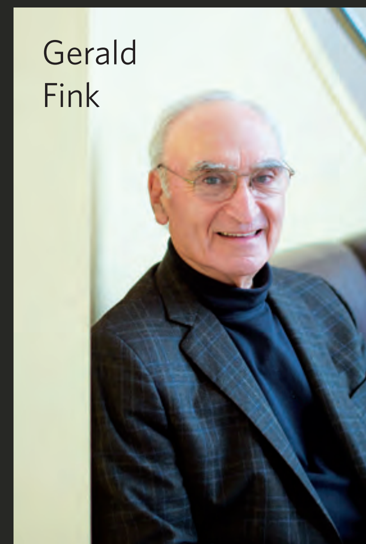
Whitehead Institute faculty will be renowned for their leadership in developing this new, comprehensive approach, which I call "Whole-Genome Biology." We will be bold as both creators and early adopters of innovative technologies. We will strive to quicken the flow of new knowledge between lab and clinical bedside. And we will build intellectual bridges between basic bioscience and computational science, engineering, physics, chemistry, and clinical medicine.

We are beginning a new chapter for ourselves and pioneering a new era for biological research. Yet we do so holding tightly to our core values and our original mission and vision. We remain committed to excellence in basic biological research; to enabling scientists to think audaciously and act boldly, both individually and collaboratively; and to giving the finest young researchers the knowledge, skills, and confidence to do the same. We continue to embrace our strong belief in the difference creative individuals can make. And we are determined that Whitehead Institute remain the organization at which stellar researchers choose to spend their careers because it is the best place in the world to realize their scientific dreams.

I invite you to delve deeply into this report on Whitehead Institute as we are today, and to join us in envisioning, creating, and exploring the future of biomedical science for the benefit of all humanity.

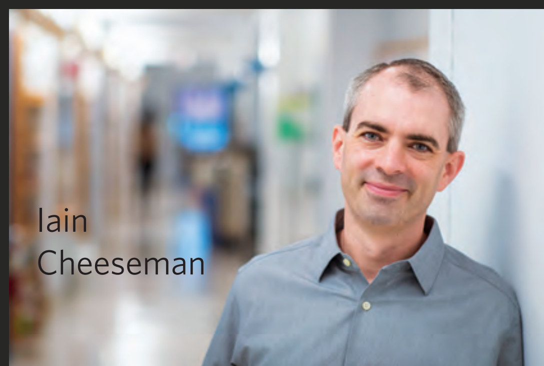
David Page

Whitehead Members



Gerald Fink

David Bartel



Iain Cheeseman

Rudolf Jaenisch

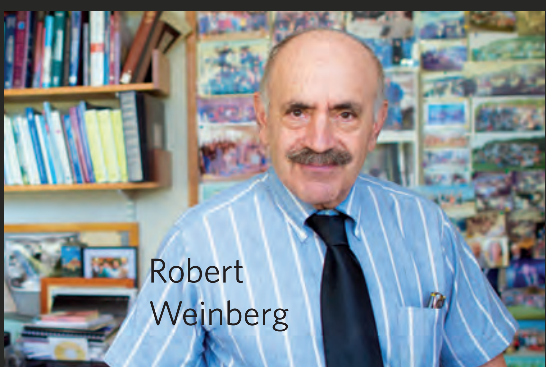
Harvey Lodish

Sebastian Lourido

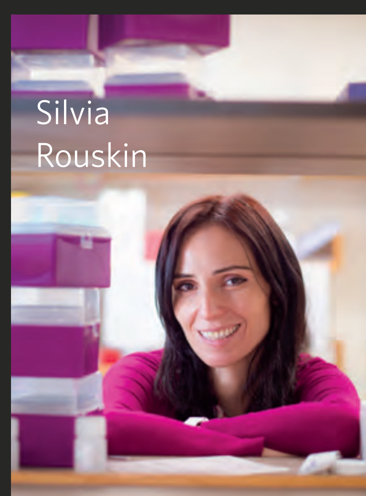
Peter Reddien

David Sabatini

Hazel Sive

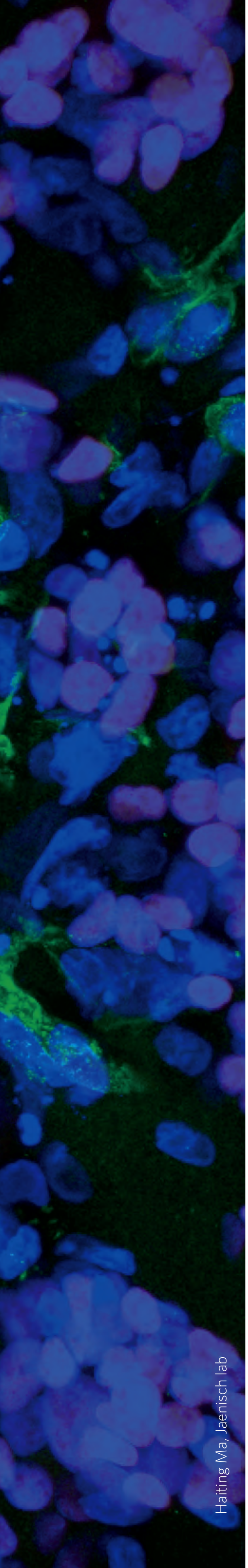


Whitehead Fellows



Whitehead Science

Discovering the Future


Haiting Ma, Jaenisch lab

There is an interesting dichotomy at work in an organization such as Whitehead Institute. We exist on a platform of knowledge and technical expertise that is built upon past accomplishments, yet we consistently cast our minds forward, directing our energies to the future—to the new questions raised by yesterday's answers.

This dichotomy is increasingly emergent now, as the organization marks its 35th birthday. It was in 1982 that businessman and philanthropist Edwin C. "Jack" Whitehead realized a decade-old vision: to establish a world-renowned, self-governed research institute dedicated to improving human health through basic biomedical science. Working with then-Massachusetts Institute of Technology professor and Nobel Laureate David Baltimore, Whitehead endowed and planned what became, within just a few years, one of the most significant research centers in the world. With fewer than 20 Members and Fellows, the impact of the Institute's scientific publications positioned it as the top research institution in the world for molecular biology and genetics. And it became a major force in fields ranging from cancer research to genomic science.

In the decades since, Whitehead Institute has stayed prolific and continued to be a bold pioneer. Its scientists have defined whole new fields of basic research and developed knowledge, tools, and methods that enable investigators throughout biomedical research to be more effective, more creative, and more courageous in uncovering the secrets of biomedicine.

Therefore, we pause—for a moment—to acknowledge the milestone we've achieved: 35 years of discovery; 35 years of innovation; 35 years of laying the groundwork for tomorrow's diagnostics, treatments, and cures.

But, true to our nature, we glance back only to put the future in context. In the following ten segments, we look at some of the most important work undertaken by Whitehead researchers. With each, we nod to the Institute's achievements, then turn our gaze to the pioneering paths our scientists are pursuing now—and to the profound promise inherent in their commitment to discovery.

Genomics

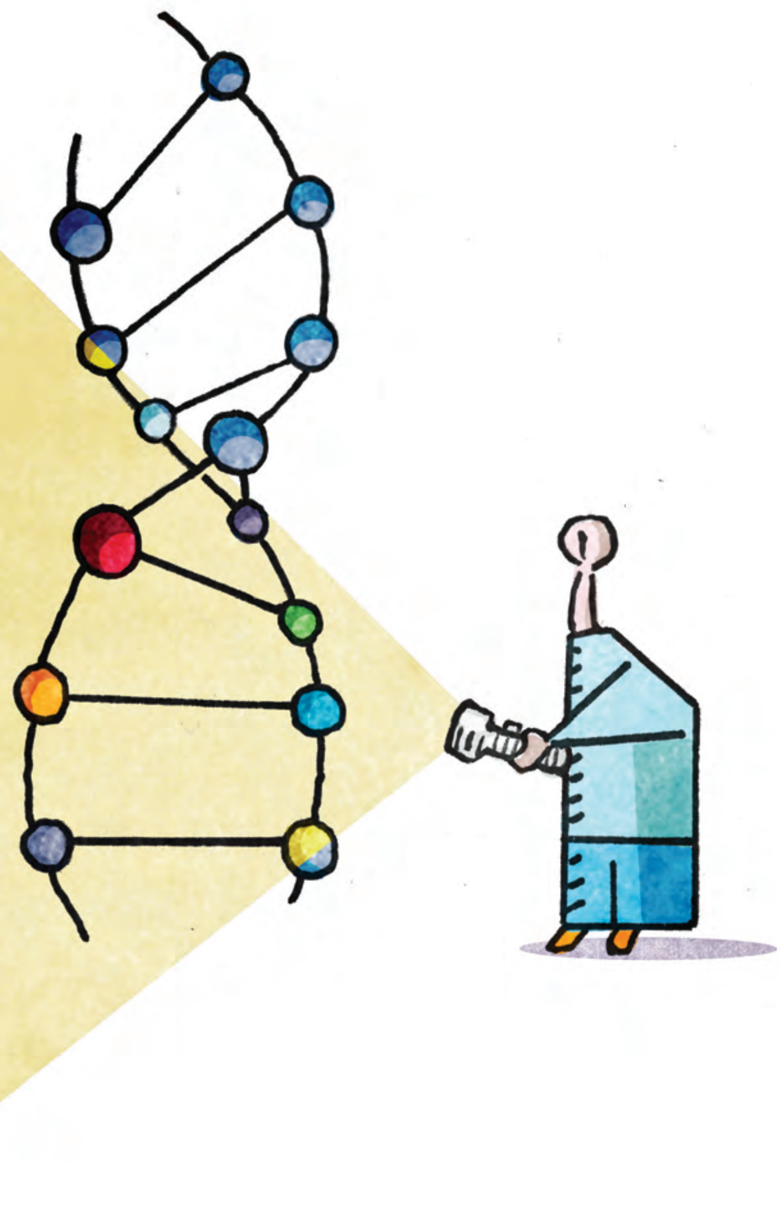
Discovery at scale

Whitehead's roots as a leader in human genomics go back nearly to its founding. The Institute has been a driver of major discoveries about the human genome and made the single largest private-institution contribution to the completion of the Human Genome Project, and the Institute continues to make impactful discoveries in genomics.

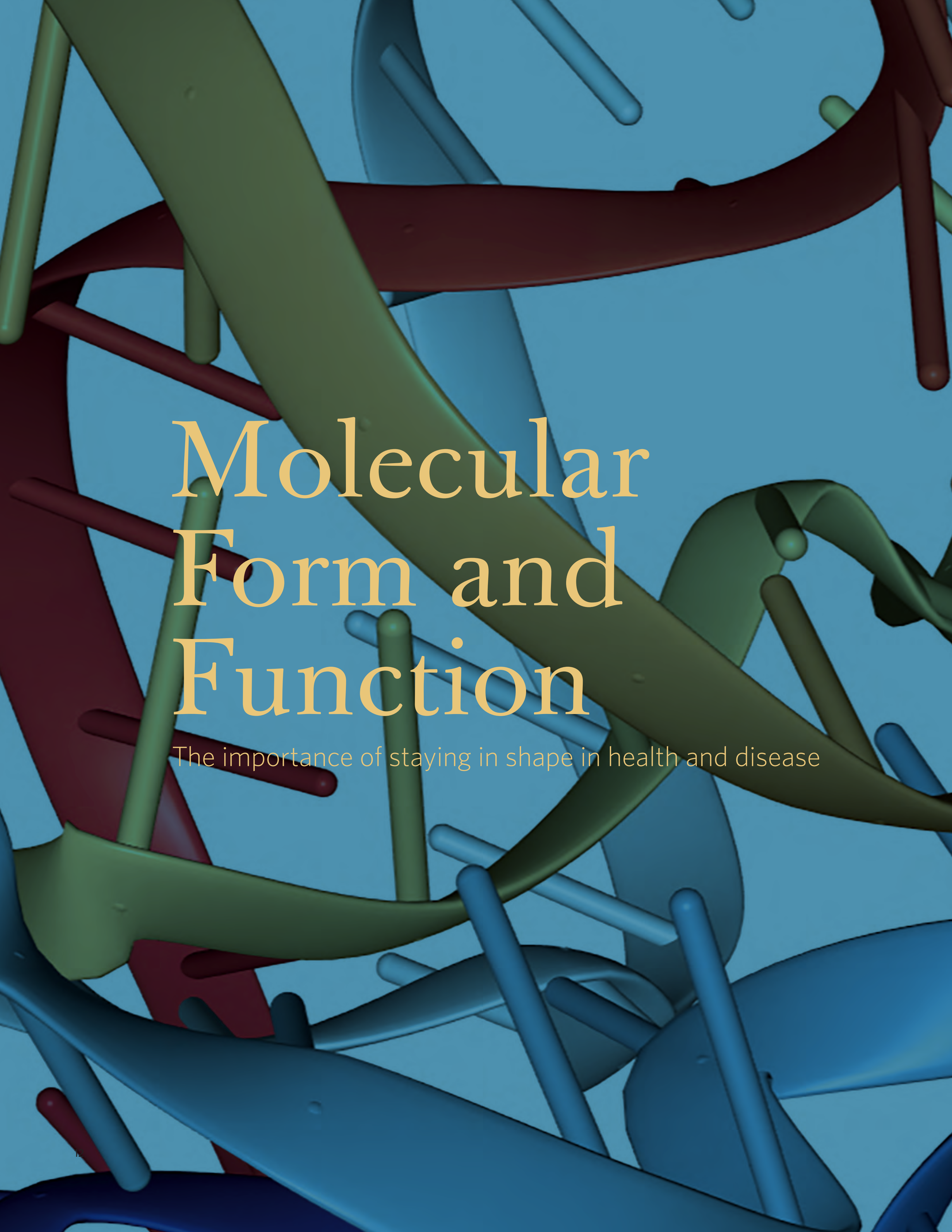
Whitehead Member and Institute Director David Page is pioneering the field of sex-based differences in biology. Human cells typically contain two sex chromosomes: two X chromosomes in the case of females, and one X and one Y chromosome in males. Page and his lab members have been comparing the sex chromosomes of birds, reptiles, humans, and other mammals in order to understand the evolutionary forces that have influenced their content. These studies revealed that while the Y chromosome has lost 97 percent of the genes it once shared with the X chromosome, the 3 percent that survive encode regulators of key biological processes and are broadly expressed throughout the body. The influence of these surviving genes creates fundamental differences between males and females, in every cell of the body, independent from the hormonal influences of the reproductive tract. However, the extent to which this fundamental sexual dimorphism impacts health and disease is not well understood. Some of these differences between men and women may manifest in disease frequency— for example, women are much more susceptible to lupus; boys experience a greater incidence of autism. Others may manifest in distinct symptoms—signs of heart attack, for example, can differ greatly between the sexes, and often are not recognized in women. Page is now guiding a deep exploration of the genomic and proteomic differences between sexes and how they contribute to sex differences in health and disease, with the goal of building a new field of knowledge.

In addition to revelations about the sex chromosomes, one of the most significant advances in our understanding of genomics involves uncovering the complex web of regulatory DNA sequences and the degree to which the proper execution of elaborate gene regulatory circuits is intimately tied to three-dimensional chromosome structure. The work of Whitehead Member Richard Young has been instrumental in parsing regulatory elements called enhancers, and clusters of enhancers, called super enhancers, and illuminating their function within the context of the DNA loops and bends within defined chromosomal "neighborhoods," that bring active enhancers in range of the genes they regulate. Young and his colleagues developed the technology to trace many of these interactions. Mapping the genetic circuitry, they then applied the method to describe the three-dimensional chromosomal landscape of embryonic stem cells, revealing the chromosomal architecture at one of the earliest stages of human development. Mutations in regulatory regions, as well as in sequences critical for chromosome architecture, have been associated with numerous types of cancer and studies such as these have the potential to reveal the layers of regulatory complexity that must be addressed in evaluating potential therapeutic targets. Young has also worked closely with Whitehead Founding Member Rudolf Jaenisch to develop "epigenetic editing" technologies that permit manipulation of genome structures that control gene expression.

Whitehead Fellow Olivia Corradin's research is also focused on the vast majority of our genome that does not encode proteins. Corradin is interested in identifying genetic variants—tiny genetic spelling differences in our DNA code—that are associated with disease. She uses the three-dimensional structure of DNA to study particular variants drawn from patients suffering from a diverse array of diseases including colon cancer, multiple sclerosis, and drug addiction to assess the impact of these genetic variants on disease formation and progression.

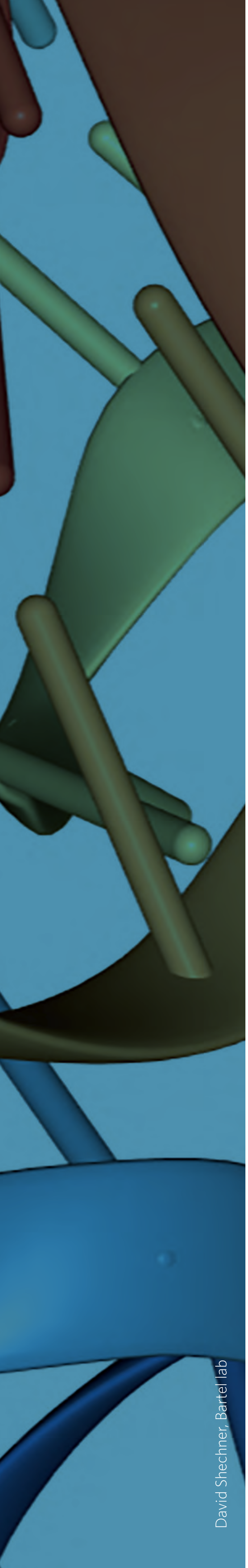


Research at Whitehead uncovering the vast amount of information contained in our genome will have an invaluable impact on our ability to delineate factors and mechanisms associated with disease.



Molecular Form and Function

The importance of staying in shape in health and disease



David Shechner, Bartel lab

In the molecular world, function follows form. If a molecule is not shaped correctly, it is unlikely to be able to perform its job. The ramifications are serious: RNA and proteins that for whatever reason cannot adopt their appropriate shape or structure can cause cell death and disease. Whitehead scientists are actively investigating connections between form and function in order to understand their impact on human health.

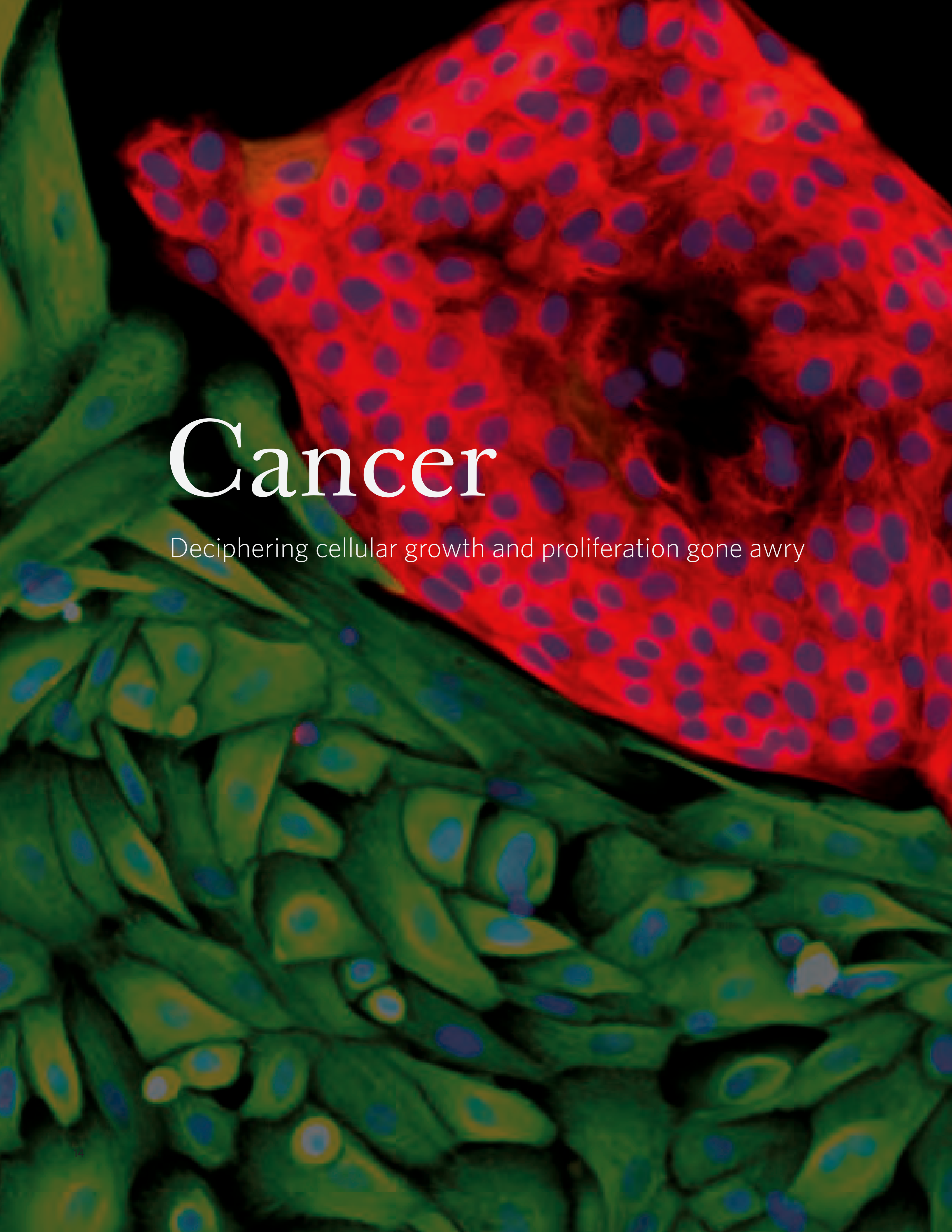
Messenger RNAs (mRNAs) are the nucleic acid strands that convey genetic information from DNA and serve as a blueprint for the proteins produced in our cells. Instead of long, free-flowing kite strings, however, mRNAs can fold and bend in ways in which we don't entirely yet know; nor do we understand the functional consequences of this folding. Previous work by other researchers indicated that under laboratory conditions mRNAs assume three-dimensional shapes, but it had not been possible to observe these structures in action in their native cellular environment; and, until recently, methods to assess RNA were not reliable. In order to decipher the structures that mRNAs can adopt in our cells, Whitehead Fellow Silvia Rouskin has created a new tool. She recently introduced a new algorithmic approach that has proven to be a robust and simple tool for the quantitative analysis of RNA structure in cells. Her method will make it far easier to study RNA folding and to recognize connections between folding patterns and disease.

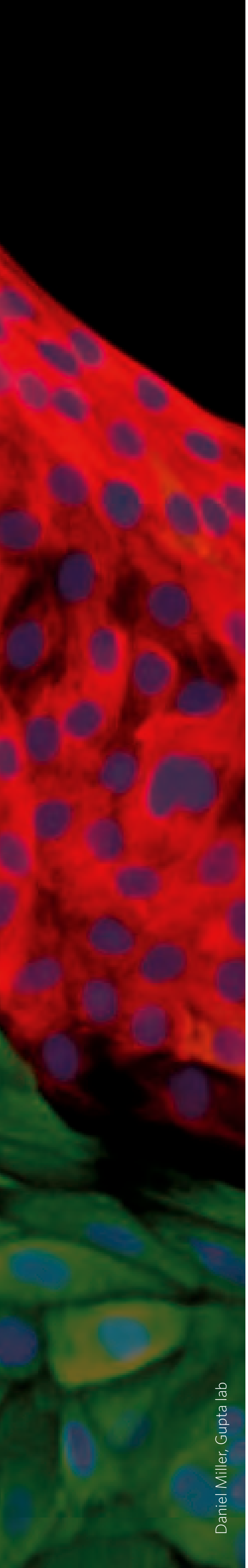
Whitehead Member David Bartel, known for his pioneering work on short, regulatory RNAs called microRNAs, is also analyzing the architecture of mRNAs, with a focus on the ends of the molecules. Modifying Rouskin's assay, Bartel has identified segments in these tail sections that reflexively fold into hairpin loops, and has discovered that these loops occur more often in the ends than in the body of mRNAs. After analyzing thousands of folded mRNAs, Bartel has concluded that folding at the ends enhances the mRNAs' processing and stability. He has also determined that thousands of RNAs that fold into special quadraplex shapes under laboratory conditions do not fold in their native cellular environment. He hypothesizes that some yet-unknown cellular machinery efficiently untangles these RNAs and prevents them from folding, since if they are allowed to fold in cells it seems to impede normal cellular functions. These findings stress the importance of assaying such molecules in their natural cellular environment.

While the Rouskin and Bartel labs have been focusing on RNA, Whitehead Fellow David Pincus has been looking at the complex, three-dimensional shapes of proteins. Proteins are chains of amino acids that fold into complex three-dimensional shapes. Given the importance of assuming and maintaining the correct shapes, it's not surprising that cells have evolved helpers known as "chaperones" to keep proteins folded. The levels of chaperones are tightly controlled in the cell, and disruption of this regulation has been implicated in both cancer and neurodegenerative diseases. Pincus is focused on understanding how a cell controls the level of chaperones to maintain cellular homeostasis, or balance. Chaperones play a crucial role when cells experience adverse conditions, such as changes in temperature, pH, or osmotic pressure. Pincus has determined how the master regulator of chaperone levels, known as heat shock factor 1 (HSF1), is activated and controlled. This insight could inform treatments for cancer, in which HSF1's activity is frequently hijacked, and neurodegenerative diseases, in which its decreased activity may lead to the build-up of protein aggregates.

Cancer

Deciphering cellular growth and proliferation gone awry





Daniel Miller, Gupta lab

Cancer is a wily shapeshifter, hijacking a cell's normal processes for its own ends and, too often, evading even the most promising treatment strategies. Whitehead researchers have helped drive steady advances in our understanding of cancer and contribute to innovative strategies in cancer therapeutics.

Whitehead Founding Member Robert Weinberg uncovered the first human oncogene, Ras, and the first tumor-suppressor gene, Rb—science's first demonstration of human genes pressing the gas pedal or failing to "slam on the brakes," contributing to cancer cell proliferation. In the decades since, Weinberg's discoveries have proven instrumental for delineating the cellular differentiation, growth, and proliferation signals that can go awry in cancer. He is now working to determine the signals that trigger and enable cancer to metastasize. When cancer cells undergo an epithelial-to-mesenchymal transition—an alteration in their pattern of gene expression that also normally functions during wound healing and embryogenesis—there is an increased likelihood of metastases. Weinberg is interested in looking for a means by which to reverse this path to metastasis in an effort to stop cancer in its tracks. He recently discovered that when a factor called protein kinase A (PKA) is activated in breast cancer cells that are mesenchymal, it can induce a reverse, mesenchymal-to-epithelial transition, informing a strategy that could one day be harnessed to prevent the conversion of cancer cells to the pro-metastatic state.

Another approach to targeting cancer cells is identifying the factors and pathways upon which their survival depends. Since that dependency also represents vulnerability, disrupting these potential targets could be lethal for the cancer cells. Whitehead Member David Sabatini and his lab recently described their discovery of a protein called SLC38A9, which functions in the membrane of a cellular compartment called the lysosome. Their research showed that SLC38A9 links two important cellular functions: activating a critical cellular growth pathway and releasing amino acids, the protein building blocks needed for cell growth, from the lysosome. They found that removing the function of SLC38A9 in pancreatic cancer human cell lines and mouse models dramatically reduced tumor growth, pinpointing a potential approach to specifically target pancreatic cancer cells.

As our approaches for the early detection of tumors advance, so too must our ability to assess the likelihood that very small tumors will ultimately grow and metastasize in order to avoid what may be unnecessary and harsh treatment. Whitehead Member Piyush Gupta recently reported his lab's discovery of SMARCE1, a protein biomarker that identifies the subset of small, early-stage breast tumors that are likely to grow and metastasize aggressively. Gupta and his clinical collaborators are now working to translate this finding into a diagnostic tool that can tell doctors which patients require immediate, intensive therapy—versus patients who may need much less therapy or could benefit equally from active surveillance in the absence of any therapy.

Whitehead's longstanding leadership in cancer discovery continues, defining the specific genetic programming that makes cancer cells act differently from normal cells and enables them to multiply prodigiously and spread, evading the body's natural defenses.

Molecular Mechanisms

Spotlight on regulatory processes

Even when you feel like nothing has gone right on a particular day, you would be pleased to know that inside your body trillions of cellular mechanisms, responsible for everything from the division of your cells, to the expression of your genes, to the replication of your DNA have been executed flawlessly. Whitehead scientists have been making important discoveries, getting a better understanding of these mechanisms as well as the consequences when things don't go quite right.

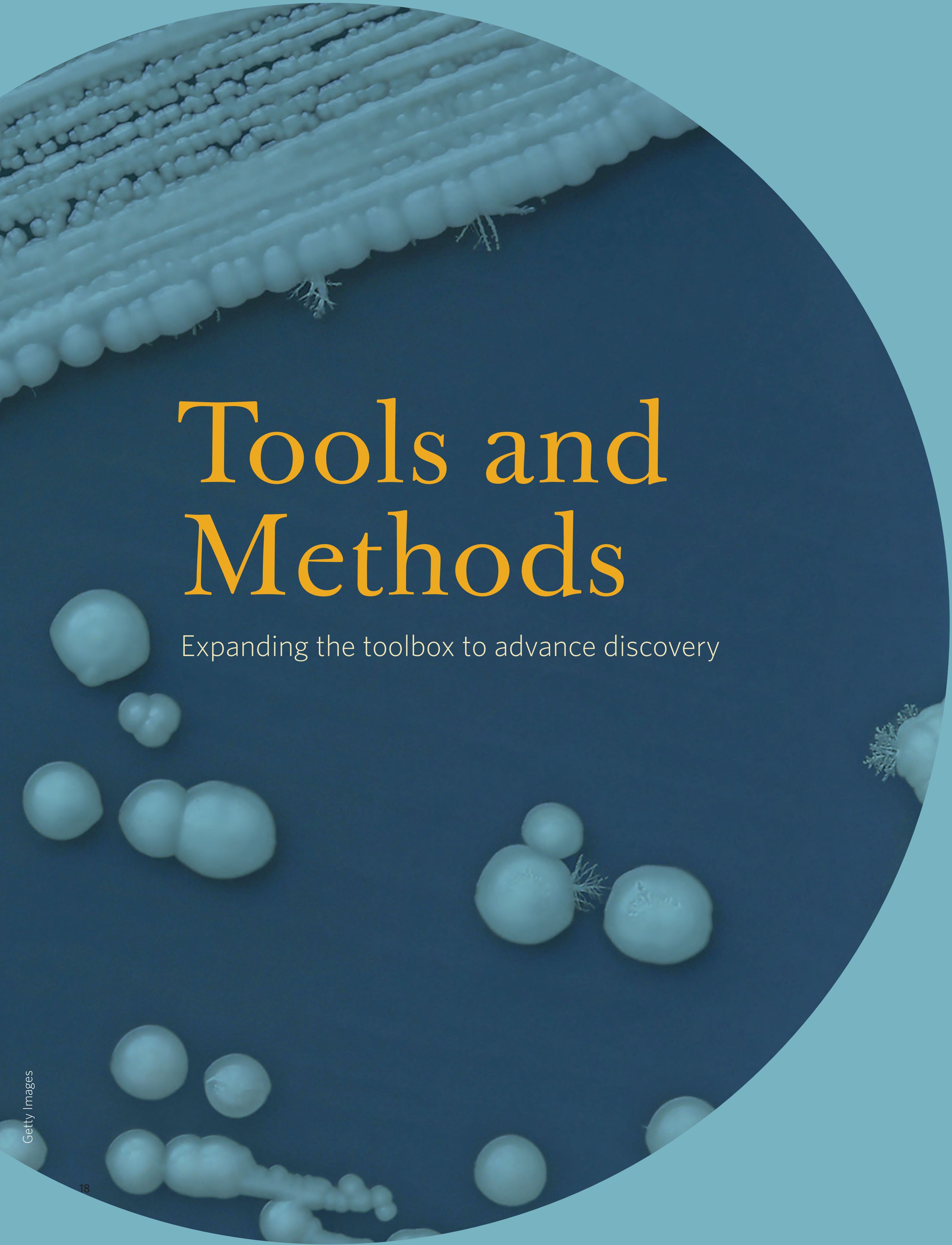
Even without changes in our DNA sequence, there can be changes in how our genes are expressed that are heritable. One way in which this type of change, called epigenetic, can happen is through methylation, in which a methyl group is added to cytosine, one of the four bases that make up the G-A-T-C code of our DNA. When a section of DNA is methylated, the cell's transcription machinery reads the DNA differently and some genes are effectively silenced. Now, Whitehead Member Mary Gehring has identified a mechanism that maintains the right combination of methylated and nonmethylated DNA in the genome. She has found, however, that interfering with this mechanism does not permanently remove methylation throughout the genome. In some sections, the methyl groups eventually return over the span of a few generations, indicating that there is another, unknown system operating to maintain methylation. In addition, she has figured out an algorithm for predicting which parts of the genome will retain methylation patterns inherited from an offspring's parents and which are likely to switch methylation states. Her work on methylation could have significant effects in agriculture, where new traits are traditionally passed through selective breeding. Gehring's research suggests that epigenetics could be harnessed as a tool for creating desired traits in plants.

As a cell divides, thin protein filaments, called microtubules, attach to the chromosomes and pull one copy of each chromosome to opposite sides of the cell. Because microtubules are unable to grasp DNA directly, this crucial step would be impossible without the kinetochore, a specialized protein complex embedded in an area of the chromosome called the centromere. If this process goes awry, cells can transform into cancer cells, die, or, in the case of sex cells, result in nonviable eggs or sperm. These critical interfaces between the centromere, kinetochore, and microtubules fascinate Whitehead Member Iain Cheeseman, who has deciphered numerous aspects of the mechanisms and players that are critical for the fidelity of cell division. Recently, Cheeseman and his colleagues uncovered how the centromere, a specialized region of the chromosome to which the kinetochore and microtubules attach, maintains its crucial stability. The researchers identified the domains and associated mechanisms of attachment by the contributing proteins, CENP-A, CENP-C, and CENP-N, to the centromere in an elaborate game of molecular Twister. These findings provide important insights into the regulation of centromere assembly and, in turn, the proper attachment of microtubules required for cell division.

Using unbiased genetic screens—powerful tools that look for particular phenotypes that reveal gene function, rather than working backward from a known gene—Whitehead Member Terry Orr-Weaver has successfully identified new regulators of cell division and cell growth during development in

Drosophila: the Shugoshin protein family, which is critical for accurately divvying up chromosomes in dividing cells, and the Cdt1 protein family, which is key for controlling DNA replication. These proteins are conserved in humans and can play important roles in cancer cells as well. Orr-Weaver's screens also identified the enzyme PNG kinase, which controls the translation of messenger RNAs (mRNAs) into proteins as the fruit fly egg transitions into an embryo. During this transition, hundreds of maternal mRNAs must be regulated at the level of their translation to protein in a matter of minutes for embryogenesis to commence, requiring that the activity of PNG be regulated precisely. This PNG-controlled switch could be a model for how human cells can massively and globally change mRNA translation in a short period of time. Because similar kinase activity during early development has been noted in worms, a comparable approach may be used in other organisms, including humans.

Red blood cells make up a sizable portion of our blood volume and play a critical role in the body, ferrying oxygen and carbon dioxide to and from our lungs. Problems with red blood cell production or function can result in diseases including anemias. The work of Whitehead Founding Member Harvey Lodish and his laboratory has been instrumental in understanding how red blood cells develop. The Lodish laboratory recently applied their expertise in red blood cell development to crack a mystery noted by doctors more than a century ago: Why do patients with an underactive thyroid also tend to have anemia? For answers, Lodish and his team searched the growth serum required in the laboratory for red blood cell progenitor maturation. They discovered that after using a charcoal filter to screen out hydrophobic factors in the serum, simply adding the thyroid hormone thyroxin back in was sufficient to steer the progenitor cells back onto the road to maturity. They then went even further and identified the specific receptor in red blood cells to which the hormone binds and a protein that is needed for thyroid hormone stimulation, regulating the final step of red blood cell production. These findings finally uncover the connection between an underactive thyroid and anemia and suggest new therapies for coaxing red blood cell maturation in patients with this condition.



Tools and Methods

Expanding the toolbox to advance discovery

Getty Images

New tools, models, and methods are catalysts for scientific discovery—and the drive for discovery, in turn, inspires novel technology and approaches as new problems and opportunities evolve. Whitehead scientists are renowned for creating methods and tools that make major breakthroughs possible. They are especially effective at creating and expanding the use of model systems—nonhuman organisms that are invaluable tools for illuminating human biological function.

The best model systems are easy to maintain, have fast life cycles so scientists can study many generations, and can be used to investigate a range of biological processes. Whitehead Founding Member and Former Director Gerald Fink was instrumental in developing two such organisms—the single-celled yeast *Saccharomyces cerevisiae*, or brewer's yeast, and the fast-growing plant *Arabidopsis thaliana*—as important models for genetics and cell biology. These models have been used to make countless key findings and have provided insights into the roots of many human and agricultural diseases.

Mice, which share many genetic and biological characteristics with humans, have long been used as models, but Whitehead Member Rudolf Jaenisch has taken this common model to the next level. He has developed the technology to create mice with virtually any genetic mutation an investigator wants to study and has launched a core facility that provides specially designed mouse models to researchers across Whitehead and at other institutions. Using the technology, Jaenisch created a unique line of mice with human B and T cells, which his lab uses to study the immune system, gaining deep insight into infectious and autoimmune diseases. Another mouse line that has been generated will allow the precise study of how environmental factors such as diet and stress affect aging and how diseases like Alzheimer's and Parkinson's alter the epigenetic state of the genome.

Although one may be spiny and one may be furry, starfish and mammals have common genetic elements that have been conserved over millions of years of evolution. In fact, starfish are actually closer evolutionarily to humans than some more commonly known model organisms like Drosophila and *C. elegans*. They also have an additional asset: Unlike mammals, a single starfish contains millions of oocytes—cells capable of maturing into eggs—that can remain quiescent for long periods. Leveraging these qualities, Whitehead Member Iain Cheeseman's lab, while still doing the bulk of their experiments in human cells, has begun using starfish specifically to study meiosis, fertilization, and initial embryonic development. The vast supply of oocytes enables Cheeseman and his colleagues to do a much larger number—and wider range—of studies than could be accomplished using standard model systems.

With a similar impetus to address a critical research question, Whitehead Member Peter Reddien has introduced the acoel *Hofstenia miamia*—otherwise known as the three-banded panther worm—a small marine worm that is an important new model for studying tissue regeneration. Reddien's lab demonstrated that genes underlying a key aspect of regeneration in both panther worms and planarian flatworms existed in their last common ancestor—which mammals shared—at least 550 million years ago. This finding shows the value of exploring new models that are evolutionary outgroups, highlighting mechanisms and molecules that have stood the test of time.

Regenerative Biology

Recapitulating development in the laboratory

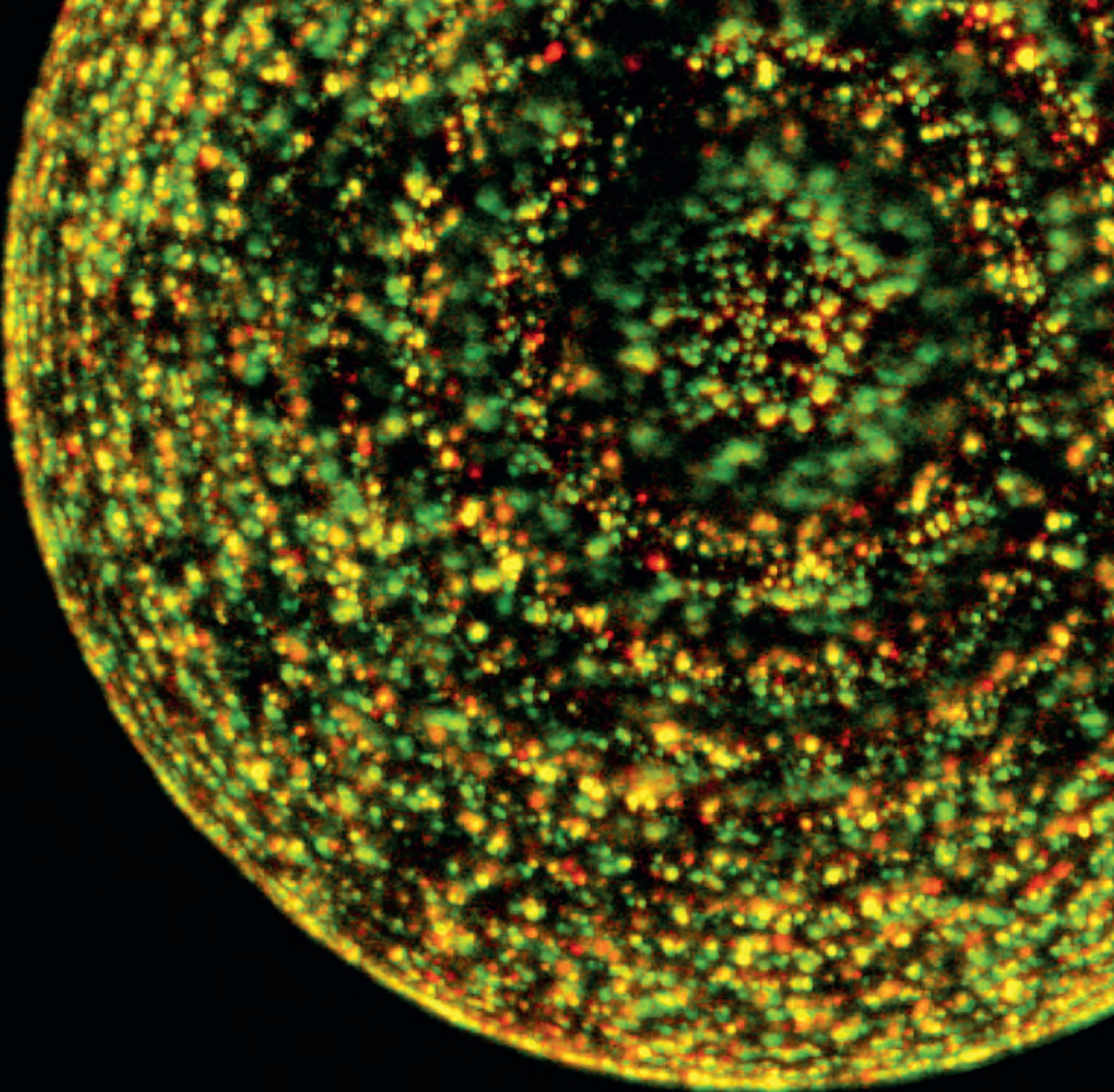
Sam LoCascio and Kutay Deniz Ataba, Reddien lab

Why are humans usually born with two arms and two legs? How do the cells in our muscles “know” to be muscle cells? Understanding the genetic programs that dictate basic body patterning information and the specification of particular cell types is crucial to our understanding of fundamental developmental processes. This knowledge not only helps us to understand the extraordinary evolution and diversity of form among organisms, but it also has the potential to be harnessed for a better understanding of certain birth defects and to inform strategies that could one day, for example, allow us to grow replacement organs in the laboratory for those in need.

Studying those animals that have retained the ability to regenerate is allowing Whitehead scientists to learn about body-plan specification in real time. For more than a century, the planarian has been studied for its regenerative ability. Incredibly, this small flatworm can replace any missing tissue: Cut one in two and both halves soon regrow the appropriate head or tail and become complete worms again. By understanding the mechanisms planaria use to regenerate, Whitehead Member Peter Reddien is gaining insights into this astounding process, not just in planaria but in other animals as well.

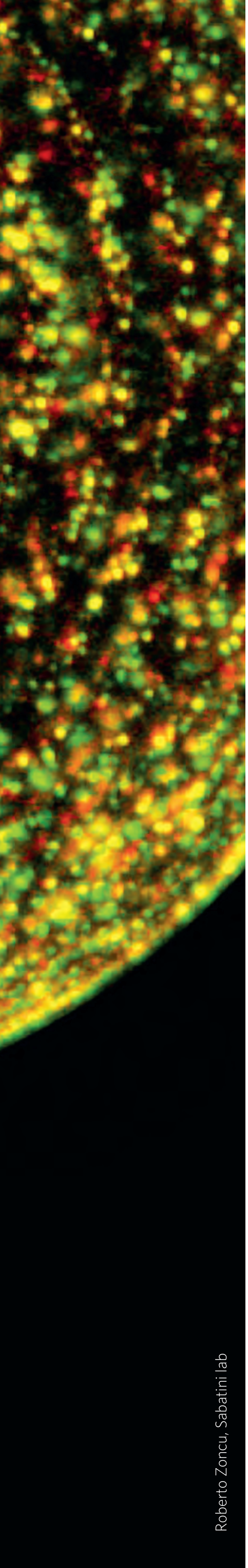
Recently, Reddien and his colleagues deciphered a GPS-like coordinate system in planaria muscle cells that instructs the animal’s stem cells about their current location and where they should go to replace missing tissue. Reddien’s research group also explored regeneration in another worm as well, the acoel. Though acoels and planaria are separated by about 550 million years of evolution, both use signals from muscle cells to direct regeneration. The findings of Reddien’s group suggest that this role for muscle is a conserved feature present in the regenerative common ancestor of all bilaterally symmetric animals. By comparing additional regenerative mechanisms in acoels and planaria, Reddien hopes to identify fundamental processes that those animals have in common.

The study of many diseases is hampered by the lack of material under investigation, such as, for example, brain cells from patients suffering from Alzheimer’s or Parkinson’s disease. By tapping into stem cells’ potential to create almost any cell type, Whitehead Founding Member Rudolf Jaenisch can generate much-needed cells and tissues for studying these and other diseases. One unique type of stem cell that Jaenisch uses is induced pluripotent stem cells (iPSCs), which are created by effectively rewinding adult cells back into a state similar to that of embryonic stem cells. Like embryonic stem cells, iPSCs can be prodded to mature into almost any cell type, including neurons and other cells that have previously been difficult to study in a petri dish. Recently, Jaenisch and his colleagues were the first to use iPSCs to create human and mouse microglia, a type of highly specialized immune cells in the brain that is emerging to play a crucial role in several neurodegenerative diseases. Because these cells reside in the brain, they have been particularly difficult to isolate and analyze, but harnessing the power of stem cells empowers research into these devastating diseases.



Metabolism

Uncovering the chemistry of daily life



Roberto Zoncu, Sabatini lab

Metabolism is the sum of life-sustaining chemical reactions in cells, including those that turn food into energy and build cellular structures. In recent years, researchers have intensified their focus on understanding the metabolic processes that underlie health and how these processes might go awry in disease. But for Whitehead Institute scientists, this is nothing new. For decades, they've been studying the role of metabolism in conditions ranging from obesity and diabetes to cardiac disease—with profound results.

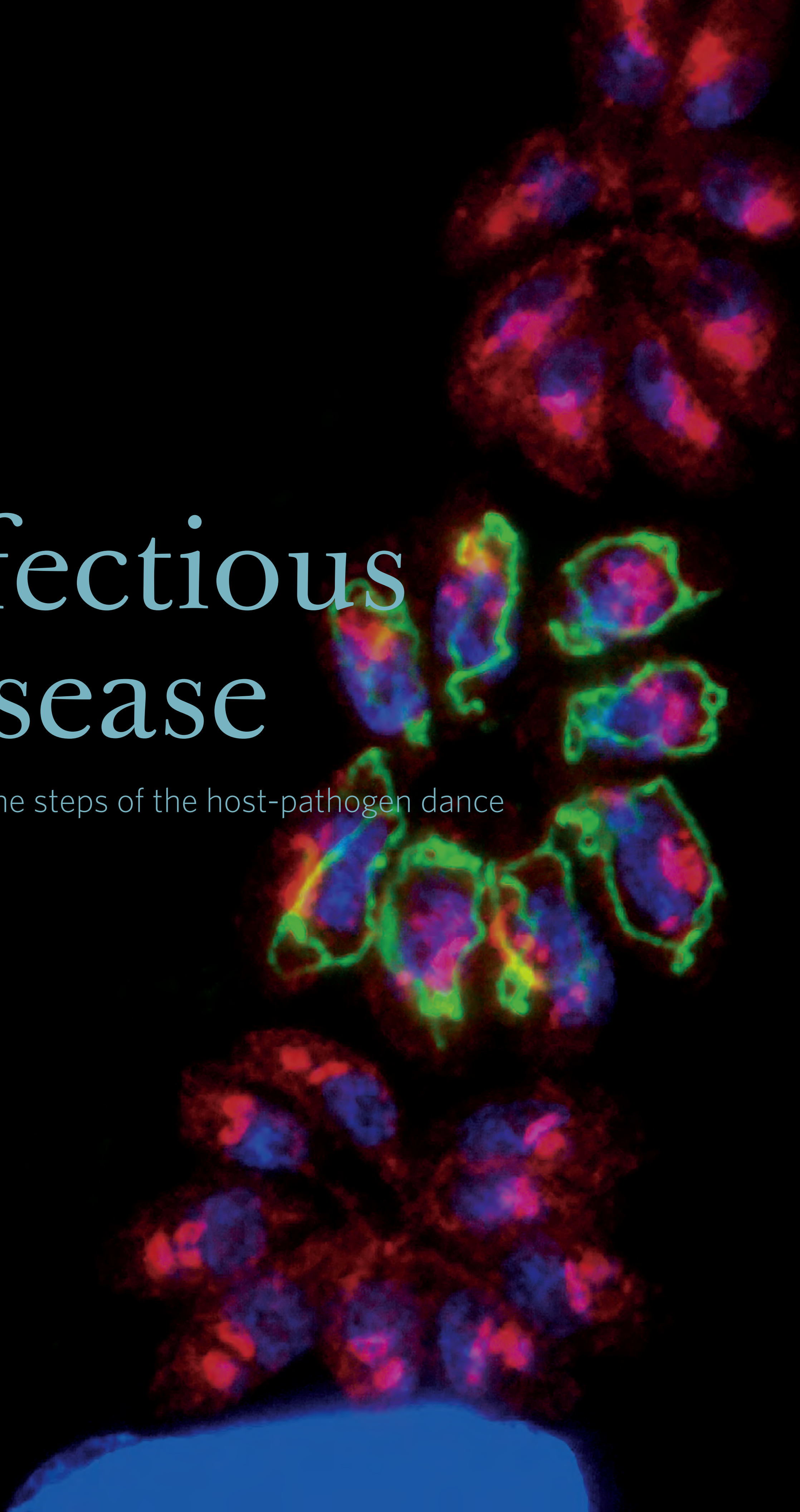
Whitehead Founding Member Harvey Lodish has made seminal advances in our understanding of metabolism throughout his career. His work on fatty acid and glucose metabolism has had important implications for our understanding of type 2 diabetes and obesity. More recently, the Lodish lab has been studying the role of regulatory RNAs, including long noncoding regulatory RNAs (lncRNAs) in adipose, or fat, cells. Lodish and his colleagues recently identified and cataloged approximately 1,500 lncRNAs identified in several types of adipose cells, including 127 selectively expressed in brown adipose cells, which burn energy to generate heat. They further uncovered that lnc-BATE1, one of those selectively expressed in brown adipose cells, is necessary for brown adipose cell development and function. These results provide key insights into how these important cells are regulated and show the utility of an annotated catalog of these lncRNAs for future studies.

Understanding how metabolites and nutrients regulate cell growth is a primary focus of Whitehead Member David Sabatini's research. Expanding on his paradigm-changing discovery of mTOR (mechanistic target of rapamycin), the key factor in a cellular pathway that helps switch cell growth on and off, Sabatini's lab is investigating the pathway's role connecting nutrients and metabolism with cell growth, as well as its role in aging and diseases such as cancer and diabetes. A recent study by Sabatini and his colleagues parsing the components of the mTOR pathway revealed an important source of its nimbleness in responding to cellular nutrient levels. The Rag GTPases play a critical role linking amino acid availability and mTOR pathway activation. Sabatini and his lab members showed that it is communication between the two subunits of the Rag GTPases, mediated by activation molecule binding and activity, that enables information about amino acid availability and growth conditions to be signaled to the mTOR pathway. This is the first instance of this type of intersubunit communication to be discovered among GTPases, and provides important insights into how amino acid availability is communicated for the mTOR pathway to function normally.

Whitehead Member Jing-Ke Weng is using cutting-edge metabolomic approaches to gain insights into myriad specialized metabolic pathways of plants. Since most plants remain stationary, "planted" in the ground, their metabolism must continually adapt to changing circumstances. Weng studies a diverse array of plants whose specialized metabolic pathways serve as a natural laboratory for learning how enzymes evolve. His lab recently discovered that an herbicide-resistance gene that had been engineered into crop plants such as corn and soybeans to make them resistant to a particular weed killer was actually acting promiscuously, affecting additional plant metabolites not intended for its original purpose. Weng and his team were able to make this finding using metabolomic profiling techniques that have only recently become available, and they were even able to engineer a more precise version of the enzyme, demonstrating the value of metabolomic analysis coupled with structure-guided engineering approaches.

Infectious Disease

Revealing the steps of the host-pathogen dance



Diego Huet, Lourido lab

Despite the profound medical advances of the past century, infectious diseases continue to take their toll globally. There have been notable success stories, such as the polio vaccine, game-changing antibiotics, and potent antivirals for infections such as those caused by the human immunodeficiency virus. But infectious diseases like malaria, tuberculosis, Lyme, and even the flu continue to cause suffering and death. Research on these diseases, which are caused by myriad viruses, bacteria, parasites, and fungi, is focused on understanding the pathogens as well as the host-pathogen relationship. Such an understanding can promote the development of effective therapies and inform control mechanisms aimed to prevent infection in the first place, particularly in places where insufficient infrastructure can compromise access to treatment.

Using an array of models and approaches, Whitehead researchers are working to close in on the biology underlying some of the most challenging infectious diseases.

Whitehead Founding Member and Former Director Gerald Fink was instrumental in developing S*accharomyces cerevisiae*, or brewer's yeast, into a powerful model for cell biology, as well as a living factory for vaccines and other drugs. Using this model organism, Fink pinpointed the genetic basis of a fungal "invisibility cloak," that enables fungal microbes to readily disguise themselves from the immune system, and uncovered how yeast transform from a single cell into long finger-like filaments that invade tissues and create the slimy biofilms that attach to catheters and prosthetic devices. Fink has also studied how a serious infectious agent—the fungus *Candida albicans*—resists antifungal treatments. Candida has unique strategies for both the invisibility cloak mechanism and filamentation, which hint that targeting these essential functions could produce novel antifungal therapies. More recently, Fink and his lab members created a CRISPR system for Candida. The Candida CRISPR system finesses many of the problems in targeting drug-resistance genes and opens up new possibilities for genetically engineering Candida to determine the mechanisms of resistance to antifungal drugs that make this fungus such a successful pathogen.

Whitehead's newest Member, Sebastian Lourido, studies *Toxoplasma gondii*, the parasite that causes toxoplasmosis. Humans can become infected with *T. gondii* from cat feces or contaminated food and water, and toxoplasmosis contracted during pregnancy can be harmful to the fetus. *T. gondii* is also an important subject of research because it is a member of a large phylum of single-celled parasites called apicomplexans, whose other members include species from the genera *Plasmodium*, which cause malaria, and species from the genera *Cryptosporidium*, which cause severe diarrhea—both leading causes of infant mortality in developing countries. By teasing apart the mechanisms *T. gondii* uses to reproduce, invade, and exit its host's cells, Lourido aims to identify specific therapeutic targets against these parasites. He recently used CRISPR/Cas9 to conduct the first genome-wide screen ever done on *T. gondii* or any of its relatives. The work revealed about 200 genes that are unique to this phylum of parasites and uncovered a new invasion factor for infection called claudin-like apicomplexan microneme protein (CLAMP). CLAMP is conserved in all apicomplexans whose genome sequence has been analyzed and is essential in *Plasmodium*, potentially identifying a key potential target to treat parasitic infection.

Neuroscience

Tackling neurodegenerative and neurodevelopmental disorders with innovative approaches

One of the major challenges facing the study of neurodegenerative disease and neurodevelopmental disorders is the relative inaccessibility of the organ in question: the brain. Whitehead Institute researchers have been fostering ingenious approaches to studying brain development and disease in order to circumvent this challenge.

Whitehead Member Hazel Sive uses the zebrafish to study early brain development. Zebrafish have a striking genetic similarity to humans and can also exhibit certain human behaviors, such as hyperactivity and seizures. One fascinating line of Sive's work focuses on a region of the genome known as 16p11.2, first identified by former Whitehead Fellow Mark Daly. This region on chromosome 16 consists of about 25 genes, and, in humans, duplications and deletions in this region have been linked to multiple brain and body disorders, including autism spectrum disorder, developmental delays, seizures, and obesity. Sive has documented, for the first time, a direct link between deletions in two genes—*doc2a* and *fam57ba*— in the 16p11.2 region of zebrafish and certain brain and body traits, such as seizures, hyperactivity, enlarged head size, and obesity. Establishing a molecular connection between a brain and a body phenotype is shifting a scientific paradigm in which the brain and body are studied separately in these conditions to contemplating common control mechanisms. This shift could help researchers identify factors that could ultimately become therapy targets.

Whitehead Founding Member Rudolf Jaenisch is studying Parkinson's disease, a progressive neurological disorder. Sporadic Parkinson's, which is about ten times more common than the inherited form, is caused by the interaction of genetic risk factors, protective factors, and environmental factors, each of which have small, cumulative effects. Jaenisch's lab was the first to define—down to the DNA sequence—a specific risk factor located in a regulatory region of the genome. Such a granular understanding may be key to uncovering the factors that contribute to sporadic Parkinson's and their interactions.

Recently, Jaenisch also began working with three-dimensional human brain organoids—miniature, lab-grown brain structures. These organoids can model the molecular, cellular, and anatomical processes of human brain development with the advantage that cell-to-cell interactions in the organoid may more faithfully replicate how our own brains actually work than cells in a Petri dish can do. Using the organoid model, Jaenisch's lab identified a specific factor that appears to regulate the growth, structure, and organization of the outermost layer of the brain, called the cortex, and documented the effects of Zika virus on its development.

The late Susan Lindquist, Director of the Institute from 2001 to 2004 and a former Member, was renowned for doing what was once unthinkable: using yeast as a model to investigate neurodegenerative disease. With this approach, Lindquist became one of the first to examine the role that protein trafficking—the processes by which newly-minted proteins travel from where they're made, to where they need to function—plays in Parkinson's disease. One hallmark of Parkinson's is the presence of Lewy bodies, clumps of a protein called alpha-synuclein found in certain neurons in the brain. Lindquist found that an overabundance of alpha-synuclein tends to cause specific disruptions in protein trafficking, and her exploration of alpha-synuclein's role in Parkinson's has altered the way scientists view the disease, both how it arises and how its devastating progression might be better controlled.

Commercializing Discovery

Accelerating progress from discovery to therapy

Whitehead Institute is focused on discovery research, exploring the basic mechanisms of life and how they go awry in disease. Our investigations create knowledge that spur new ways to improve human health; discovering the underlying mechanism of a disease, for example, opens a new opportunity to develop a new way to treat it. But turning the opportunity into a product that benefits patients is an extraordinarily complex and expensive process.

Navigating this process successfully requires not only exceptionally talented people with an array of skills, but also substantial financial capital and an appetite for risk—because only a minority of drug-development efforts succeed in delivering an effective product to market.

Given the challenges of developing therapeutics, the most efficient way for academic researchers to realize the therapeutic benefits inherent in their basic science discovery is to work with established companies or launch new companies that can license the discovery's intellectual property (IP) for development. These companies have product-development capabilities not available to most academic scientists.

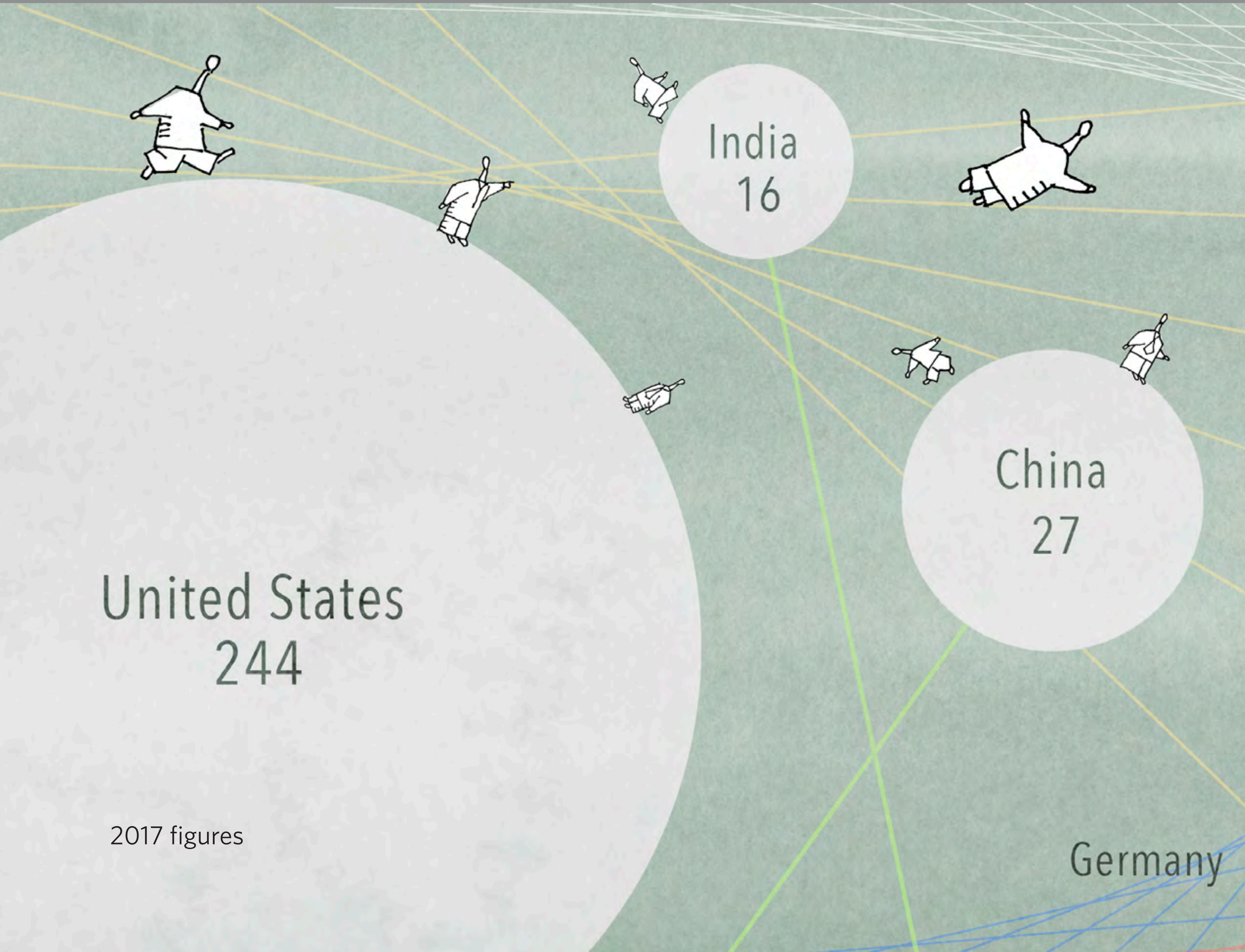
If, for example, the IP targets a disease-producing protein, the drug development team might include biologists to manage the assays, medicinal chemists to design small chemical molecules, structural biologists to explore interactions between proteins and drugs at atomic resolution, and clinical experts to evaluate the potential effectiveness or toxicity of the product. Should the resulting drug be deemed safe and effective in preclinical tests, then a series of clinical trials are carried out to test the drug's safety and efficacy for humans. This process can take a decade or more.

During the past five years, Whitehead has pursued patent protection on 81 inventions, entered into 53 licenses for the commercial development of intellectual property, and provided the foundational IP for eight start-up companies in various stages of developing, testing, and marketing new therapeutics. Together, these start-up companies have raised well over $1 billion in commercial funding and have created jobs for more than 300 people.

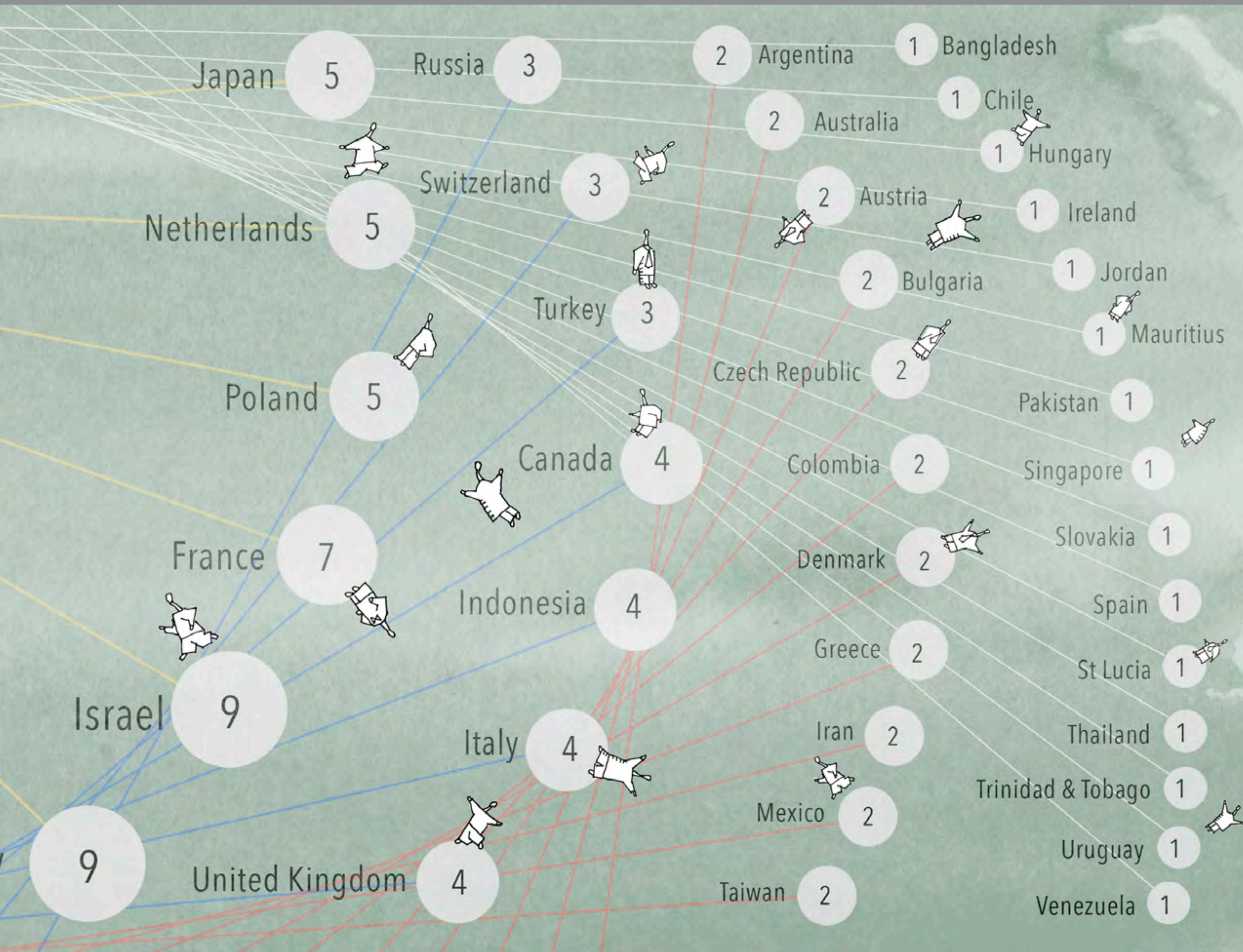
One of the most mature of the Whitehead-affiliated start-up companies, Alnylam Pharmaceuticals, was created in 2002 to apply pioneering work on microRNAs by Whitehead Member David Bartel and other scientists. The company has become a highly productive driver of new treatments for conditions ranging from hemophilia to cardiac amyloidosis to high cholesterol. In 2016, *Forbes Magazine* included Alnylam—which has a market value of approximately $10 billion—on its 100 Most Innovative Growth Companies list.

A more recent start-up, Rubius Therapeutics, was established in December 2015 with Whitehead Member Harvey Lodish as a scientific founder. Launched by venture capital firm Flagship Pioneering with an initial commitment of $25 million, Rubius has been developing a new class of drugs based on the approach Lodish and his colleagues developed to engineer red blood cells to express therapeutic proteins on the surface of, or inside the cell. The approach holds therapeutic promise for conditions ranging from autoimmunity and enzyme deficiencies to cancer and infectious disease. Motivated by preclinical proof-of-concept results, investors provided an additional $120 million in private funding in mid-2017. The company plans to start human clinical trials in 2018.

Extending the Whitehead Legacy



The legacy of Whitehead Institute manifests in the accomplishments of its pioneering Members and in its unique environment, which has produced decades of paradigm-shifting discoveries. From its earliest years, the Institute's impact has also been realized far beyond Cambridge, embodied in the work of the stellar young scientists who do their graduate or postdoctoral research at the Institute and then go on to assume faculty positions and scientific leadership roles at universities, research institutes, and biotech and pharma companies around the world.




ISOProx II

“Although the research discoveries from Whitehead laboratories are incredibly impactful,” says Iain Cheeseman, Whitehead Member and an associate director of the Institute. “I am particularly proud of the contributions that the Institute has made to training the next generation of scientists. Whitehead’s devotion to its training mission is reflected in an attitude and a philosophy that pervades the Institute, creating an atmosphere that elicits inspiration and perspiration from the trainees, whose work drives our labs’ discoveries.”

Whitehead’s formidable reputation enables it to recruit the cream of the global crop of newly-minted PhD scientists. The Institute currently hosts 90 postdoctoral researchers from 25 countries, in addition to 68 biology doctoral students from Massachusets Institute of Technology (MIT). “We are fortunate to recruit truly outstanding scientists to Whitehead,” says Cheeseman, “and once they are here, we do everything we can to support their training and professional growth.”

In fact, Whitehead has been repeatedly named the best place to work for postdocs by *The Scientist* magazine. “Whitehead has been a leader in supporting postdocs through increased salaries and child care support,” he says. “And we have a multifaceted professional development program.” For example, the Institute sponsors the weekly Whitehead Forum series, where Whitehead trainees present and discuss their work, as well as a dynamic annual scientific retreat. In addition, the Whitehead Postdoc Association organizes training, networking, and professional learning activities supported by Institute faculty and administration and provides grants for trainees to attend national and international meetings.

Here we meet five of Whitehead’s current trainees—each already an impressive scientist and emerging leader—and find out what brought them to Whitehead and the research paths they are currently pursuing.

Yun Li

Postdoctoral researcher Yun Li grew up in Wuhan, China. She knew from childhood that she loved both biology and academia—perhaps not surprisingly given that her mother was a high school biology teacher and her father a university professor who specialized in Chinese literature. “Watching them,” she says, “I came to appreciate academic life and the deep sense of purpose that teaching gave my parents.” She studied biology at Wuhan University, then earned her PhD at the University of Texas, Southwestern, where she focused on neurobiology and neurological diseases in mice. “At that time, in the early 2000s, there was no way to directly study human brain develop-

ment and diseases *in vivo*," she says, "so we focused on animal models." But that was about to change with the introduction of sophisticated methods for creating human stem cell lines and powerful new gene-editing techniques.

By 2010, when Li was finishing her doctorate, the lab of Whitehead Founding Member Rudolf Jaenisch had become one of the first to use stem cells to create human models of neurological development and disease. Learning of that work, Li knew where she wanted to do her postdoctoral research. "Not only was Rudolf a pioneer in the field," she says, "but my mentor had been a PhD student in [Whitehead Founding Member] Bob Weinberg's lab and spoke very highly of his experience at Whitehead." For the past seven years, Li has worked in the Jaenisch lab studying human brain development and autism spectrum disorders. In her most recent published study, she and her colleague Julien Muffat reported using small, three-dimensional models of human brain structures, or organoids, to pinpoint what may be the molecular and cellular catalyst for the development of the cortex, the brain's folded structure.

Li's experience at Whitehead—particularly Rudolf Jaenisch's mentorship—has prepared her well for the next step in her career. At the end of this year she'll take a faculty appointment at the University of Toronto and a research appointment at its world-renowned affiliate, the Hospital for Sick Children. (Li is pleased that her Whitehead colleague and life partner, Muffat, will also be going to the University of Toronto to start a lab.) Li's research there, building on the knowledge and skills she gained at Whitehead, will continue to uncover the roots of autism and the ways in which the development of autistic and neurotypical brains differ. But, she notes with pleasure, "I'll also have the opportunity to return to one of my earliest interests: studying the diverging evolutionary paths that led to human and nonhuman mammalian brains."

Tomáš Pluskal

Postdoctoral researcher Tomáš Pluskal, who works with Whitehead Member Jing-Ke Weng, took a circuitous and rather serendipitous path to biomedical research. "I grew up in Prague, in the Czech Republic," he says, "and studied computer science at Charles University. I'd long had a passion for martial arts and Japanese culture, and after college, I moved to Japan." To earn money there, he took a job as a lab technician at the Okinawa Institute of Science and Technology. It was his first experience working in basic science and he enjoyed it so much that he decided he wanted to pursue his own research projects.

"I entered a PhD course at Hiroshima University," he recalls, "and my computer science background naturally drew me to high-throughput 'omics' methods." His doctoral work focused on fission yeast metabolomics and, although the research was very quantitative, he became fascinated by the mysteries surrounding the purpose of a variety of small molecules. Those mysteries drew him deeper into the study of specialized metabolism.

When it came time to find a home for his postdoctoral research, Pluskal investigated a number of institutions. Though he was initially attracted to Whitehead by its reputation, it was a more personal connection that sealed his decision to come to Kendall Square in 2015. "I was motivated by the scope of research being done in the Weng lab," he says, "and by the personal chemistry I felt with Jing-Ke." In the Weng lab, Pluskal is leveraging his computer science background to develop a new software platform that permits rapid structural analysis of the largely-unexplored chemistry of Earth's vast flora. He is currently exploring *Piper methysticum*, or kava kava, a domesticated Pacific Islands plant whose roots are used in a beverage reputed to help resolve conditions ranging from insomnia and stress to urinary tract infections. With colleagues in the Weng lab, Pluskal is identifying the genetic and proteomic roots of the metabolites that spur these effects and looking forward to the day they can be synthesized in the laboratory and applied as treatments for a variety of health problems.

Asked what success at Whitehead might look like for him, Pluskal says, "While in broad terms researchers have a fairly good understanding of specialized metabolism in microbiota, plants are a completely different story, because the genes that drive the creation of metabolites are distributed randomly across complex genomes. But if we could develop a high-throughput method to track the production of metabolites in plants, that would be a major success with huge implications for the development of naturally-based products that promote human health."

Amelie Raz

"I'm fascinated by regeneration—the fact that, with certain species, you can cut an individual into two pieces and watch the head grow back on one and the tail grow back on the other," says MIT graduate student Amelie Raz. "Almost as amazing is that the organism knows which part to grow back."

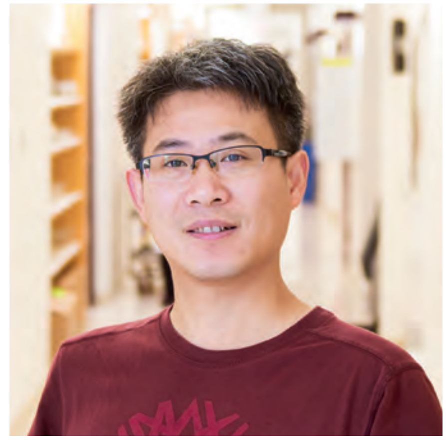
Raz grew up in the suburbs of Philadelphia and went to Bryn Mawr College, where she worked in a lab studying epigenetic regulation, which results from changes to DNA that do not involve alterations of its sequence. She was fascinated by how varied phenotypic characteristics can arise from identical genomes and after graduation studied breast cancer in a University of Pennsylvania lab. "I very much liked the lab environment," she says, "and found that I was most interested in questions about basic biological functions." That realization brought her to MIT's biology department to earn her PhD, and to a series of first-year rotations in several Whitehead labs.

It was the rotation with Whitehead Member Peter Reddien's group that spurred her interest in regeneration. Reddien has made foundational discoveries in the field, working with two evolutionarily distinct worms—planarian and acoels—that share robust capacities for regeneration: Cut off any portion of the worm's body and that portion will grow into a completely new individual.

Says Raz, "The big questions we're asking include, Why can some animals regenerate fully, while others, such as mammals, have very limited regenerative capacity? Do all animals with regenerative capacity use the same mechanisms to accomplish it? And how do these animals know to regenerate the right part of the body?"

As Raz ticks through those questions, one can hear in her voice the intellectual energy created by being part of the lab's vibrant research community and the deep satisfaction she receives from Whitehead's rigorous scientific training.

Xu Zheng



Born in a village in China's Sichuan province, postdoctoral researcher Xu Zheng studied agricultural economics and finance in college and then began working in a civil service bureau. But he found the job uninspiring and cast around for a different career track. "Science was always fun to me," he says, "and since my interest in agriculture remained very strong, I chose to become a biology researcher." He earned his master's degree in plant breeding and his PhD in plant biochemistry and bioengineering at the Chinese Academy of Agriculture Sciences, studying the use of light signaling to promote genetic changes in plants.

It was a web search and a fortuitous meeting that brought Zheng to Whitehead in 2013. Approaching the end of graduate school, he began educating himself about the best research centers in the world. Intrigued by what he found on Whitehead Institute, he downloaded a prior year's annual report and learned of *The Scientist* rankings naming Whitehead among the best places for postdocs to work. Coincidentally, not long after that, Zheng attended a workshop at Peking University and joined a discussion team led by Whitehead Fellow David Pincus. Later that day, Zheng and Pincus had a one-to-one conversation. "David described his plans for creating his new lab at Whitehead," Zheng recalls. "I am a plant biologist and David is a cell biologist. But he told me, 'We may use different materials, but biology works in similar ways.'" Zheng is sure it was that talk that led Pincus to look favorably on his application to Whitehead.

Skip ahead to 2017: Zheng is wrapping up a nearly five-year program of research in the Pincus lab. He's preparing to leave early next year to become a founding faculty member at Henuan Agriculture University's new Institute on Agriculture Engineering. "Henuan is China's most productive agricultural province," he says. "Our charge will be to help maintain that productivity by identifying or engineering new kinds of food crops that are well-suited to the environment being created by the changing climate."

Zheng's investigations over the past five years have provided a solid foundation for that work. They've also given him a clear vision for the kind of working environment he'd like to help create at the new institute and the type of mentor he would like to be. "David is very interested in hearing everyone's ideas and making decisions as partners," Zheng says. "That kind of guidance is very important." Just as significant, he adds, is having an engaged and interactive community. "That's what makes Whitehead such a special environment. Here, anyone will help you if they can, whether you have worked together before, or you're a new face at the door. That is unlike almost any other research center I know."

Benjamin Williams

Postdoctoral researcher Benjamin Williams grew up about 20 miles outside of London, in an old farm-house. From an early age, he was intrigued by nature and biology and enjoyed the time he spent watching

birds and investigating plants around his home. That interest continued to mature and by the time he finished high school he knew he wanted to pursue a career in scientific research.

“I did my PhD in the Plant Sciences Department at the University of Cambridge,” says Williams. “While I thoroughly enjoyed it, I felt that I was missing out on the diversity of discoveries and progress being made from the study of other systems.” His solution: seek postdoctoral research in a top-notch plant biology laboratory at an institute with a real diversity of research areas—one, if possible, that offered opportunities for multidisciplinary collaborations with really smart people working in varied kinds of organizations and environments. Whitehead Institute, Kendall Square, the “other Cambridge”—check, check, check. “This is a really exciting place to work,” Williams says, “because you encounter amazing minds and ideas here almost daily, beginning with Mary.” (Whitehead Member Mary Gehring, that is—the renowned plant biologist who studies epigenetics and the myriad implications of DNA methylation, and who leads the lab Williams landed in.)

“Epigenetics really highlighted so many blank spots in my understanding of biology that I felt compelled to start working on some of those questions,” Williams says. “I was also fascinated by the fact that in plants, epigenetic modifications can be passed on to future generations, adding new complexity to the supposed laws of genetic inheritance.”

Plants have evolved ways to maintain patterns of DNA methylation through successive generations, and studying these phenomena has required Williams to cultivate the patience to do some very slow experiments. “But there are definitely rewards,” he says. “I’ve managed to identify one of the mechanisms that has evolved to maintain consistent inheritance over several generations of a plant’s lineage.”

Given the breadth and time scales of the mechanisms he is studying, how does Williams define success? “Ultimately,” he says, “I will feel successful if I’m able to contribute, even in a small way, to understanding some of the big open questions in the field, beyond just satisfying the curiosities that appeal to me.” One of the particular benefits of training at Whitehead may be the opportunity to achieve both.

Philanthropy

Partners in Research

By Charles D. Ellis, Chair
Board of Directors, Whitehead Institute

Soon after World War II, presidential advisor and former Massachusetts Institute of Technology dean Vannevar Bush wrote a prophetic report entitled "Science, The Endless Frontier." In it, Bush asserted that basic scientific research was one of the best investments the United States could make to ensure its long-term economic and geopolitical strength.

Bush's foresight was translated into a national policy that eventually included creation of the National Science Foundation and National Institutes of Health to foster the growth of world-class research programs at major universities and independent research centers throughout the country.

For over 70 years, large federal investments in basic research have produced amazing results across many areas and, most particularly, in basic research that led to major advances in the life sciences. Study the roots of important medical advancements—from MRI and laser surgery to affordable insulin and therapies for cancer and HIV—and you'll find they all started with basic scientific research driven by great scientists' instincts for cutting-edge discoveries and inspired, rigorous peer review. The results: America's global leadership.

Surprisingly given past success, as a share of the gross domestic product, federal research funding has actually fallen by a third since 1976. This reality challenges private philanthropy to provide essential support.

In these grim times of uncertain federal funding, we must think innovatively and deeply about how to fund Whitehead scientists' ambitious research objectives. Because infrastructure is critical to advancing scientific discovery, we have undertaken a $25 million renovation of our building. That is a necessary investment, but not sufficient; the continuous advancement of scientific methods and technical tools requires us to keep Whitehead Institute's research facilities at the leading edge of technology. And as whole new fields of biomedicine evolve, we look for opportunities to build the breadth of our researchers' expertise, adding to the number of postdoctoral researchers and senior scientists in our Members' labs, staffing core support facilities, and sustaining the Whitehead Fellows Program—the world's leading program for emerging bioscience leaders.

By bringing together a group of world-class research scientists and giving them the financial and intellectual freedom to blaze new trails, Whitehead Institute expands the boundaries of biomedical knowledge and creates new ways of overcoming disease. This past year alone, our scientists' intrepid work has brought scores of major advances including—to mention just a few examples—engineering red blood cells to help tackle early-stage multiple sclerosis and diabetes, identifying early-stage breast cancer tumors that are likely to metastasize, and pinpointing potential new therapeutic targets to treat infection by HIV.

Thanks to Whitehead's extraordinary research productivity during the Institute's first 35 years of achievement, the time has come to expand the scale of the organization that Edwin C. "Jack" Whitehead and our founding faculty have created. In partnership, generous philanthropists and world-class scientists can build on the record of past discoveries and advance Whitehead Institute into its next generation of scientific creativity and discovery in the service of human health advances for our grandchildren and their world.

Sparking Innovation

Corporate sponsor helps inspire innovators of tomorrow with middle school program support

The Amgen Foundation has been a longtime supporter of nonprofit organizations that spark students' interest in STEM (science, technology, engineering, math) fields through hands-on, inquiry-based science experiences.

Three years ago, Whitehead Institute was honored to become a recipient of an Amgen Foundation grant designed to help strengthen Expedition: Bio, the Institute's popular science education program for middle school students.

The Expedition: Bio program consists of week-long immersion courses that combine stimulating lessons, hands-on experimentation, and group activities to generate enthusiasm for science among rising sixth, seventh, and eighth graders in Greater Boston. Sessions are held in the summer and during the February school vacation week, and are run in partnership with Science from Scientists, a leading in-class science/STEM enrichment program in Massachusetts.

"The Amgen Foundation is committed to making grants to programs such as Expedition: Bio, during which students can develop an understanding and appreciation for science through hands-on experiments and direct interactions with scientists," says Aine Hanly, Amgen Massachusetts site head and a vice president. "We are proud to support Whitehead Institute's dedicated efforts to delivering high quality, creative STEM programming to inspire tomorrow's innovators."

The foundation's support has been instrumental to Whitehead's ability to continually enrich the program experience. For example, Amgen helped to underwrite the addition of wildlife- and ecology-oriented field trips and the purchase of new laboratory equipment. It also helped make Expedition: Bio available to more students by increasing the number of summer sessions and providing financial assistance for underprivileged students.

Advancing excellence in science education has not been the Amgen Foundation's only focus. Community life is also important, and strengthening the communities where Amgen staff members live and work is a priority. Direct engagement between local Amgen scientists and Expedition: Bio students through lunchtime mixers has offered students a first-hand glimpse into the day-to-day life of a working scientist, exposing them to the myriad ways they can pursue science as a career. These interactions have, in turn, given volunteers an opportunity to actively engage students within the community, helping to inspire the next generation of scientists.

"We couldn't be more thrilled with the Amgen Foundation's support," says Amy Tremblay, Whitehead Institute's public programs manager. "It has better enabled us to help reduce perceived barriers to entry into science fields, eliminate the 'uncool' stereotype associated with science jobs, and, most importantly, spark a love of science."

Accelerating Solutions

Cure Alzheimer's Fund

Cure Alzheimer's Fund is a nonprofit organization committed to accelerating research that will help prevent, reverse, or limit the progression of Alzheimer's disease. It was founded in 2004 by three families frustrated by the slow pace of research. They leveraged their collective experience in venture capital and corporate start-ups to build a funding organization designed to dramatically advance Alzheimer's disease research by making bold bets focused on finding a cure. To date, the Cure Alzheimer's Fund has provided nearly $60,000,000 for impactful research projects with the potential to drive breakthroughs.

"The Fund's approach is to support early work on brilliant, untraditional ideas," says Meg Smith, the organization's senior vice president. "We aim to help generate the data necessary to convince conventional funders to provide longer-term grants to develop the work further. We support projects pursuing visionary ideas from well-established investigators with proven track records."

Two of the visionary ideas supported by the fund are the products of Whitehead Founding Member Rudolf Jaenisch's fruitful mind. One project builds on his unparalleled expertise using stem cells to develop disease models; the Jaenisch lab is differentiating induced pluripotent stem cells into neurons, treating them with stressors, and then monitoring alterations in the patterns of particular chemical changes to the DNA called methylation to see if they mirror those observed in Alzheimer's.

In the second project, the Jaenisch lab, in collaboration with a world-renowned Salk Institute scientist, is characterizing genome-wide DNA methylation patterns by examining post-mortem human neurons in subjects with normal aging and in those with Alzheimer's. The goal of both projects is to understand the fundamental effects of changes in methylation on the disease state and what causes them.

Jaenisch is excited that the Cure Alzheimer's funding has allowed him to jumpstart a complex area of research that is technically challenging and scientifically high risk. It has also enabled him to engage with a large consortium of researchers who bring their diverse, complementary expertise to the challenge of understanding more about the molecular basis of the disease.

For its part, the Cure Alzheimer's Fund loves working with Jaenisch. "We're very impressed by the environment surrounding Rudolf," says Smith. "Whitehead provides brilliant colleagues, great infrastructure, a collaborative culture, and access to the best technology. It creates a context for achieving real results."

Catalyzing Discovery and Growth

In Memoriam: Landon T. Clay

When Landon Clay died in July 2017, the Whitehead community lost a true friend and—along with his wife, Lavinia—a strong philanthropic supporter of the Institute's scientific mission.

Clay was first introduced to Whitehead Institute in 2001. Over the next few years, he and Lavinia took an increasing interest in the Institute's research in general and in the individual scientists driving its pioneering work. In 2006, Clay was elected to Whitehead Institute's Board of Directors, where he served three terms.

Among his many contributions to the Institute's strategic leadership, Clay advocated for a more aggressive pursuit of intellectual property licensing. "It was Landon's vision that spurred the creation of the Whitehead's Intellectual Property Office," notes Institute Director David Page. "That program has significantly quickened the translation of Whitehead discoveries into potential therapeutics." For his wise counsel and tireless engagement, in September 2015 the Board of Directors elected Clay Director Emeritus.

Clay was not only generous with his time and insight; he and Lavinia were the Institute's second greatest benefactors after founder, Edwin C. "Jack" Whitehead. Two of their gifts were particularly notable. One created the Clay Fellowships, supporting eight postdoctoral researchers pursuing immunology research; the other established a fund to support a multi-lab collaboration seeking new approaches to studying autoimmune and infectious diseases. The collaboration fund advanced highly productive work on subjects ranging from the immune response to genetic control of cell identity. The Clays' gift also enabled Whitehead to launch the Genetically Engineered Models Core Laboratory, which has become an extremely productive facility for generating defined-mutant mice. And it helped support the training of dozens of talented and highly skilled young scientists—many of whom have gone on to faculty positions at major universities and leadership roles in the multiple startups that emerged from Clay-supported discoveries.

Landon and Lavinia's philanthropy was catalytic in many ways. Their generous support helped create new knowledge, spur technological advances, and seed the development of potential therapeutics. It also provided leverage for more than $20 million in additional external funding for Whitehead research built on Clay-supported work.

"Landon and Lavinia had a deep appreciation for world-class talent, and saw an extraordinary treasure in Whitehead Institute's research, its people, and its mission," says Page. "They understood and appreciated Whitehead Institute's potential and became our partner in countless ways."

Community

New Board Members Helping to Drive Whitehead Institute Forward

L to R: Michael W. Bonney, Amy Schulman, Deval Patrick, Andrew Lo

Over the past two years, Whitehead Institute has added four exceptional leaders to its Board of Directors. Bringing with them diverse and complementary expertise, they share a passion for advancing biomedical research. Their appointments are representative of the Institute's longstanding commitment to bringing new perspectives, backgrounds, and talents to the eighteen-member Board.

Two of the new Board members, **Michael W. Bonney** and **Amy Schulman**, have celebrated track records in pharmaceutical and biotech company leadership. Bonney brings to Whitehead a wealth of experience in the life sciences industry. As chief executive officer of Cubist Pharmaceuticals, he oversaw the company's growth from startup to biotech powerhouse to its acquisition by Merck. Previously, he served as vice president of sales and marketing for Biogen and as national business director of Zeneca Pharmaceuticals. Currently, Bonney is CEO of Kaleido Biosciences and chair of the board of directors at Bates College, his alma mater. He is also a board member for Alnylam Pharmaceuticals and Celgene Corporation. "I accepted this role first, because of Whitehead's renown for both delivering scientific advances and training bioscience research leaders," Bonney says. "And second, because I can provide a point of connection between Whitehead's world-class scientists and investors seeking to commercialize their discoveries. In an environment where the federal commitment to research funding is uncertain, the Institute's capacity to develop alternative sources of support is crucial."

Amy Schulman has held top leadership positions in both large pharmaceutical companies and innovative start-ups, and has been an attorney in private practice. She is widely recognized for growing global businesses and fostering inclusive cultures. *Fortune* magazine named her one of its 50 Most Powerful Women in Business; she was cited in *Fierce Biotech*'s Top 15 Women in Biotech, *Scientific American*'s Worldview 100 List, the *National Law Journal*'s 100 Most Influential Lawyers in America; and she was recently honored with the 2017 *Xconomy* Newcomer Award. Schulman was named general counsel for Pfizer, Inc. in 2008 and soon thereafter was appointed to lead the company's $4 billion consumer healthcare business (while serving as Executive Vice President and General Counsel). Subsequently, she left Pfizer to join the venture capital investment firm Polaris Partners and led several life sciences startups: She was CEO of Arsia Therapeutics (acquired in 2016 by Eagle Pharmaceuticals), and she is currently co-founder and CEO of Lyndra, CEO and executive chair of Olivo Laboratories, and executive chair of SQZ

Biotechnologies. Schulman is also a member of the board of directors of Alnylam Pharmaceuticals, Blue Buffalo, and Ironwood Pharmaceuticals. "I am a long-time admirer of Whitehead Institute," she says, "both for the caliber of its science and for its commitment to entrepreneurial development. As its engagement with the biotech community grows, I'm committed to helping advance Whitehead's most exciting discoveries to the point where they directly benefit patients."

Deval Patrick brings to the Whitehead Board an extraordinary background and deep expertise in both public and private leadership. He has degrees from Harvard College and Harvard Law School and has served as general counsel at Coca-Cola and Texaco. He was appointed as United States Assistant Attorney General for Civil Rights and was elected to two terms as governor of Massachusetts. As governor, he oversaw the expansion of affordable healthcare to more than 98 percent of state residents, created initiatives stimulating clean energy and biotechnology, and launched the Massachusetts Life Sciences Initiative—a ten-year, $1 billion investment in life sciences research, infrastructure, and education that has transformed the region. He now serves as a managing director of Bain Capital's Double Impact business, which seeks investments that deliver both a competitive financial return and significant positive societal benefit. "For more than three decades, Whitehead has been a symbol of Massachusetts's and the nation's excellence in biomedical research and a leader in the biotech ecosystem," says Patrick. "It's an honor to work with an organization so passionate in its scientific pursuit of improved human health and so successful in pioneering the future path of bioscience."

Andrew W. Lo is a thought leader whose current research focuses include the use of financial engineering to develop new funding models for biomedical innovation. He is the Charles E. and Susan T. Harris Professor at the MIT Sloan School of Management, director of MIT's Laboratory for Financial Engineering, and has taught at MIT since 1988. Lo is also a prolific writer who has written or co-written several books including *The Econometrics of Financial Markets, A Non-Random Walk Down Wall Street, The Heretics of Finance, The Evolution of Technical Analysis,* and, most recently, *Adaptive Markets: Financial Evolution at the Speed of Thought*. When he's not teaching, writing, or conducting research, Lo is an advisory board member for the United States Securities and Exchange Commission, the Commodity Futures Trading Corporation, and the New York Federal Reserve Bank. He serves as chairman and chief investment strategist of the quantitative investment management company AlphaSimplex Group and is on the board of drug developer Roivant Sciences. He also advises the drug-discovery/development firm BridgeBio. Among Lo's many recognitions and awards, *Time* magazine has named him one of its 100 Most Influential People and he is a fellow of the American Academy of Arts and Sciences. "The Whitehead Institute has pioneered a number of breakthroughs in the life sciences, but the best is yet to come," says Lo. "Biomedicine is at a turning point and Whitehead researchers will continue playing a leadership role in using science to help patients around the world."

Reflecting on the four new Board members, Whitehead Director David Page observes, "We are truly fortunate to have these amazingly accomplished people join our ranks. Together, the breadth and depth of their public and private sector experience and expertise are unrivalled. I know their perspectives and insights will be enormously valuable as we move Whitehead Institute forward."

New Leaders Build Philanthropic Support and Public Awareness

T to B: Sharon Stanczak, Susan Korsmeyer, Lisa Girard

In a time when federal support for discovery research is uncertain, Whitehead Institute is developing the additional resources and capabilities it will need to play an increasing leadership role in the global scientific enterprise. To that end, the Institute is strengthening its fundraising and communication programs, and three dynamic leaders have taken the reins in its Institutional Advancement and Communications and Public Affairs offices.

Sharon Stanczak joined Whitehead in July 2016 as its vice president for Institutional Advancement, responsible for strategic leadership of the Institute's fundraising and communications initiatives. She brings more than 20 years of progressive experience developing resources for academic, arts and culture, research, and science organizations—working closely with executives, faculty, donors, and top volunteers. Prior to joining Whitehead, she served for 11 years as a lead philanthropic advisor and strategist at Massachusetts Institute of Technology (MIT), guiding fundraising initiatives to launch the David H. Koch Institute for Integrative Cancer Research and MIT.nano, the University's new nanotechnology facility, and to support MIT's libraries and art programs. Stanczak also co-developed the fundraising model for the Bridge Project, a vibrant research collaboration between the Koch Institute and the Dana-Farber/Harvard Cancer Center. Before joining MIT, she raised philanthropic support for the Smithsonian Institution, the University of Maryland, and the Folger Shakespeare Library. She holds a Master of Fine Arts from the University of Maryland, College Park, and a bachelor's degree from the University of Houston, and has held Certified Fundraising Executive status since 2003.

“Whitehead Institute was born through an act of philanthropy—Jack Whitehead’s generous gift, in 1982—and its future will depend, in large measure, on a new generation of philanthropists stepping forward to support the unique and uniquely productive science done here,” Stanczak observes. “My goal is to help current and prospective Whitehead donors understand the necessity of their support and the outsized impact they can have by fueling our researchers’ work.”

Stanczak appointed **Susan Korsmeyer** to direct the Whitehead fundraising program as senior managing director for Institutional Advancement. Korsmeyer was recruited from Dana-Farber Cancer Institute (DFCI), where she served for 12 years as senior director for the Division of Development and the Jimmy Fund. At DFCI, she achieved a series of major fundraising and programmatic milestones, collaborating closely with researchers and clinicians to build funding for basic science research in chemistry, immunology, and genomics, as well as for clinical care. Known for her strategic vision and collaborative style, Korsmeyer partnered with fundraisers at Koch Institute and participating members of the Dana-Farber/Harvard Cancer Center to bring innovative ventures to life. Prior to her fundraising career, she spent 12 years in nursing at University of California, San Francisco and Georgetown University Hospital and led Georgetown’s Phase 1-2 Clinical Protocol Office; and while living in St. Louis, she served as an Alderman for nine years. Korsmeyer earned a bachelor’s in nursing from the University of Delaware and a master’s in health administration from George Washington University.

To direct the communications team, Stanczak appointed **Lisa Girard** as director of strategic communications. A former bench scientist, Girard has nearly two decades’ communications leadership and content-development experience at California Institute of Technology (CalTech), the Harvard Stem Cell Institute (HSCI), and, most recently, the Broad Institute of MIT and Harvard. As Broad’s director of scientific communication, she provided strategic leadership for teams developing high-level scientific content for a variety of audiences, and worked directly with principal investigators to raise awareness of individual discoveries and to inform the public about basic science research. Earlier in her career, she was HSCI’s associate director of strategic alliances and scientific editor, as well as creator and editor of HSCI’s StemBook and CalTech’s WormBook. Girard earned a bachelor’s in biology from the University of California, San Diego and a PhD in plant biology from the University of California, Berkeley, and completed postdoctoral work at CalTech in *C. elegans* genetics.

“This new leadership team is talented, smart, experienced, and innovative,” says Whitehead Director David Page. “They and their skilled staffs are raising our public profile, building our connections with philanthropic organizations and individual donors, and strengthening Whitehead’s capacity to do courageous science.”

Emerging Investigative Leader

Sebastian Lourido, an emerging leader in investigating deadly parasitic infections, has been appointed as a Member of Whitehead Institute and an assistant professor of biology at the Massachusetts Institute of Technology. His appointments come nearly five years after he joined the Institute as a Whitehead Fellow.

"We are absolutely delighted that Sebastian will continue to be part of our community, now as a Member of the faculty," says Whitehead Institute Director David Page. "His formidable talents as an investigator, scientific leader, and research colleague are matched by his skills as a writer, teacher, and explicator of science. And his innate creativity is an essential part of his special capacity as a researcher and communicator. We believe that Sebastian's work—uncovering fundamental processes behind some of the most ubiquitous and lethal infections burdening global health—will substantially broaden and deepen Whitehead Institute's worldwide impact."

Lourido studies apicomplexan parasites, single-celled organisms that are among the most common and dangerous microbial pathogens, capable of causing devastating infections in humans and animals. Toxoplasma gondii (*T. gondii*), for example, infects an estimated 25 percent of the world's population and can cause serious disease in pregnant women, infants, and immunocompromised patients. Lourido focuses on how *T. gondii* invades host cells and establishes its site of replication. The work holds great promise for exposing targetable vulnerabilities in the parasite, as well as in other apicomplexa like the closely-related plasmodia, which causes malaria and contributes to more than a half million deaths each year.

"I am very interested in the adaptive capability that allows *T. gondii* to invade and establish a replicative niche within host cells," Lourido says. "To understand this ability, we performed the first genome-wide functional analysis of an apicomplexan, revealing the genes needed to infect human cells. We have also teased apart the structure of enzymes vital to the infectious process, identifying a potentially druggable target that could prevent parasites from entering and exiting host cells."

Remembering Susan Lindquist

On October 27, 2016, Whitehead mourned the loss of one of its own, Susan Lee Lindquist. Professor Lindquist was a Member and Former Director of Whitehead Institute, and one of the nation's most lauded scientists. Her career was defined by conceptually daring research and a passion for nurturing new generations of scientific talent.

"Sue has meant so much to Whitehead as an institution of science, and as a community of scientists, and her passing leaves us diminished in so many ways," said David Page, Director of Whitehead Institute. "She was a risk-taker and an innovator. She believed that if we were not reaching for things beyond our grasp, we were not doing our job as researchers; if we were not constantly striving for that which we could only imagine, we were not fulfilling our obligations to society as scientists."

Lindquist was best known for her work on prions—proteins that have the unusual ability to exist in multiple stable structural states, with altered functions depending on the state. Using yeast as a model, she and her colleagues demonstrated that prions have the capacity to drive change in an organism's inherited characteristics without changing its DNA or RNA—relying instead on an ability to change how proteins fold. In humans, devastating neurodegenerative diseases such as Alzheimer's, Parkinson's, Creutzfeldt-Jakob, and Huntington's are associated with the misfolding and aggregation of specific proteins. A better understanding of how they become misfolded could provide much needed, therapeutically relevant insights into the pathology of these diseases.

"I met Sue when I arrived at the University of Chicago in 1980, and we were close friends ever since," recalls Elaine Fuchs, a professor at Rockefeller University and an investigator with the Howard Hughes Medical Institute. "I was Sue's maid of honor at her wedding, and she introduced me to my husband. I've never met another scientist as creative and visionary as Sue, nor a person so caring and loving. She was the gentle giant of science, and her work will continue to shape research and medicine—and inspire her family, friends, colleagues, students, and postdocs—long into the future."

Whitehead Leadership

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

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

FACULTY ACHIEVEMENTS
Whitehead Institute's world-renowned faculty includes 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, Terry Orr-Weaver, 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).

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