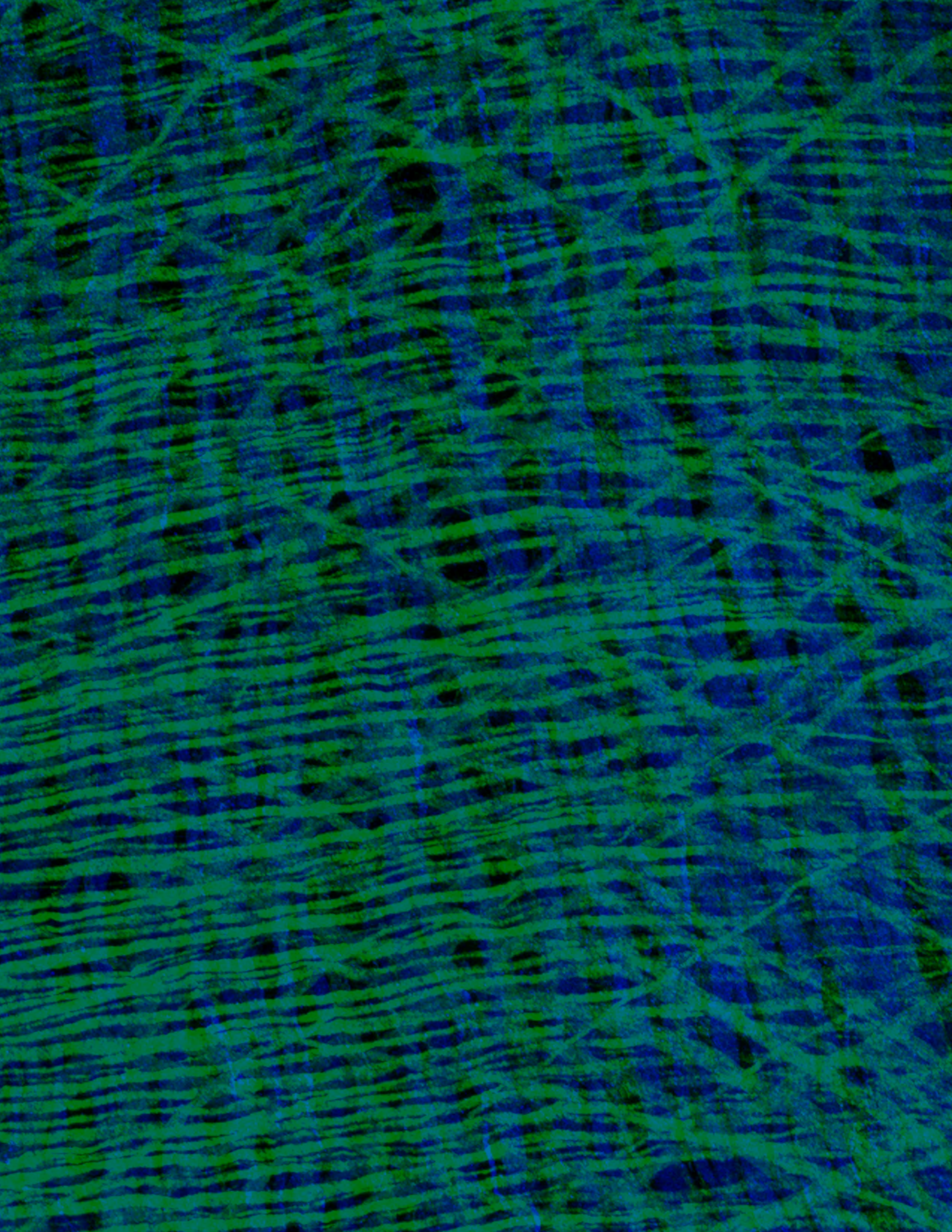
Whitehead Institute

ANNUAL REPORT 2018



Paradigm-shifting scientific achievement through a deeply collaborative culture and the pursuit of bold, creative inquiry

Contents

The Energy of a Scientific Community

Each fall, Whitehead Institute holds its annual Scientific Retreat. It is an opportunity for our community to discuss the questions we are pursuing and the most recent fruits of those investigations. Virtually everyone attends — Members and Fellows, senior scientists and postdocs, operational and technical staff, and graduate students. Three days of scientific talks and poster sessions prompt deep and wide-ranging conversations — discussions that frequently yield "aha" moments of unanticipated connection and opportunities for partnership. Almost as important, there is laughter, there are conversations about books we've read and the families we're nurturing, and Saturday night brings dancing into the small hours.

The Retreat is a key to the sense of community and collaborative spirit that are hallmarks of the Institute's culture. It is also a potent reminder that our people are the beating heart of our organization. State-of-the-art laboratories and technical facilities are crucial to advancing science. But it is human intellect, curiosity, passion, and resilience that truly move science forward. Our scientists — the unique intellectual engine they collectively constitute — make Whitehead Institute such a special place.

I was particularly conscious of this fact during this year's Scientific Retreat, because it was backgrounded by the ongoing recruitment and welcoming of new faculty and Whitehead Fellows. In September, we welcomed Ankur Jain as the newest Member of the Whitehead Institute faculty. He is representative of the kind of investigators we are recruiting: researchers whose intelligence, skill, and creativity signify the potential for great scientific achievement in the decades to come. I encourage you to read the Report article about Ankur's work in the emerging field of RNA aggregation.

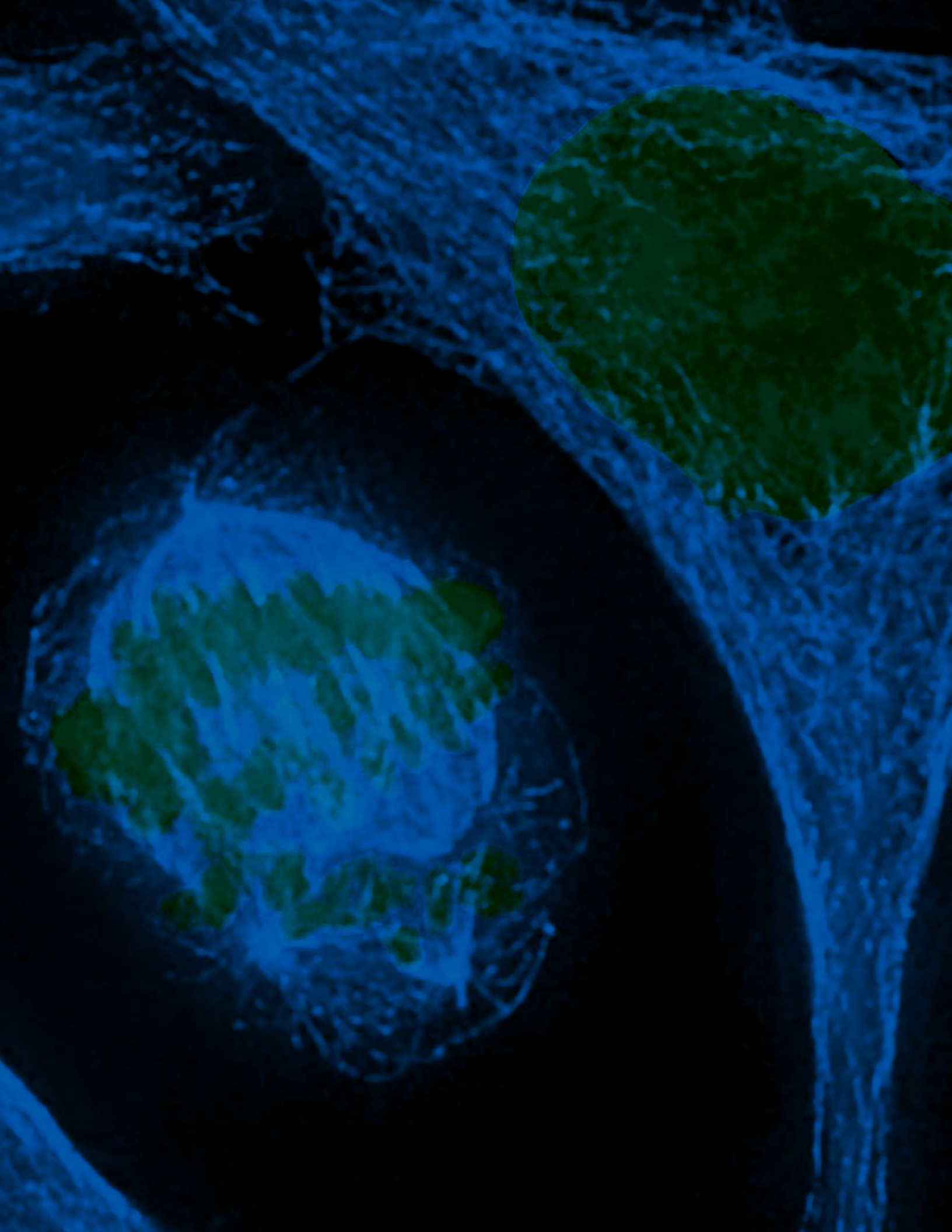
The Whitehead Fellows Program continues to be a launching pad for the finest young biomedical scientists in the world — creating the next generation of scientific leadership. Our newest Whitehead Fellow, Kristin Knouse, joined us in June, fresh from the joint Harvard-MIT MD/PhD program. Kristin's laboratory is exploring the regenerative properties of hepatocytes, the primary cells of the liver. (Kristin and former Whitehead Fellow Angelika Amon — winner of a 2019 Breakthrough Prize — are featured later in this Report.) In coming months, we will be recruiting a successor to recent Whitehead Fellow David Pincus — who, we are very pleased to note, has joined the faculty of the University of Chicago.

Ankur and Kristin have joined a community of pioneering, innovative, and courageous researchers whose work you can read about in the following pages. With this community of scientists at our core, Whitehead Institute is animated by intellectual energy — a frisson from new ideas, new board of directors, and fresh discoveries. That, I passionately believe, will never change.

As our board of directors chair Charles Ellis reminds me, it's not only scientists who advance discovery: A organization like Whitehead Institute also depends on its funding partners. In particular, we are lucky to have the support of philanthropists, foundations, and companies who are passionately committed to bioscience research and discovery. We call your attention to them — and offer our deep thanks — in the Partners in Science: Philanthropy at Whitehead Institute report accompanying this document.

These generous people and organizations are an essential part of the Whitehead Institute community. Together, we are accelerating discovery and shaping the future of biomedicine.

David Page



Assessing Future Performance

We are all familiar with the caveat for financial investors: "Past performance is not an indicator of future results." Yet when it comes to scientific research organizations, past performance is the most effective indicator of future accomplishment. While we cannot know exactly what a specific group of investigators will discover as they push into previously unexplored territory, there are certain constants we can count on. We know, for example, the qualities of the researchers' intellect and creativity, their level of technical knowledge and skill, and their willingness to take on difficult questions.

We know how committed the organization is to investing in technologies that permit investigators to employ — indeed, to create — novel tools and methods. We can track the number of collaborative projects undertaken, the variety of ways that information is proactively shared across laboratories and technical platforms, and the frequency of non-hierarchical interactions between faculty, professional staff, students, and postdoctoral researchers.

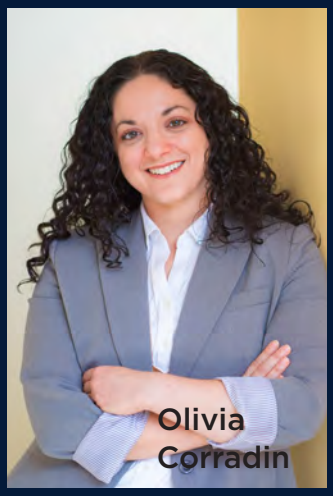
We can track the number of peer-reviewed studies published and how often they are cited by other researchers in the field. We can count how many awards and honors researchers receive and can track the continuing flow of those recognitions. We can note the level of competition for postdoctoral research positions and from how many countries the candidates hail.

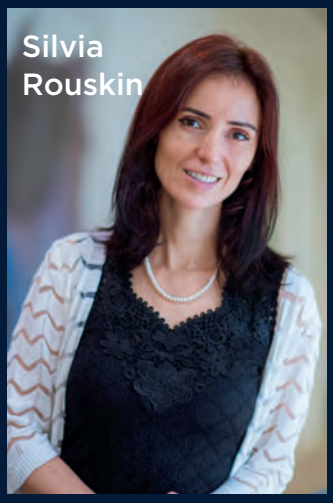
By all these quantitative measures, Whitehead Institute stands out among the world's elite biomedical research institutions — as it has for decades. Equally important are the qualitative strengths of the institution, its culture of collegiality, its leadership and management, and the strength of its finances.

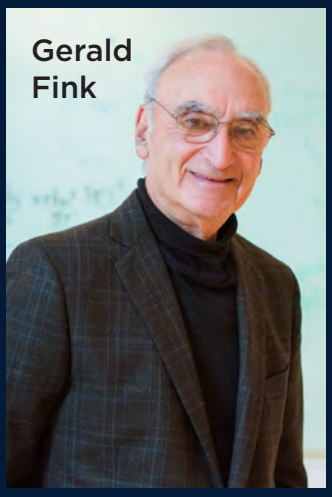
This Annual Report provides a snapshot of the level of excellence and accomplishment that characterize Whitehead Institute today, and makes clear why those fortunate to serve on its board of directors are excited about Whitehead Institute's ability to continue its outstanding performance well into the future.

Charles Ellis
Chair, Whitehead Institute Board of Directors

Whitehead Members & Fellows






Gerald
Fink


Mary
Gehring


Piyush
Gupta


Harvey
Lodish


Sebastian
Lourido


Terry
Orr-Weaver


David
Sabatini


Hazel
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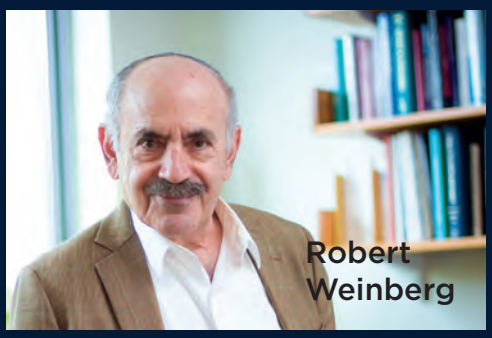
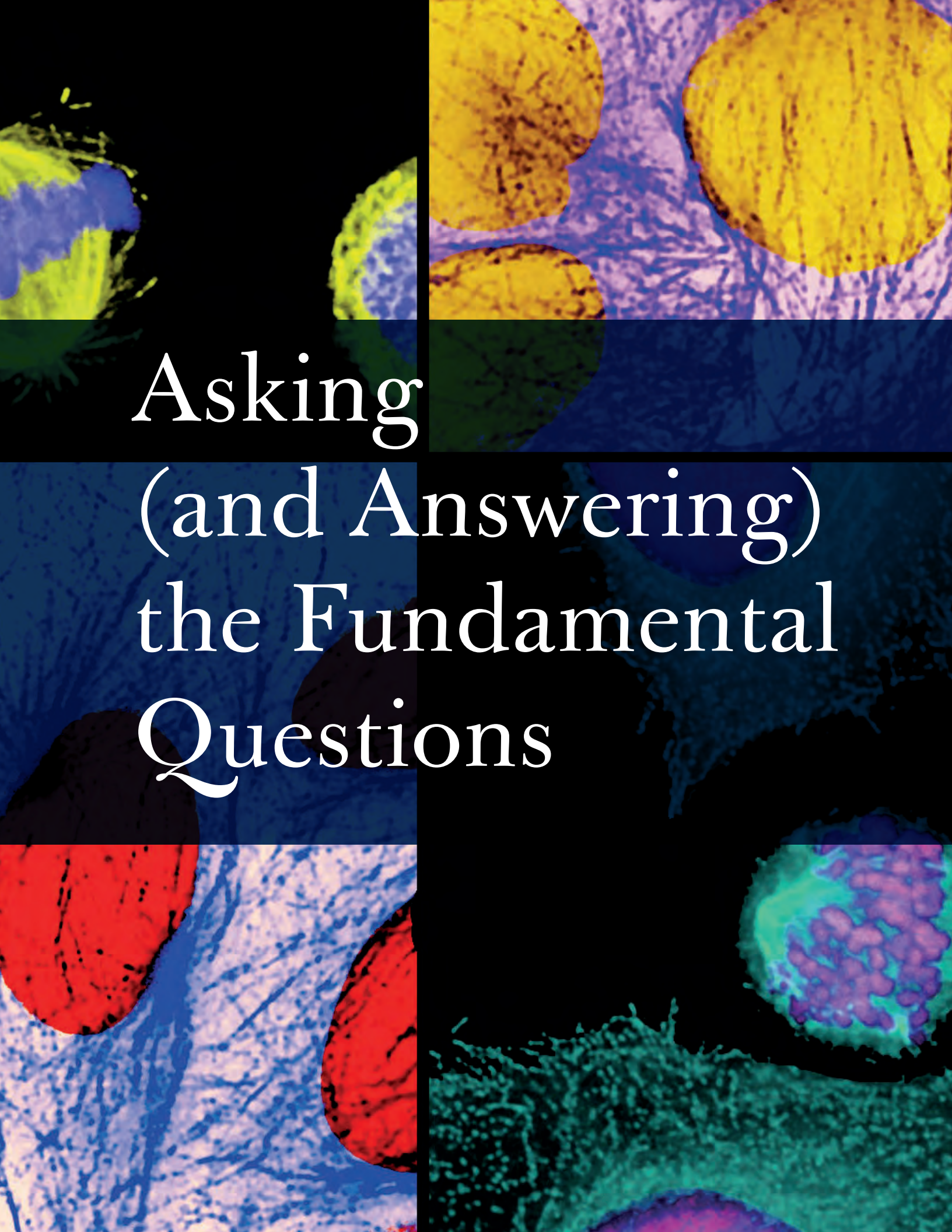

Robert
Weinberg


Jing-Ke
Weng


Richard
Young

Whitehead Science


Asking
(and Answering)
the Fundamental
Questions

It all starts with a question that lodges in a scientist's brain, a point of intense curiosity about a specific facet of biology: What is actually happening and where? When is it triggered and how? Why does it happen this way, not that? How did it come to be?

These queries, applied across the whole of biology — from viruses and bacteria, plants and fungi, to animals of every shape and size — form the rich tapestry of biomedical research. The answers to researchers' questions, ultimately, drive a growing understanding of health and disease. And they form the basis for medicine's increasing capacities to prevent, diagnose, and cure disease and injury.

Basic science investigators ask the most fundamental of questions — striving to understand biology's foundational structures and processes — without knowing exactly where the answers may lead. But, trace the origins of most breakthrough medical treatments or technologies and you will come to an investigator who asked (and answered) a question about the basic workings of biology.

While Whitehead Institute scientists are pursuing studies on a wide array of basic biomedical questions, their studies can be viewed through the lenses of five fundamental questions. In the following pages we explore these five questions and consider the potential medical implications of finding answers:

How does it organize? How does an organism that starts as one cell divide into tens of trillions of cells that differentiate and form organs and tissues with highly specialized functions?

How does it grow? How do cells — both normal and malignant — take stock of their environment and tailor their growth in response, and why are parasites and deadly fungal infections able to proliferate and spread?

How does it regulate? What are the myriad factors that influence whether, when, and in what quantity genes are expressed in a given cell — and what are the effects of a regulatory dysfunction?

How did it get here? How did present plants, animals, bacteria, viruses, and fungi come to have the characteristics they possess — and how might we apply that knowledge in medicine?

How do we do it? How do we conceptualize and create the new kinds of tools, methods, and instruments needed to uncover deeper or more complex knowledge about biological processes?

In raising these key questions, we highlight the underlying connections among Whitehead Institute's investigations — the lines of shared curiosity that underpin this unique, creative, and collaborative community of scientists.


How does it
ORGANIZE?
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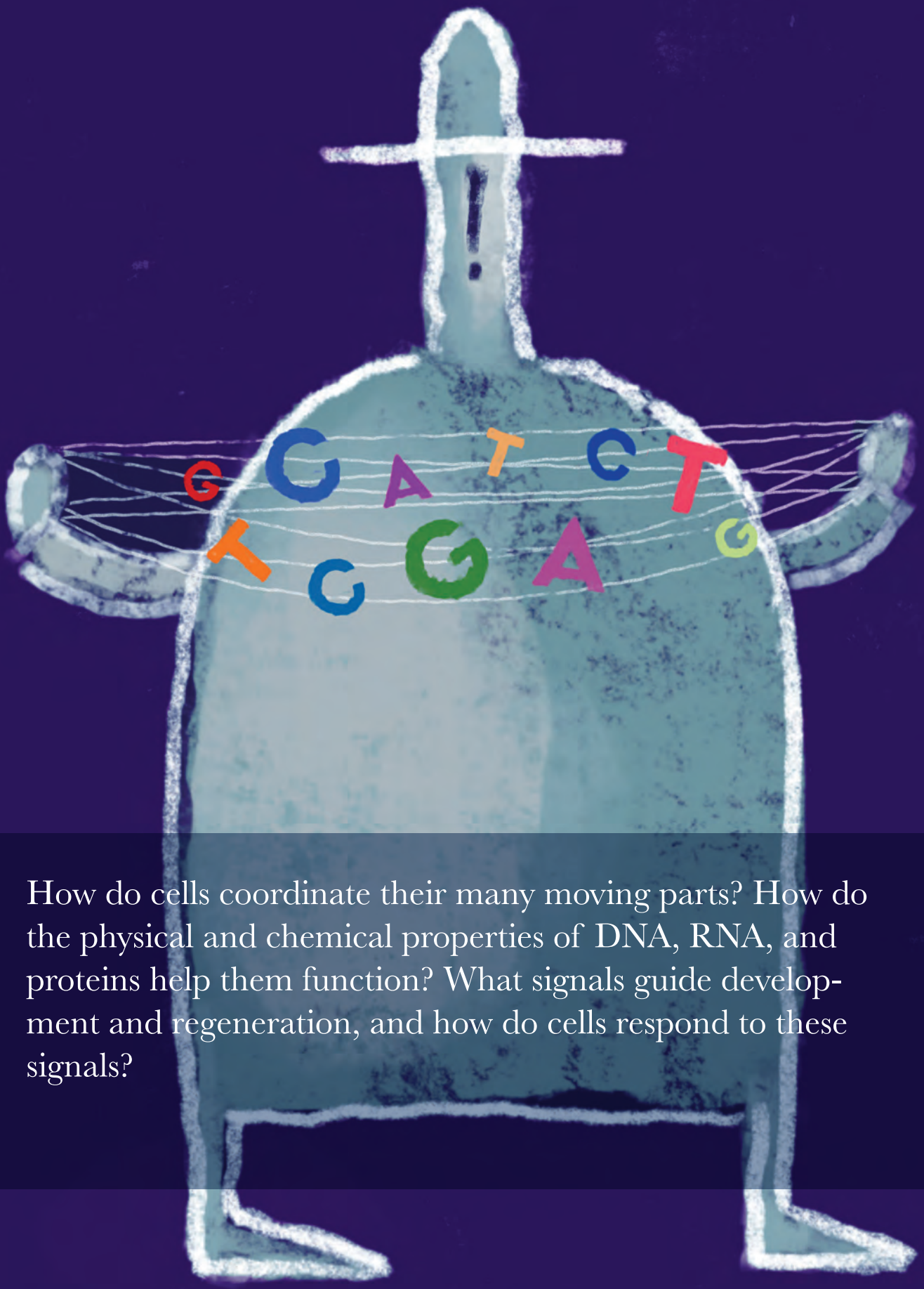


How do cells coordinate their many moving parts? How do the physical and chemical properties of DNA, RNA, and proteins help them function? What signals guide development and regeneration, and how do cells respond to these signals?

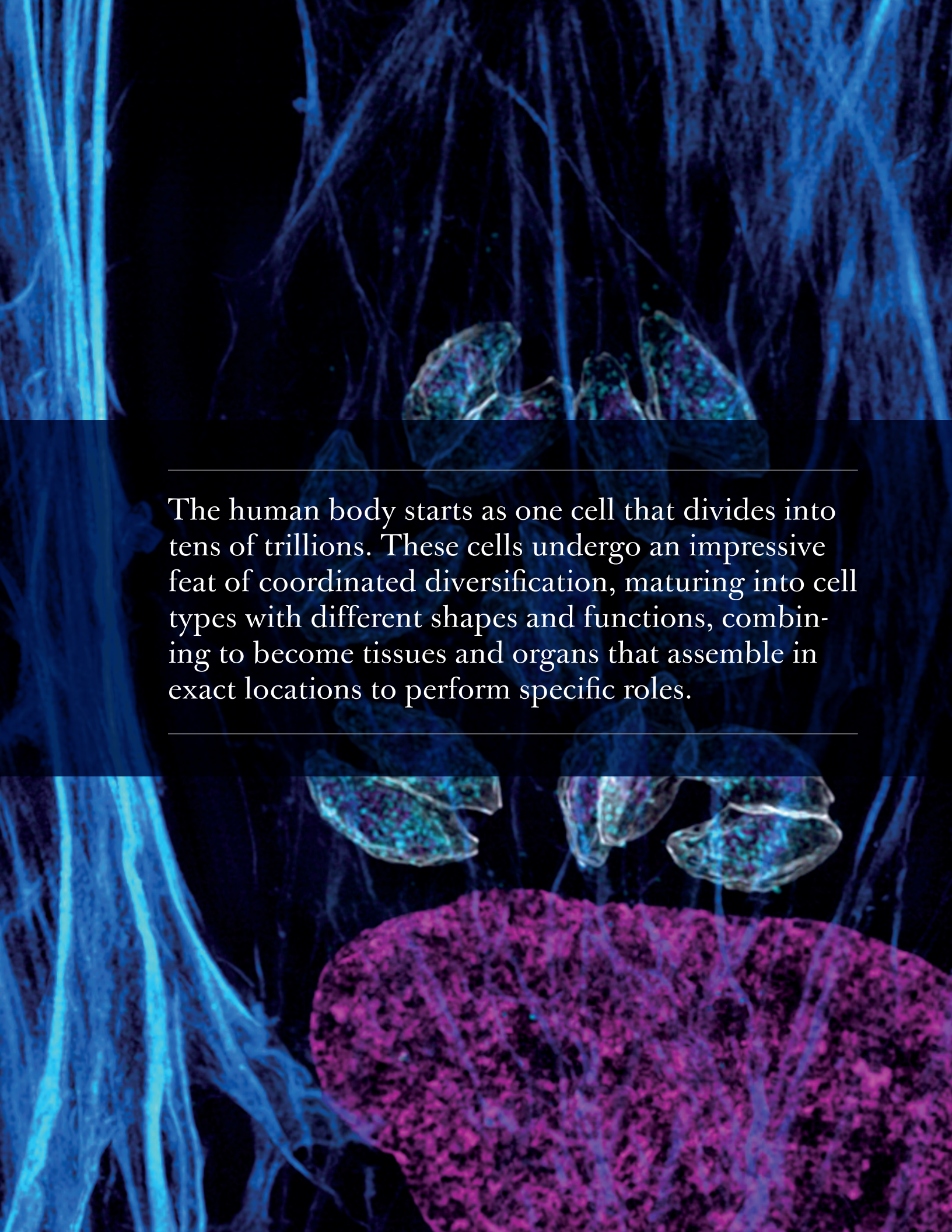
The human body starts as one cell that divides into tens of trillions. These cells undergo an impressive feat of coordinated diversification, maturing into cell types with different shapes and functions, combining to become tissues and organs that assemble in exact locations to perform specific roles. For the cells to remain operational, countless copies of RNAs, proteins, and other molecular machinery must constantly be built and interact. The tiniest mistake in any part could prove disastrous for the whole, leading to cell death, disease, or errors in body pattern formation. How do so many signals and pieces operate in harmony to give rise to a complex living organism? Whitehead Institute researchers have discovered many of the organizational characteristics of cells and their components that help orchestrate fundamental biological processes. These discoveries may provide valuable frames of reference to search for differences that may exist in instances of disease.

Unlike cartoons or schematics in which DNA is depicted as long flat ropes, our genome actually exists in complicated three-dimensional structures in the cell's nucleus. Whitehead Institute Member **Richard Young** studies the role that this three-dimensional structure plays in regulating gene expression. Strands of DNA sometimes form loops cinched closed by proteins. The loops create insulated neighborhoods in which certain genes and their regulators are brought closer together and other genes are kept out. If a loop is not cinched properly, proteins that regulate gene expression may gain inappropriate access to certain genes, effectively hijacking their regulation. Perhaps unsurprisingly, mutations in the genes that encode proteins that tie off loops in DNA are commonly found in cancers. Recently, Young investigated a protein called YY1 that is important for closing DNA loops. He found that YY1 regulates gene expression by altering the structure of DNA to form these loops rather than by recruiting transcription machinery as was previously thought.

A common type of regulator found in insulated neighborhoods in DNA is an enhancer, a regulatory stretch of DNA that increases the likelihood that a target gene will be turned on. Young extended the understanding of enhancers by describing super-enhancers, clusters of enhancers that regulate genes key to cell identity. Recently Young's lab found that some of the proteins involved in transcribing DNA, the process that "reads" DNA into RNA, tend to gather around super-enhancers and mesh together to form liquid droplet-like condensates via a process known as phase separation. Such condensates appear to serve as a sort of simulated membrane. By densely joining together, it is thought that the transcriptional machinery cordons off and monopolizes the space around super-enhancers, ensuring the efficient transcription of key cell identity genes. Cancer cells can use super-enhancers to promote the expression of genes that drive tumor development, and further study of these transcriptional condensates may reveal new insights into thwarting their growth.

Proteins are not the only biomolecules that can aggregate and phase separate. The newest Whitehead Institute Member, **Ankur Jain**, has discovered that RNAs can also assemble into liquid droplets or harden even further into gels. Jain's research suggests that RNA aggregates may contribute to repeat expansion diseases, a set of neurological diseases including fragile X syndrome and ALS that are associated with excessive repetition of short genetic sequences in the disease gene. Repeat-containing RNAs are more likely to clump together, making them less accessible and disrupting normal cellular processes, perhaps by sequestering important proteins. Jain is investigating the mechanisms cells use to prevent harmful RNA aggregation and is searching for therapeutic agents that could safely dissolve RNA gels. He is also interested in how healthy cells use RNA aggregation. Understanding RNA aggregation may shed light on the mechanisms underlying neurodegenerative diseases such as Parkinson's and Alzheimer's disease as well. Just as condensates may improve the efficacy of super-enhancers, Jain suspects that when formed in the right circumstances, RNA gels may help to concentrate and compartmentalize certain processes within cells.

Compartmentalization is crucial during mitosis, when a cell that has replicated its DNA divides in two. Each daughter cell must end up with the right parts, including one complete and accurate set of chromosomes.



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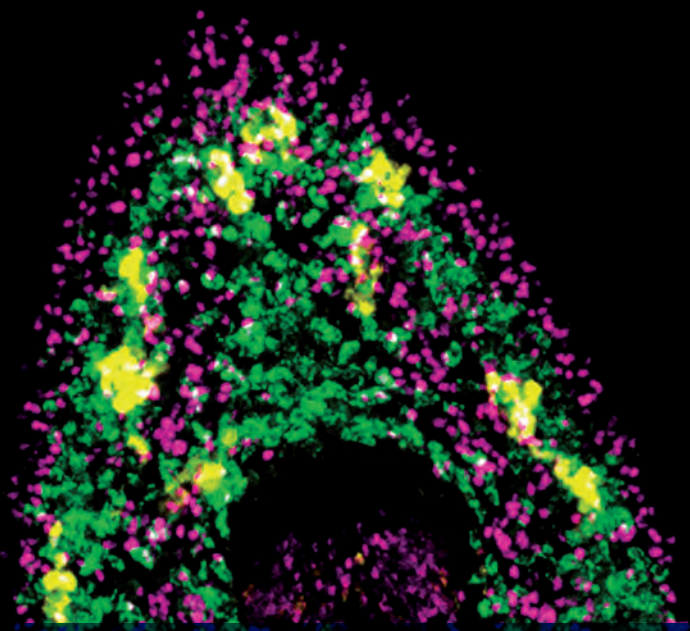

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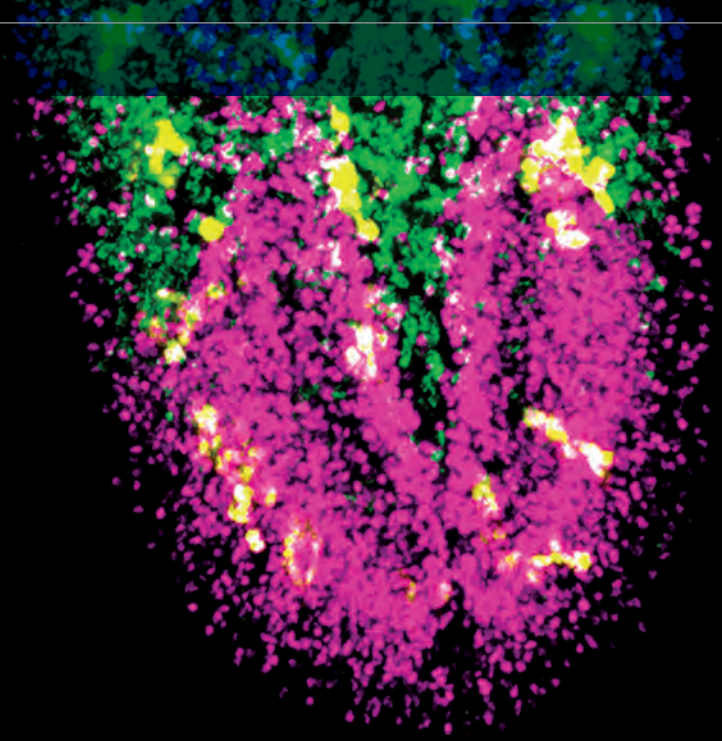
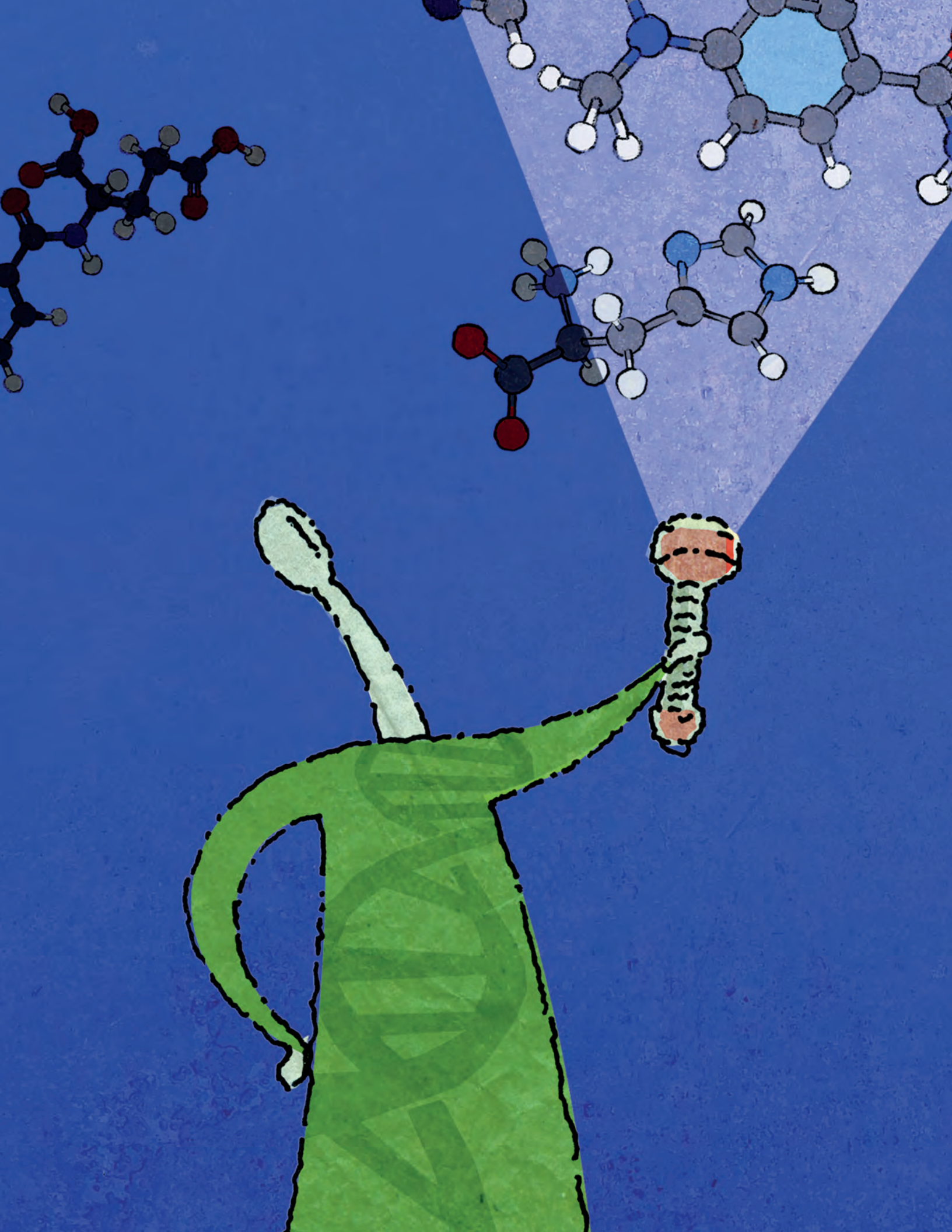
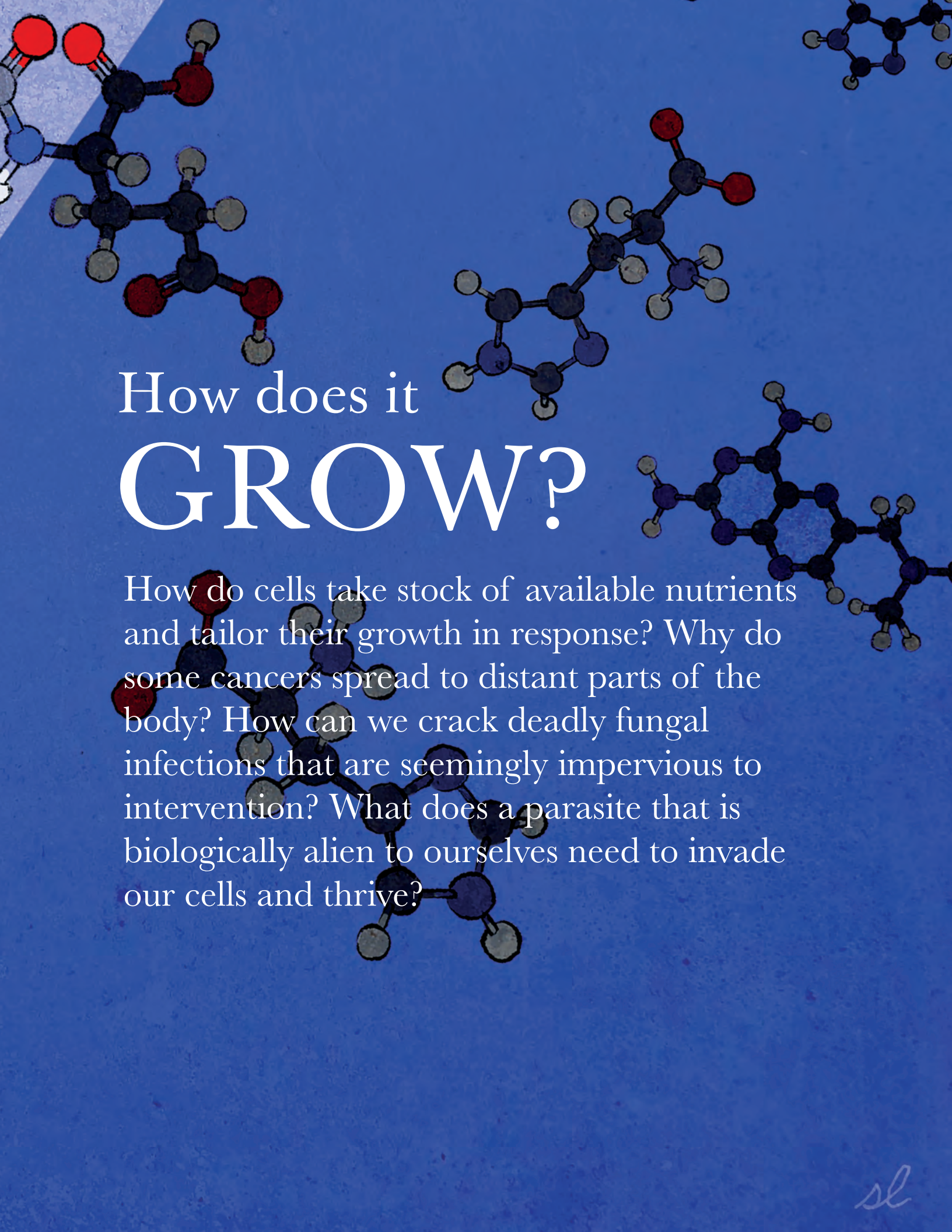


Whitehead Institute Member **Iain Cheeseman** studies the kinetochore, a structure composed of proteins that forms on chromosomes to help organize and manage their correct partitioning during mitosis. The kinetochore assists in this process by tethering the identical copies of a cell's original chromosome to the microtubules, hollow protein tubes that will pull them apart and help distribute one into each daughter cell. If this process, known as chromosome segregation, goes wrong, entire chromosomes can end up duplicated in one daughter cell and missing in the other. This aneuploidy, as it is called, is a hallmark of cancers and certain genetic disorders. One focus of Cheeseman's research is how the kinetochore manages to hold onto the dynamic microtubules as they grow, shrink, and move. Recently, the lab discovered that a group of proteins called the Ska1 complex in the kinetochore uses multiple surfaces on its exterior to associate with microtubules and enable Ska1 to undergo something akin to molecular somersaults. These somersaults help the kinetochore to maintain its association with the dynamic microtubules and give the structure its sticky grip. Cheeseman found that another component of the kinetochore, Astrin-SKAP, then stabilizes the connections between the kinetochore and microtubules, like a final layer of glue that seals everything into place.

Whitehead Institute Member **Peter Reddien** investigates how planarians, a type of flatworm, regenerate missing body parts. If you remove the head of a planarian, for example, stem cells in the planarian body, called neoblasts, migrate and differentiate to become the types of cells needed to regenerate the missing head. How do these cells know to become head cells and rebuild the head in its original location, instead of becoming tail cells or regrowing the head somewhere else? What signals and positional information are they receiving and how are they integrating them? Recently, Reddien studied these questions by examining eye regeneration. He found three main factors that direct eye progenitor cells — the stage between stem cell and mature eye cell — to the right place. First, as a progenitor cell migrates, it receives signals originating from position control genes that supply a coordinate map of the body, directing the cell to the right location to begin regeneration. However, if the progenitor cell comes across a regenerating or existing eye, it will become part of that structure rather than continuing to follow the coordinate signals. This process is described as self-organization, in which interactions of the component parts of a system determine the pattern of the outcome. Third, the progenitor cells operate within a broad anatomical zone, which gives them a fair amount of flexibility in where they end up. By manipulating which cues progenitor cells received when, the Reddien lab was able to create planarians with offset eyes or too many eyes. Their findings help illuminate how principles of self-organization inform cell fate and position and how cells prioritize signals within the noisy cellular environment, ensuring that body parts are regenerated in the right places.

Unlike planarians, mammals have limited regenerative abilities. Most cells are terminally differentiated, meaning that they have acquired a distinct identity, such as becoming a neuron, heart cell, or red blood cell, and then stay in that role until they die. These cells are unable to revert to a more malleable cell state or divide to create new cells. If these terminally differentiated cells are lost to disease or injury, they are gone forever. New Whitehead Institute Fellow **Kristin Knouse** studies an exception to this rule: hepatocytes, the main cell type in the liver. The liver has a unique capacity for regrowth. The majority of the organ can be removed, and it will recover, because hepatocytes retain the ability to divide and proliferate, even in adults. Knouse's research aims to answer two questions: How are hepatocytes able to reenter the cell cycle and multiply as differentiated cells, and why can't other differentiated cell types do the same? Understanding how liver cells regenerate could provide clues for how to reverse terminal differentiation in other cells and spark the regenerative process in damaged organs.





How does it GROW?

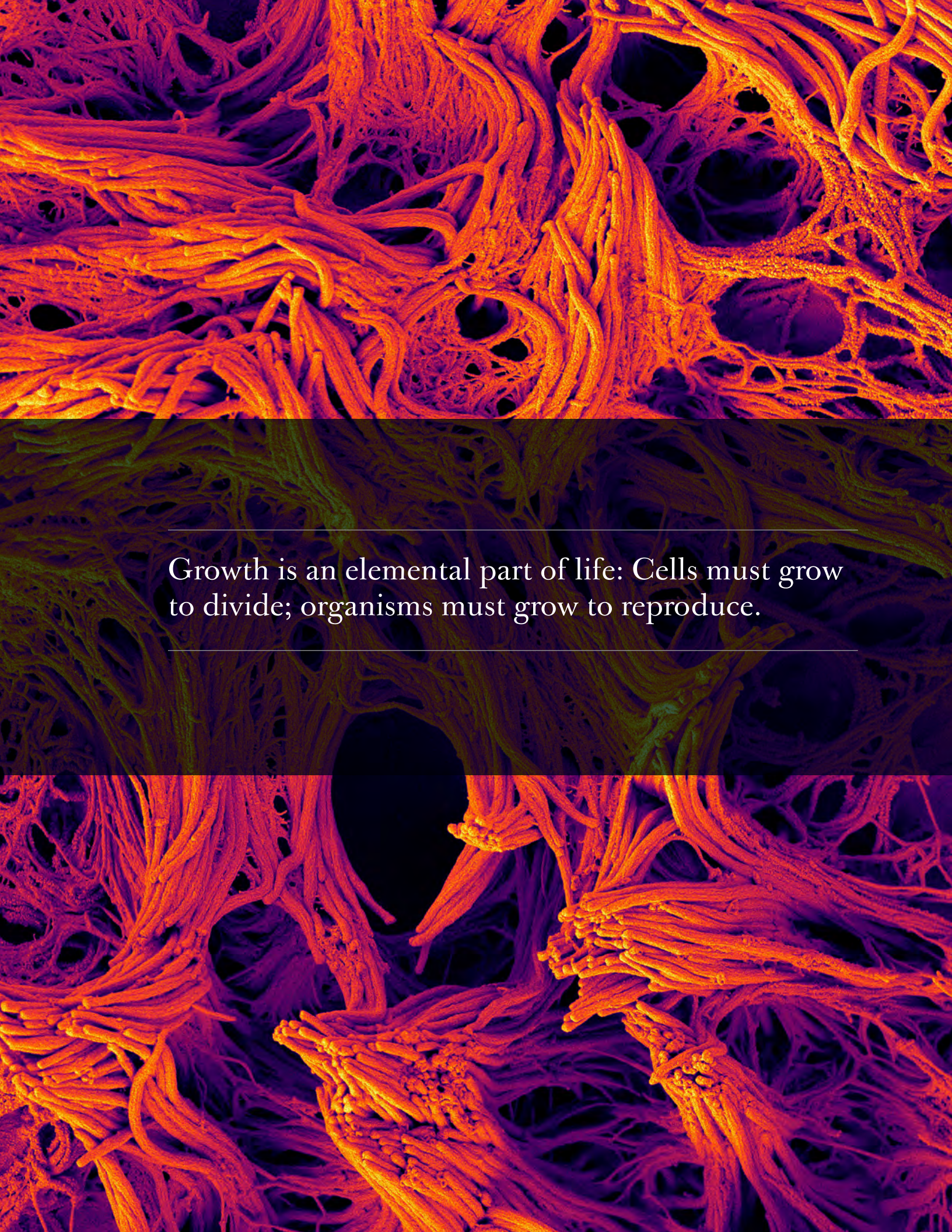
How do cells take stock of available nutrients and tailor their growth in response? Why do some cancers spread to distant parts of the body? How can we crack deadly fungal infections that are seemingly impervious to intervention? What does a parasite that is biologically alien to ourselves need to invade our cells and thrive?

Growth is an elemental part of life: Cells must grow to divide; organisms must grow to reproduce. Scientists strive to understand the factors and processes at both the cellular and organismal levels that are involved in normal growth and development, and also what happens when these systems go awry in diseases, such as cancer, or cause serious infections. By studying the mechanisms of growth in hardy pathogenic fungi, resilient parasites, and in our own cells, Whitehead Institute investigators are making profound insights into fundamental cellular processes and the conditions that can affect them.

Understanding the factors controlling cancer cell growth could provide important clues about its spread to distant parts of the body. According to the National Cancer Institute, an estimated 600,000 people will die from cancer in the United States this year. Most of those deaths will not result from the initial tumor but instead from its spread, the process termed metastasis. Yet how initial tumors are treated could affect their ability to metastasize. Researchers have noted that metastatic relapses spike in breast cancer patients about 12-18 months after their primary tumors are surgically removed. This behavior piqued the interest of Whitehead Institute Founding Member **Robert Weinberg**, whose group began to investigate this association further using a mouse model of cancer development. His findings suggest that the healing of surgical wounds occurring after tumor surgery may spur the outgrowth of groups of cancer cells that have settled in distant sites in the body. When Weinberg mimicked post-surgical wound healing in mice, it seemed to incite the outgrowth of groups of cancer cells implanted at these sites. These cancer cells had otherwise been kept under control by the immune system, which failed to do so when wound healing was occurring. Weinberg theorizes that the ability of the immune system to hold tumors in check was compromised by the inflammatory response elicited by wounding. This work may explain the striking results of a 2010 retrospective clinical trial conducted in Belgium: Breast cancer patients taking a non-steroidal anti-inflammatory (NSAID) for pain following tumor removal had a significantly lower incidence of metastatic relapse during this peak period than patients taking opioids for post-surgical pain. If these results could be confirmed by further clinical trials, this might lead to the routine use of NSAIDs after breast cancer surgery in order to mitigate such a systemic inflammatory response and decrease the frequency of delayed metastasis.

Taking a different tack to decipher how cancer spreads, Whitehead Institute Member **Piyush Gupta** is delving into the cellular level mechanisms that promote breast cancer progression and metastasis. One of these is the PERK (for "protein kinase RNA-like endoplasmic reticulum kinase") receptor, which activates a signaling pathway that plays a role in regulating glucose levels as well as is required for metastasis. Although a tempting drug target, mice whose PERK pathway is shut off typically develop diabetes. By further teasing apart the contributions of the various members of the PERK pathway, Gupta identified a downstream component, called CREB3L1, that promotes metastasis but is not required for the other functions regulated by the PERK receptor. By more specifically blocking CREB3L1's activation with a small molecule drug, Gupta was able to stop metastatic growth in mouse models of breast cancer without causing the diabetic side effects associated with PERK inhibition. His work suggests a new strategy for inhibiting the critical PERK pathway to selectively halt metastasis.

For cells to grow in pace with available resources, they must be able to assess their environment. In mammalian cells, mTOR (mechanistic target of rapamycin), which was identified by Whitehead Institute Member **David Sabatini** as a graduate student, is the keystone molecule in a pathway that regulates cellular processes in response to environmental cues, such as oxygen and energy levels, as well as amino acid availability. Sabatini is interested in determining the components of the mTOR pathway and understanding their role as cellular sensors. Teasing apart the pathway could enable researchers to discern ways to dial the pathway up or down, which could ultimately lead to novel therapies for diseases in which mTOR may be dysregulated, such as



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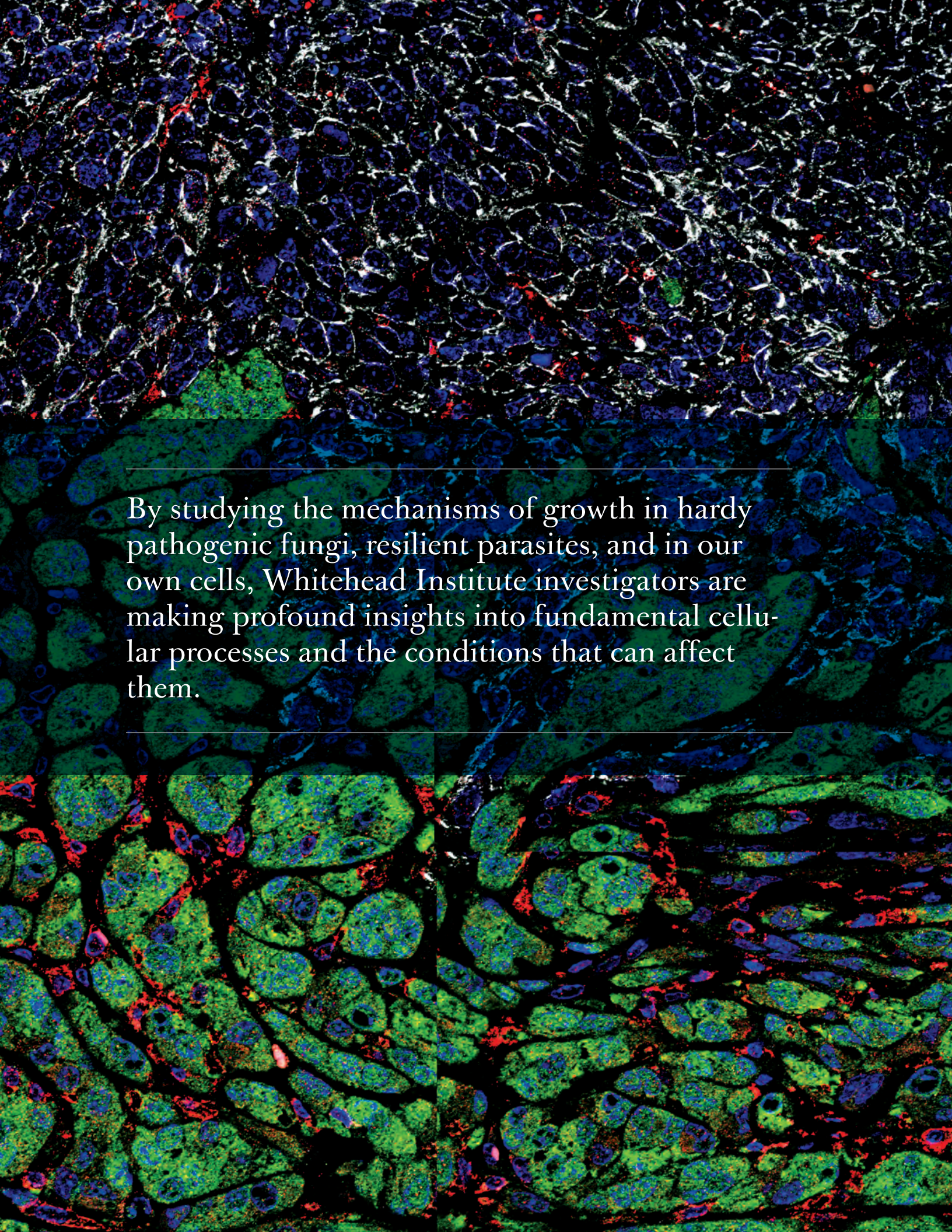

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cancer, diabetes, and neurodegenerative diseases. Curbing mTOR pathway activity has also been linked to longer lifespans in mice and other organisms. Interestingly, restricting methionine — an essential amino acid required for protein synthesis — at the organismal level has been linked to increased insulin tolerance and lifespan, similar to the anti-aging effects associated with inhibition of mTOR pathway activity. But the connection between mTOR, methionine, and aging has remained elusive. Recently, Sabatini identified a protein, SAMTOR, that appears to function as a sensor in the mTOR pathway for the methionine-related molecule SAM (S-adenosyl methionine): In methionine-starved cells, SAM and SAMTOR interact to inhibit the mTOR pathway; when methionine and SAM are abundant in cells, SAMTOR activates the mTOR pathway. According to Sabatini, the existence of SAMTOR provides tantalizing data suggesting that the phenotypes associated with methionine restriction and mTOR inhibition — extended lifespan and improved insulin tolerance — may be mechanistically connected.

Understanding the cellular pathways and factors that pathogens need to grow can also lead to new insights into treating people, plants, and animals that are infected with them. Take yeast, for example, which is a type of fungus. Although the growth of yeast can be beneficial for humans — beer is brewed and bread is baked with *Saccharomyces cerevisiae* — other fungal species, such as *Candida albicans (C. albicans)*, can cause serious infections, particularly in people that are immunosuppressed. Compounding the problem, many of these types of infections are becoming increasingly resistant to the few available antifungal drugs. Whitehead Institute Founding Member **Gerald Fink** has been studying how fungi like *C. albicans* can flourish in wide-ranging conditions, evade the immune system, and remain impervious to the current limited arsenal of antifungal drugs. More therapies are needed to combat these infections. In order to identify potential drug targets in other organisms, scientists frequently rely on genetic screens, which systematically knock out one gene at a time. Although the CRISPR/Cas9 gene editing system has been used in other organisms to create such genetic screens, it has been difficult to apply in *C. albicans* and other fungal species due to certain DNA repair mechanisms that they employ. However, by tweaking the CRISPR/Cas9 tools, Fink has used the gene editing system to identify genes that are essential for the survival and growth of *C. albicans* and its relatives — a process that could pinpoint potential therapeutic targets.

Whitehead Institute Member **Sebastian Lourido** studies another pathogen, *Toxoplasma gondii (T. gondii). T. gondii* and its close relatives are part of a group of parasites called apicomplexans, which cause infections such as toxoplasmosis (the reason pregnant women are advised against changing kitty litter), malaria, and cryptosporidiosis. Each year, these diseases sicken hundreds of millions of people worldwide, kill hundreds of thousands — most of them children — and cost billions of dollars, according to the World Health Organization. Despite their impact on global health, little is known about many aspects of their existence. Most tools used to study model organisms, such as mice, worms, yeast, and fruit flies, cannot be directly transferred to apicomplexans, because the parasites' genomes and molecular mechanisms are so dissimilar to these models. In fact, apicomplexans are more closely related to plants than to animals. Also, most apicomplexans, including the Plasmodium species that cause malaria, are difficult to grow in the lab. *T. gondii,* which causes toxoplasmosis, is amenable to culture in the lab, and Lourido uses it as an exemplar for the phylum Apicomplexa. Lourido performed the first genome-wide screen to be performed in an apicomplexan in 2016 after adapting the CRISPR/Cas9 gene-editing tool to work in *T. gondii.* Having identified hundreds of new genes necessary for the parasite's survival in human cells, Lourido has identified an essential subunit of a critical protein complex involved in energy production. Although the structure of this complex is highly conserved from yeast to humans, the apicomplexan version's distinct subunits emphasize unique adaptations that allow apicomplexans to colonize diverse niches during infection and survive within the cells of their hosts.


How does it
REGULATE?
How is gene expression controlled? What factors can influence it? What are the consequences if these factors are disrupted?
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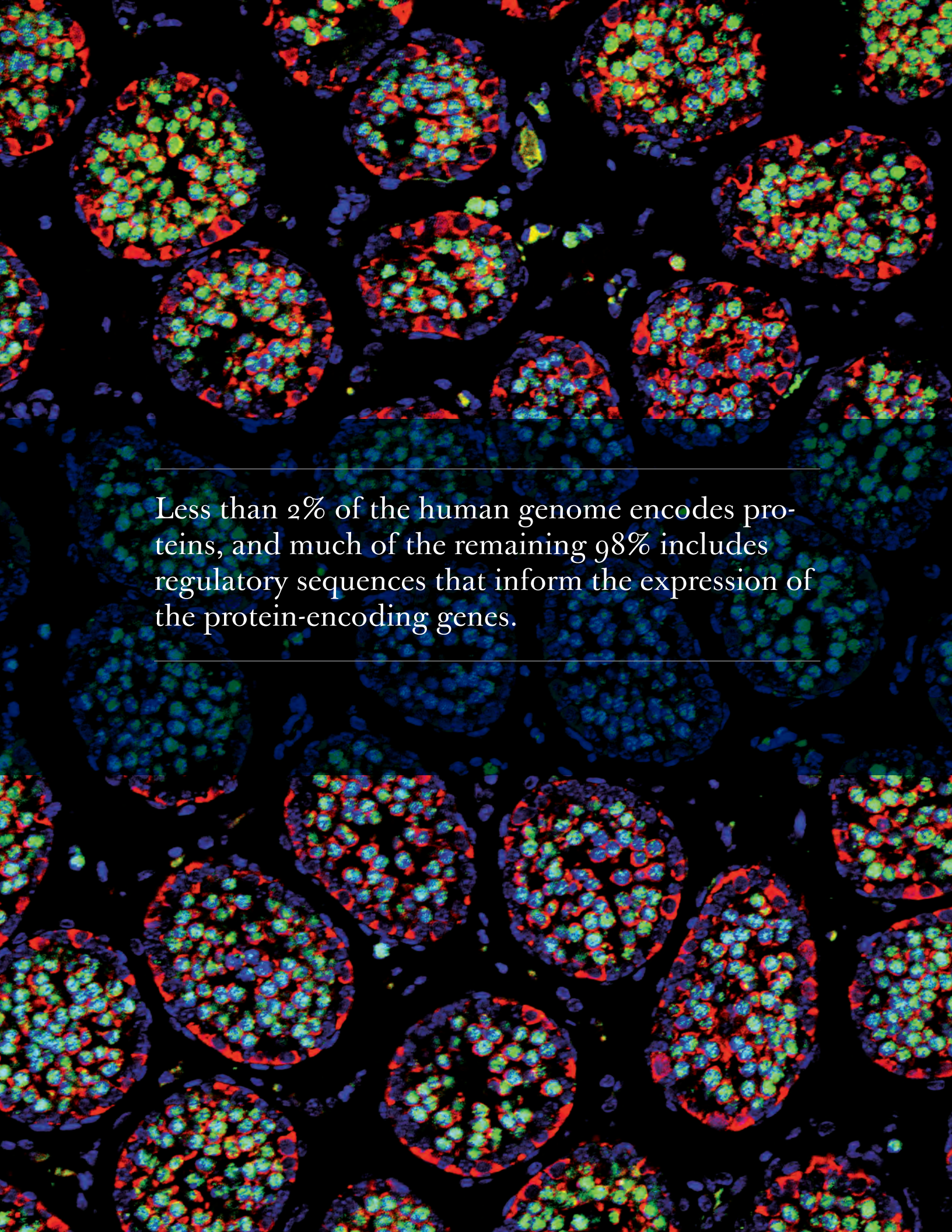
Every cell in the human body contains the same DNA, yet cells adopt distinct properties and fulfill different roles in order to provide the full complement of parts and tasks comprising our bodies. We owe this specialization to a myriad of regulatory factors that influence whether, when, and in what quantity genes are expressed in a given cell. These factors can silence a gene entirely, enhance its expression, or otherwise dictate its activity. The players involved in this complex orchestration include RNAs, proteins called transcription factors, chemical tags, and even other genes: Less than 2% of the human genome encodes proteins, and much of the remaining 98% includes regulatory sequences that inform the expression of the protein-encoding genes. Whitehead Institute researchers are mining the biology of these regulators and have identified elements and pathways that factor into everything from embryonic development, to disease risk, to the fitness of major crops.

While many of us are taught that RNA is just an intermediate "reading" of our genes, on its way to becoming a protein, there are in fact numerous additional types of RNAs, and we are learning more about their biology. Noncoding RNAs (ncRNAs) are RNAs that do not encode a protein. While the functions of many ncRNAs remain unknown, a growing number have been identified as regulators of gene expression. Recently, Whitehead Institute Member **David Bartel** discovered a gene regulatory network in the mammalian brain composed of three types of ncRNA: a long noncoding RNA (lncRNA), a circular RNA, and two microRNAs. Bartel found that one of the microRNAs, called miR-7, is able to prevent the accumulation in neurons of circular RNA Cdr1as with the help of a second microRNA. However, the lncRNA Cyrano prompts the destruction of miR-7. Due to Cyrano, in most neurons miR-7 levels are very low and Cdr1as levels remain high. Because this regulatory network appears to have been retained since the common ancestor of all mammals, Bartel thinks that it plays an important role in brain function, and he is working to figure out its specific role.

Whitehead Institute Fellow **Olivia Corradin** is also interested in regulators found in noncoding sections of the genome. Corradin seeks to understand how DNA sequence variants, or changes, in noncoding sequences may contribute to diseases such as autoimmune disorders, drug addiction, and colon cancer. Her lab is currently focused on how DNA sequence variants that are associated with an increased risk for multiple sclerosis (MS) can impact the function of myelinating cells in the central nervous system. In a healthy person, nerve cells are coated in a myelin sheath, a layer of fatty insulation that increases the speed at which signals can move through the nervous system. People with MS lose their myelin, weakening the brain's ability to send and receive signals, which can lead to fatigue, loss of muscle control, problems with walking and coordination, and vision loss. The causes of MS are poorly understood, and Corradin hopes her work studying genetic variants associated with the disease will provide insights that could one day benefit patients.

DNA and RNA sequences are not the only things capable of altering gene expression. Genes are frequently regulated by the addition of simple chemical tags. The addition of a chemical tag called a methyl group to DNA typically turns a gene off. Whitehead Institute Member **Mary Gehring** studies the effects of DNA methylation on gene expression in the model plant Arabidopsis. She made the surprising discovery that the gene *ROS1* has a rare opposite reaction: DNA methylation turns the gene on, which prompts ROS1 to begin demethylating itself and other genes. Once *ROS1* loses its methylation, it turns off. Gehring postulates that the *ROS1* gene operates as a sensitive control point for methylation, a rheostat that maintains consistent methylation levels throughout the genome like a thermostat maintains a consistent temperature. Gehring has found evidence that while *ROS1* appears to be important for this maintenance it likely does not work alone. She is now searching for other mechanisms that contribute to this function.

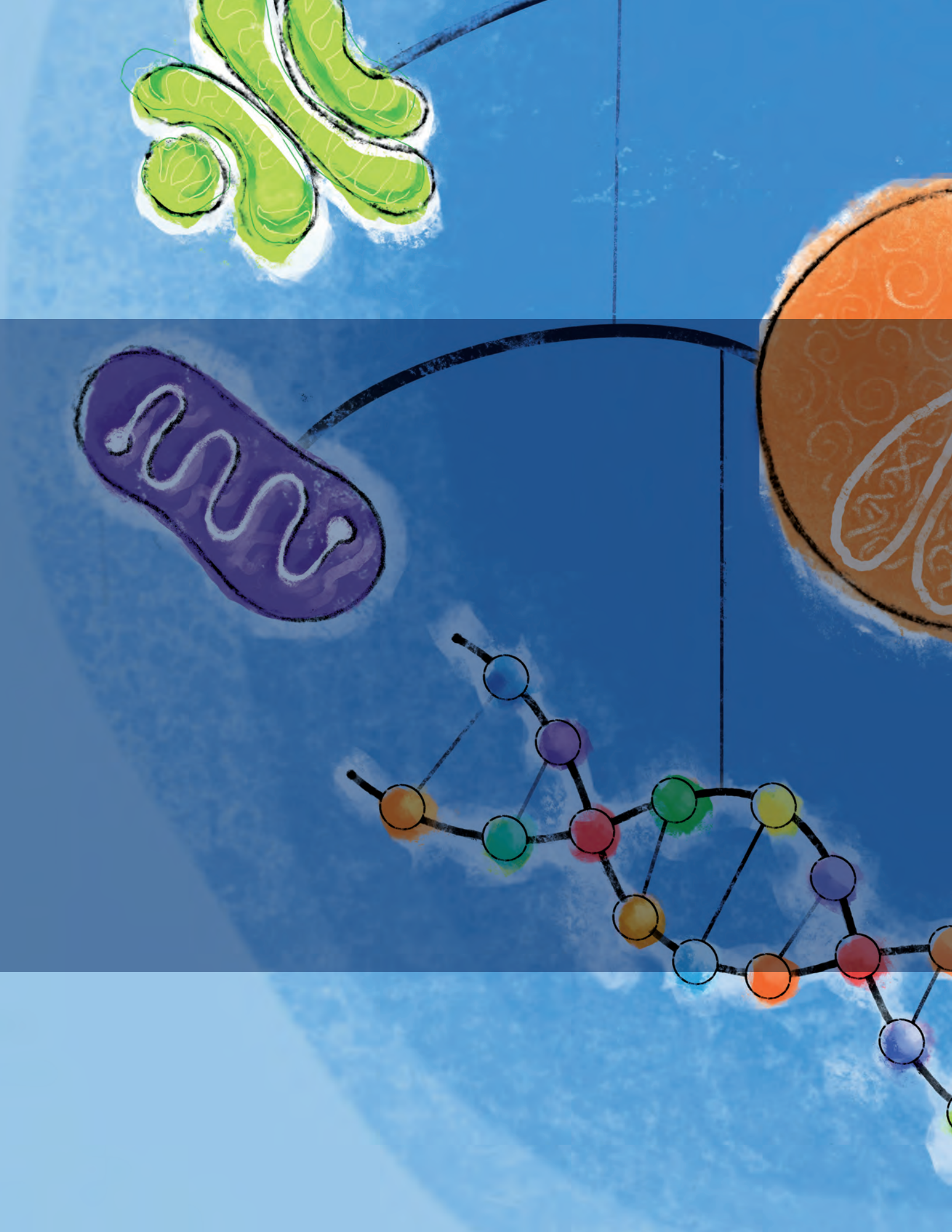


Less than 2% of the human genome encodes proteins, and much of the remaining 98% includes regulatory sequences that inform the expression of the protein-encoding genes.

Whitehead Institute researchers are mining the biology of these regulators and have identified elements and pathways that factor into everything from embryonic development to disease risk to the fitness of major crops.

Gehring is also interested in understanding imprinting, the process by which either the mother or father's copy of a gene is silenced in the plant offspring using differential methylation. Recently, Gehring found that the balance between the expression of maternal and paternal copies of a gene is not only passively maintained through inherited methylation, but also actively managed by a type of RNA called regulatory small RNAs. This active maintenance is critical to the health of the endosperm, the starch-dense part of the seed that feeds the embryo and is the cornerstone of the global food supply, forming the bulk of rice, wheat, corn and other cereals.

Regulation of cell size is critical in plant and animal development, both because it impacts tissue and organ size and also because it can affect cell function. Whitehead Institute Member **Terry Orr-Weaver** recently discovered how the size of the subperineurial glia (SPG) in the fruit fly nervous system, cells that form the blood-brain barrier, is regulated to match the pace of their growth to that of the growing brain without compromising the integrity of the barrier. To prevent breakages in the barrier, the cells cannot divide and so cannot increase in number; instead each cell has to become extra large. In animals, large cell size is attained by increasing genomic DNA content. This increase in DNA, called polyploidy, can be achieved by altering the cell division cycle in one of two ways, the endocycle or endomitosis. During the endocycle, a copy of the genomic DNA is made as if the cell were about to undergo mitosis, but the cell never divides. This leads to a large cell with many more copies of the genomic DNA than normal. Endomitosis is similar, except that the cell undergoes some of the steps of cell division and so may end up with multiple nuclei. Either process may be used to enlarge cells during development, but Orr-Weaver found that the SPG, atypically, use both, starting by endocycling and then switching to endomitosis later in larval development. This finding reveals distinctions between these two mechanisms, and work from the Orr-Weaver lab indicates that endomitosis can yield larger cells than the endocycle, a way to boost cell size even more. She discovered that the choice between the two processes is regulated by the Notch signaling pathway, a conserved system in most multicellular organisms that controls numerous cell differentiation processes, and a Cdc25 phosphatase called String, a key activator of mitosis.



How did it GET HERE?

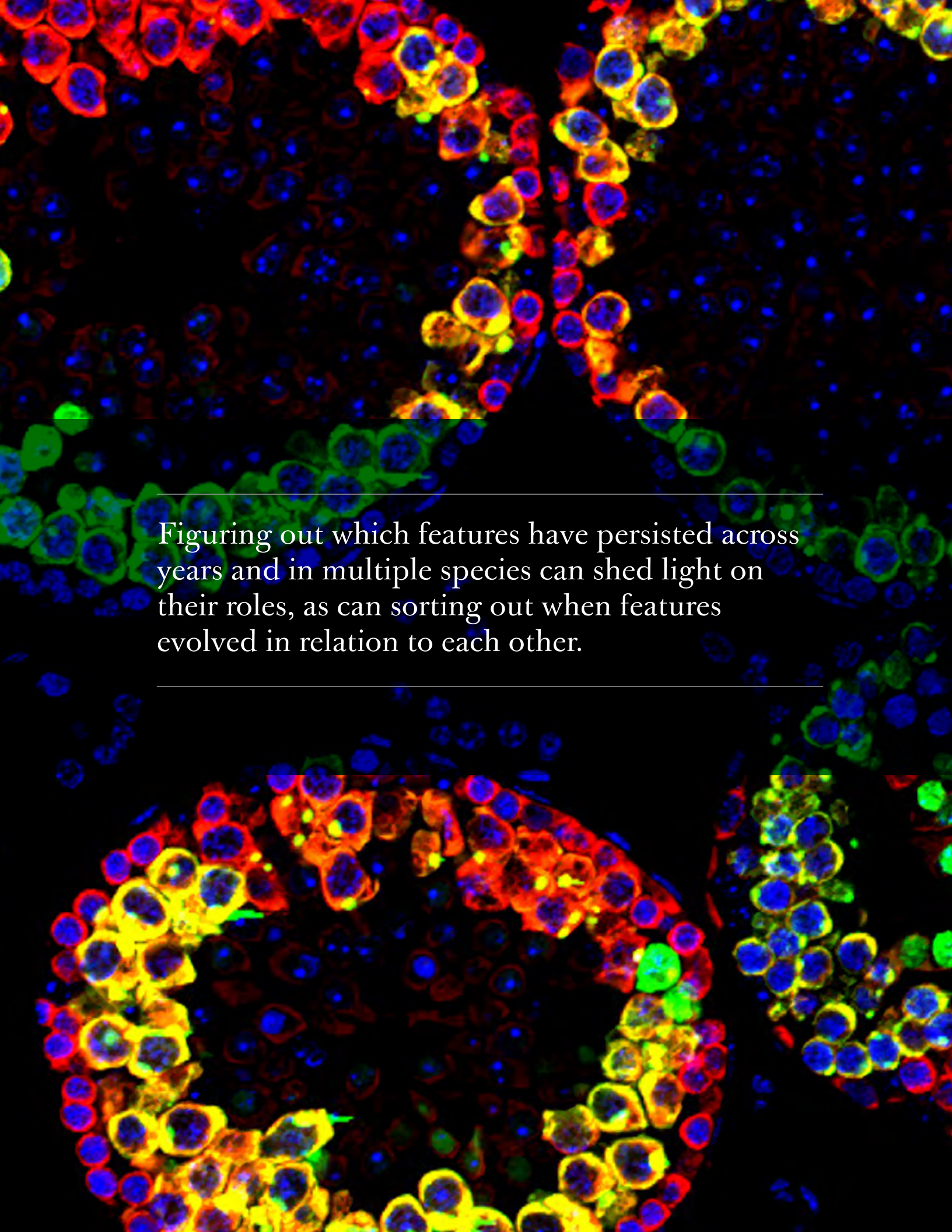
How do researchers use clues from evolutionary history to solve current problems? What can our shared ancestry with other species tell us about our own biology? How can investigating the origins of human biology inform our understanding of health and disease?

One of the best ways to understand the biology of an organism, biomolecule, or gene is to delve into its evolutionary history and trace the steps of its origin. Figuring out which features have persisted across years and in multiple species can shed light on their roles, as can sorting out when features evolved in relation to each other. Most genes originate as either duplicates or descendants of an existing gene that then evolve new functions. Genes with the same shared ancestral gene often have related functions, meaning that if one knows what one gene does, it becomes easier to predict the function of the genes most closely related to it. This is one way to narrow in on the genes contributing to a process or phenotype of interest. Investigating evolutionary history reveals the relatedness of species or molecules, which in turn provides useful context with which to answer other biological questions.

Most human cells contain 22 pairs of chromosomes called autosomes and a 23rd pair of sex chromosomes consisting of a combination of X and Y chromosomes: XX for a biological female, XY for a male. Whitehead Member and Institute Director **David Page** is investigating the idea that differences in the proteins expressed between XX and XY cells may contribute to differences in health and disease between men and women observed in medicine, such as disparate incidence of autism, autoimmune disorders, and more. The X and Y sex chromosomes in mammals evolved from autosomes 200-300 million years ago. Autosomes have maternal and paternal copies of the same genes, and they exchange some of those copies when a cell divides to produce gametes, or eggs and sperm. However, in order to isolate the genes that code for "male-ness" to the Y chromosome, the X and Y largely stopped being able to participate in this kind of DNA exchange. The resulting genetic isolation of the Y chromosome has led to differences in proteins coded by X versus Y throughout the body.

Another consequence of the Y's genetic isolation has been its deterioration in size due to unchecked mutations and deletions. Page's research indicates, however, that this deterioration stopped at least 25 million years ago. His lab recently analyzed Y chromosome DNA collected from more than 1200 men around the world to study amplicons, large repetitive stretches of DNA. Page found that the number of amplicons on the Y chromosome has remained remarkably consistent throughout modern human evolution, suggesting that the chromosome is subject to evolutionary pressures that maintain its configuration. These studies may shed light on factors related to fertility as well as other aspects of human health.

Whitehead Member **David Bartel**, in collaboration with Whitehead Member **Hazel Sive**, recently cracked an evolutionary puzzle that began with a genetic mishap in the ancestor of most modern fish. Bartel's lab wanted to figure out why a common approach to studying gene function does not work in zebrafish. The approach relies on co-opting the common biological process of RNA interference (RNAi), an important defense mechanism against viruses and transposons that is used in the lab to silence target genes in many model organisms. To solve the puzzle, Bartel and his team looked closely at the DNA sequences related to RNAi in fish. They found that 300 million years ago, ancestral fish experienced two small changes in the gene coding for the RNA-slicing protein Argonaute (Ago). These changes damaged the efficacy of RNAi. This finding explained why RNAi-based approaches don't work in zebrafish, but it also led to a new mystery: How have fish survived with damaged Ago? One of the Ago protein's most essential roles is helping to produce a microRNA that regulates red blood cell maturation. Without a fully functional Ago protein, fish should be anemic. However, Bartel found yet another modification in ancient fish, this time in the microRNA precursor, that enabled it to still be produced. Further research based on these discoveries could reveal whether there are advantages to losing RNAi and



Figuring out which features have persisted across years and in multiple species can shed light on their roles, as can sorting out when features evolved in relation to each other.

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using other defense mechanisms. Moreover, identifying how RNAi lost its efficacy has opened up the possibility of using gene editing to restore it, which could increase the utility of zebrafish as a model organism.

Fish may have lost a tool from their defense kit, but meanwhile plants have assembled a chemical arsenal. Plants cannot move, so in order to protect themselves from pests and adapt to their changing environments they have evolved to produce myriad useful chemical compounds instead. Some of these chemicals have potent medicinal properties, such as paclitaxel (Taxol®), a chemotherapy drug, and artemisinin, an antimalarial. Whitehead Member **Jing-Ke Weng** investigates plant compounds that have been used in traditional global medicine. He uses plants' evolutionary history to help identify the genes that produce these medicinal compounds. Some of the plants Weng studies are rare or hard to cultivate, and many plants with known medicinal value have been overharvested to satisfy demand. Weng is working to develop a solution. Once he identifies the plant genes responsible for producing a chemical, he can transfer those genes to a new host so it will begin producing the chemical. Recently, Weng identified the genes in the golden root plant that make salidroside, which has been traditionally used to treat depression, anxiety, and stress. With the genes in hand, Weng was able to recreate salidroside production in yeast. This work allows for sustainable, scalable production of medically important compounds while protecting the original plants from over-harvesting.

In addition to his work elaborating the chemical toolbox of plants, Weng is is also studying organisms that bioluminesce, or naturally emit light. Luciferase, the enzyme that causes fireflies to glow, is used in biology research to visually track gene expression and other processes. Weng's lab led an initiative to sequence the genome of the most common North American firefly and then they sequenced two of its relatives in order to discover the evolutionary origins of luminescence. They discovered to their surprise that the trait evolved independently in fireflies and other beetles.

How do we DO IT?

How can we use model organisms to make difficult questions tractable? How can we tweak existing tools to expand their repertoire? How can we fly under the immune system's radar to deliver therapies? How can we use computational and mathematical approaches to build predictive models?

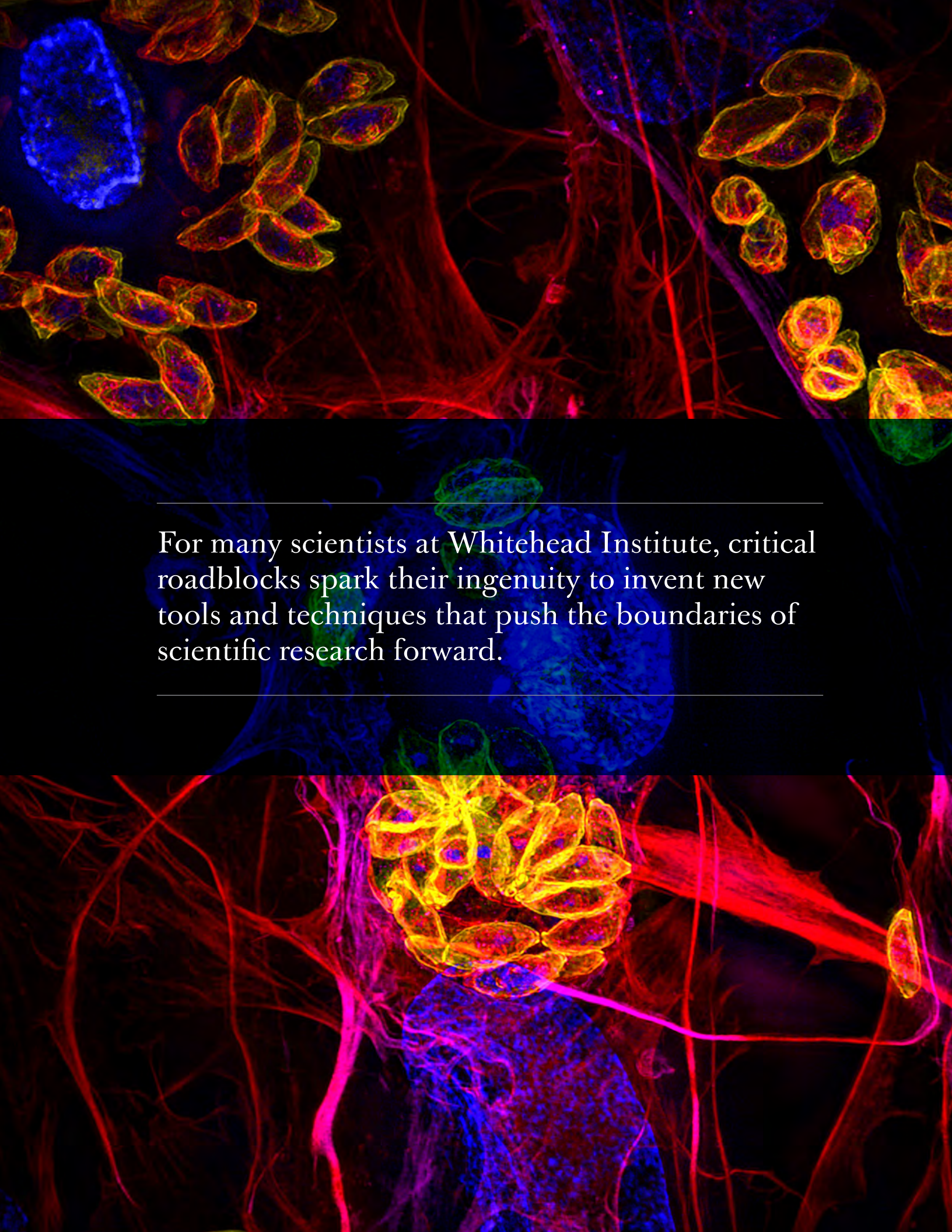
At Whitehead Institute scientists tackle questions that have perplexed researchers for years. Critical to the discovery process are the tools and instruments that enable the journey from research question to answer. But sometimes a vital tool does not yet exist. For many scientists at the Institute, that critical roadblock sparks their ingenuity to invent new tools and techniques that push the boundaries of scientific research forward.

The CRISPR/Cas9 gene editing system has revolutionized genetic and genomic research: Using this tool, researchers can remove, add, or alter one or more genes in the genomes of many organisms. Because the tool may hold the promise that it could someday correct disease-causing genetic mutations in patients, its potential is still unfurling. Whitehead Institute Founding Member **Rudolf Jaenisch** studies the genetic and epigenetic basis of diseases including Parkinson's, Alzheimer's, and other neurodegenerative and neurodevelopmental diseases. Recently, Jaenisch further broadened the tool's potential impact — and possible therapeutic use — by adapting it to change not a gene's sequence, but its methylation status. Adding or subtracting molecular tags — called methyl groups — from a gene can turn that gene's activity on or off. Jaenisch demonstrated the usefulness of this tailored CRISPR/Cas9 technique by reactivating the gene associated with fragile X syndrome in neurons derived from induced pluripotent stem cells. Fragile X syndrome, in which a section of the *FMR1* gene is repeated too many times, is the most frequent cause of intellectual disability in males, affecting 1 out of 3600 boys born. The excessive repeats are coated with methylation tags that ultimately shut down expression of the *FMR1* gene. Jaenisch determined that removing the methylation from a specific segment within *FMR1* with the modified CRISPR system can reactivate the gene and rescue neurons affected by fragile X syndrome. When rescued neurons were engrafted into the brains of mice, the *FMR1* gene remained active in the neurons for at least three months, suggesting that the corrected methylation may be sustainable in the animal. Jaenisch's CRISPR/Cas9-based technique may also prove useful for other diseases caused by abnormal methylation, including facioscapulohumeral muscular dystrophy and imprinting diseases.

Unlike fragile X syndrome, which has an identified genetic basis, neurodevelopmental disorders remain huge medical challenges because of their multiple symptoms and complex genetic basis. These disorders begin in the embryo, making essential model animal systems where earliest stages of brain formation are readily studied. Whitehead Institute Member **Hazel Sive** is a pioneer in the use of the zebrafish *(Danio rerio)* to study the most intractable human developmental disorders. Normal brain development includes cerebrospinal fluid (CSF) that fills the cavities of the brain ventricular system. Sive's group developed the first zebrafish "CSF drainage assay" and showed that CSF is essential for neural progenitor survival. The Sive group further identified a protein — retinol binding protein 4 (RBP) — that is important for survival of certain brain cells as the brain forms. Anomalies in RBP and other CSF proteins likely contribute to etiology of multiple neurodevelopmental disorders.

Many neurodevelopmental disorders affect development of the face and skull. To study these aspects effectively, Sive turns to the African claw-toed frog *(Xenopus laevis)*, whose broad faces can be readily studied from their earliest beginnings. The Sive group developed a novel "facial transplant assay," where effects of genes on specific parts of the face can be precisely studied. Using this assay the group has shown that the extreme anterior domain (EAD), a region named by Sive, not only gives rise to the mouth, but is a signaling center that controls progenitor cells as they build the jaws and facial structures. The EAD is present in humans, and Sive group research suggests it governs certain human anomalies.

Sometimes the immune system needs a boost to quell a pathogen or eliminate a toxin. For that assistance, Whitehead Institute Founding Member **Harvey Lodish** has turned to an unexpected source: alpacas and the



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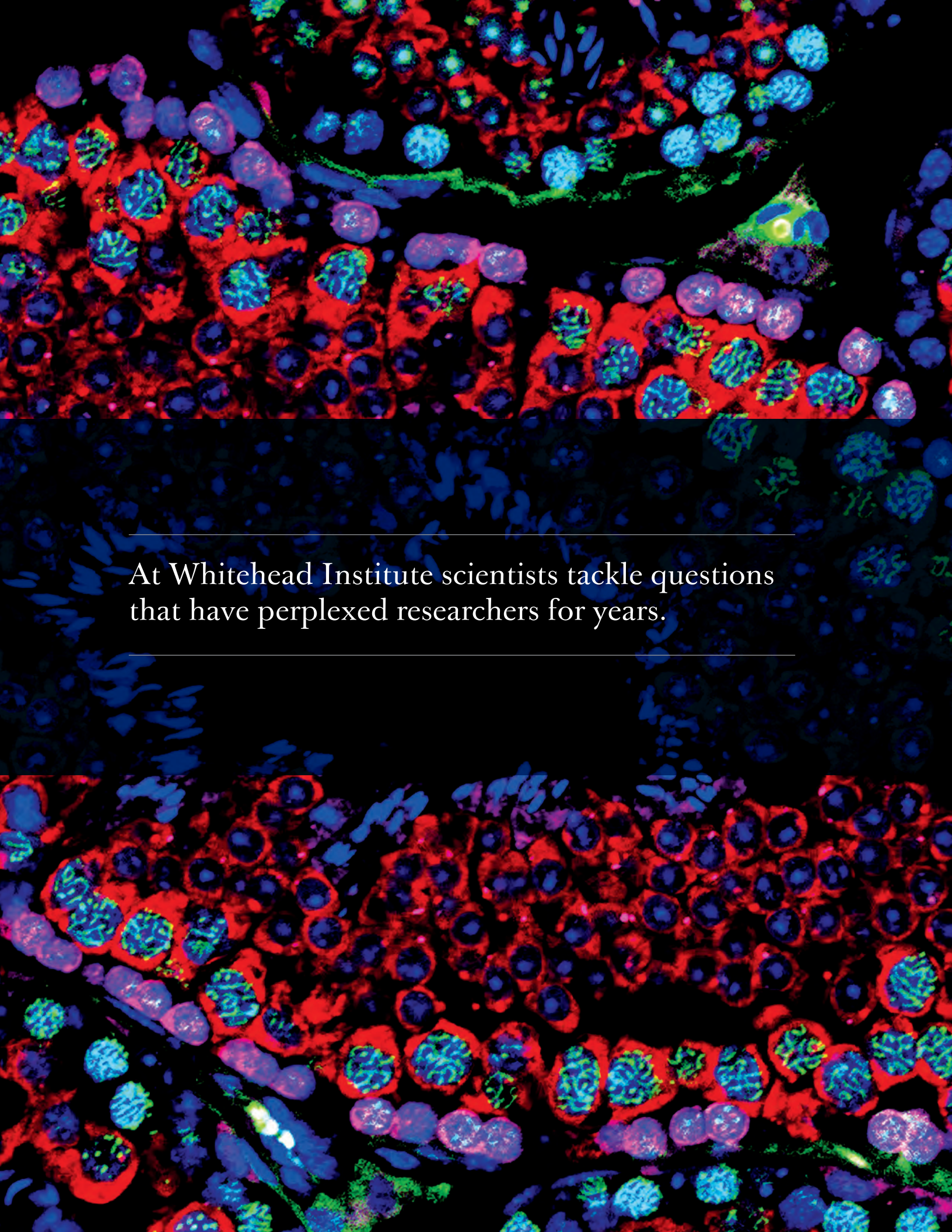


At Whitehead Institute scientists tackle questions that have perplexed researchers for years.

antibodies they produce. The immune systems of alpacas and other camelids like llamas create antibodies, called VHHs, that are more stable than most other antibodies and efficiently neutralize neurotoxins. Yet VHHs, like other antibodies, are still vulnerable to destruction by protein-degrading enzymes that eliminate the antibodies from the bloodstream within a few days, a timeframe that limits their use in aiding the immune system. To prolong the lifespan of VHHs in circulation, Lodish genetically engineered mouse red blood cell progenitors to produce VHHs against botulinum A, a potentially fatal food poisoning toxin, on their surface. When Lodish transfused mice with human red blood cell progenitors that express the VHH against botulinim A, the mice were protected against ten times the lethal dose of the toxin. Considering that alpacas can create VHHs specific for a vast array of toxins and pathogens, Lodish has likely only scratched the surface of how modified red blood cells could bolster the immune system.

When cells in organisms from yeast to humans experience environmental stresses, such as extreme temperatures, dehydration, or decreased nutrient availability, they mount a specific reaction called a heat shock response that allows the cells to adapt by bracing proteins into functional forms. In his research, Whitehead Institute Fellow **David Pincus** has used myriad tools to tease apart the heat shock response, which also plays a critical role in cancer and in neurodegenerative diseases: Cancer cells hijack the heat shock response in order to support the excessive protein production required for their growth, whereas reduced heat shock response activity is linked to neurodegenerative disorders, such as Alzheimer's and Parkinson's diseases. By identifying the Hsp70 protein as the primary on/off switch for the master regulator of the heat shock response, called heat shock factor 1 (Hsf1), Pincus has solved one of the more stubborn puzzles regarding this intrinsic cellular mechanism. He also created a mathematical model that mimics the heat shock response in yeast. In the context of his model, Pincus can alter one factor, such as increasing the temperature, and determine the resultant effects on Hsf1 availability, Hsp70 levels, and protein folding. This year, Pincus validated two assumptions that the model was based on and experimentally confirmed that the relationship between Hsf1 and the Hsp70 switch is a simple feedback loop between the two proteins. His research provides valuable insights into a fundamental cellular process that underpins diseases affecting millions worldwide.

Like proteins, many RNA molecules must have the correct, complex shape to properly function. RNAs perform numerous roles in the cell, such as acting as templates for protein synthesis, comprising the transcription machinery that reads DNA sequences into RNA, and regulating gene expression. Some viruses, such as HIV, rely on RNA — not DNA — to carry their genetic information. But the tools that allow scientists to discern an RNA's shape are limited to the test tube and lag far behind those available for analyzing protein structure. Whitehead Institute Fellow **Silvia Rouskin** is changing that status quo. She recently created an approach that takes data from a chemical probe of a cell's RNA through an algorithm that she developed, which identifies the multiple structures that a given sequence of RNA could form. Using Rouskin's tool, scientists can obtain higher resolution data from living cells and tissues for a much wider spectrum of RNAs than ever before — even RNAs with very low levels in the cell. Rouskin has used the tool to determine that HIV's RNA commonly forms multiple structures, and is currently investigating how these different structures regulate the expression of genes from the virus' nine-gene genome. Such a powerful and versatile tool could help researchers better understand the relationship between an RNA's shape and its function, including its role in HIV and other diseases, such as cancer and neurodegenerative diseases.

Master of the Opening Game:

Gerald Fink Reflects on His First 50 Years in Science

From the moment he began working toward his Ph.D. in biology at Yale in 1962, Founding Member Gerald Fink has been a groundbreaking and prolific researcher. Fink's seminal discoveries — DNA transformation in yeast, jumping genes, and invasive growth of pathogens — have provided key insights into basic science and the understanding of infectious disease.

But Fink's 50-plus years in the lab reflect only part of his contribution to science. He's also mentored graduate students and postdoctoral fellows, and taught courses at Cornell and Massachusetts Institute of Technology (MIT). Fink created and taught the legendary yeast molecular biology course at Cold Spring Harbor Laboratory. Fink is the recipient of the 2018-2019 James R. Killian, Jr., Faculty Achievement Award. He is also a respected global and national scientific leader as well, serving as president of both the Genetics Society of America and the American Association for the Advancement of Science. Moreover, he was also director of Whitehead Institute from 1990 to 2001, leading Whitehead Institute through major undertakings: expansion of the Whitehead Institute building; creation of the Center for Genome Sciences (which later became Broad Institute); and leadership as the largest private contributor to the Human Genome Project.

Fink recently closed his laboratory and is now intently focused on his roles as Whitehead Institute Member, professor of biology at MIT, mentor to younger scientists, advisor to a new biotech company, and éminence grise on national science policy in several domains, including the challenges of bioterrorism. Recently, the Annual Report's editors asked Fink to reflect on his experiences in research, teaching, and leading Whitehead Institute.

An Interview with Gerald Fink

Annual Report: You are recognized as a pioneer in bioscience research. Did you make a conscious choice to cut new scientific paths?

Gerald Fink: In chess, there are three phases — the opening, the middlegame, and the endgame. As a scientist, I've found that the opening is tailored to my disposition. I'd rather be a tiller of new soil than someone who harvests mature fields. There are advantages to the opening: You don't have to read legions of detailed papers because they don't exist yet; you can instantly become an authority; and there's more freedom to explore uncharted territory.

When I began working with yeast in graduate school, yeast was considered suitable for baking or brewing with little potential as a model for biomedical research. In fact, my professors urged me not to pursue it. However, I enjoyed the opportunity that investigating novel aspects of yeast biology afforded me to pursue my own ideas. My yeast work ended up being fundamentally important to research and medicine. It's been fascinating to watch the field of yeast-focused research move from the brewery and kitchen to the laboratory. The field has grown from maybe thirty people in the early 1960's to the thousands today who populate academic and commercial laboratories.

My lab's success in tilling a new field of science was repeated yet again when my students and I helped pioneer the use of the plant *Arabidopsis thaliana* as a model organism. Scientists have learned more about Arabidopsis than any other plant; this important new knowledge is being used to increase food crop-yields in changing environments. One reason why yeast and Arabidopsis research proved so attractive is that scientists in these new fields were comfortable sharing their new information and reagents with colleagues. This cooperative habit of sharing continues to this day, and I encourage it in my students. I believe that the unimpeded flow of information is essential to move science forward and create a culture conducive to the most productive research. My students have carried on this legacy and have become prominent leaders in science both here and abroad.

I believe that the unimpeded flow of information is essential to move science forward and create a culture conducive to the most productive research.

AR: How do you balance collaboration and competition in science?

GF: That's a very complicated balancing act. I've always felt that while competition can be stimulating, excessively competitive environments are not the best atmosphere for training students. Perhaps it's an extension of my preference for the opening. For that reason, I had many different projects running in my lab simultaneously; it was a mechanism to help students create fruitful paths for their own careers. Of course, that challenged me to continue to imagine novel questions and problems for them to investigate — and then educate myself about those topics to guide my students' efforts. This style kept me on my intellectual toes, forcing me to voyage well beyond my areas of expertise.

Of course, serious competition will inevitably develop when there's a gold rush. And that's good. I faced lots of world-class competition in the hunt to discover a transformation system that enabled the introduction of exogenous DNA into yeast. There were at least 10 labs worldwide trying to achieve this goal. I enticed talented postdocs to work on this project and we figured out how to overcome a key hurdle — so we got there first and struck gold. Our success laid the groundwork for the benefits of yeast as biological factories for manufacturing pharmaceuticals and biofuels. Yeast is key to making both the hepatitis B vaccine and the ethanol that powers your car.

AR: What attracted you to move from Cornell to Whitehead?

GF: Joining the brand-new Whitehead Institute in 1982 fit my preference for the opening. What an opportunity to be present at the beginning! In addition, Whitehead offered a unique opportunity for collaboration — to work with scientists like David Baltimore, Rudolf Jaenisch, Harvey Lodish, and Bob Weinberg. I also appreciated the ethos that Jack Whitehead instilled. Jack thought that Whitehead Institute was the scientific Taj Mahal. Each year at our scientific retreat he told our students: Whitehead Institute provides so many opportunities, you should be the best.

AR: What were the primary challenges you faced when you succeeded David Baltimore as Whitehead Institute Director in 1990?

GF: My challenge as director was to guide the organization toward its middlegame. We were well established as one of the world's foremost drivers of bioscience discovery. Yet, to continue taking chances on new ideas and brilliant young scientists, we would need more space and new facilities. A good example was our bet that the mouse and not the guinea pig or rat would become the model mammal for biomedical research into human disease. That choice required a dramatic investment in new facilities, but the gamble paid off; and today, ours is still the model that others emulate. That was part of a broader physical expansion of the Institute that involved organizational risk-taking: choosing farsighted research strategies; investing in advanced technologies; financing the building expansion; and learning to attract philanthropic support to build the addition to the original structure.

Whitehead Institute Founding Member Gerald Fink (R) with Edwin C. "Jack" Whitehead (L) and then-MIT president Charles Vest (Center)

Demonstrating one his many skills outside the lab, Amherst College basketball guard Gerald Fink takes a rebound away from a taller opponent.

Whitehead Institute Founding Member Gerald Fink in his lab with postdoctoral fellow Mark Rose in the early 80s.

AR: What was your strategy for addressing those challenges?

GF: Partnership and collaboration have been fundamental to the Institute's world-class success. And partnership and collaboration were my most valuable tools as a leader. Moreover, John Pratt, our chief operating officer, shared in the faculty's vision of path-breaking and intrepid discovery; and his skills and interests were a perfect complement to my own. Together we built a consensus for action among our board members.

I also had an enormous stroke of luck when former Senator Paul Tsongas agreed to chair our board of directors. Although he was suffering from lymphoma, he agreed to help me raise the funds for the expansion. Despite his illness, he was a great public advocate for Whitehead Institute and his efforts catalyzed our success in achieving the new addition.

However, the most important collaboration by far was the cooperation and enthusiasm for this endeavor among my fellow Whitehead Institute faculty. I believed then — and still believe — that our most important decisions need to be reached through consensus. Collaboration and consensus were also fundamental to one of Whitehead Institute's most significant organizational accomplishments under my watch — development of the Center for Genome Science (CGS). In the early 1990s, when [Former Whitehead Institute Member] Eric Lander and [Whitehead Institute Member] David Page became focused on genomics, the path forward was not clear at all, and the risks we took were significant. But the results have been even more significant. Whitehead Institute became the leading private contributor to the Human Genome Project and we grew the CGS into what has become the Broad Institute, a major force in basic science research. We also witnessed David Page change biomedical science's understanding of the structure of the X and Y chromosomes — setting the stage for major changes in the practice of medicine in decades to come.

Today, the Whitehead Institute faculty and board face two of the same challenges that we grappled with 25 years ago: developing the resources to provide innovative scientists the freedom to follow their curiosity wherever it leads, and acquiring the advanced instrumentation that will permit them to explore new frontiers.

AR: We haven't touched on the endgame. Is there one?

GF: The professional endgame is not in sight for me. I will continue to teach at MIT, and help to recruit new faculty at Whitehead. I also hope to spend more time on science diplomacy. When I was president of the American Association for the Advancement of Science, I led a delegation of American scientists to Cuba. The official relationship between Cuba and the United States had been frozen for over half a century, restricting scientific cooperation. During this 2014 meeting in Cuba I signed an agreement with the head of the Cuban Academy of Sciences to cooperate in four areas — infectious disease being the one of most interest to me, because many mosquito-borne diseases such as dengue, chikungunya, and Zika pose a dire threat to both countries. We have a lot to learn from Cuba about these diseases. Our agreement spawned a number of highly productive scientific interchanges, and I thought the opening had begun. Although the current political situation has halted this initiative, I will do everything in my power to reinvigorate our healthy connection to Cuba.

I've also joined the scientific advisory board of the Nuclear Threat Initiative's Program on Bioterrorism. As Chair of the National Research Council's 2004 Report, "Biotechnology Research in an Age of Terrorism," I developed expertise on the challenge of bioterrorism threats. Science has developed new technologies that can detect and identify pathogens quickly. Now what is needed are new public policies that enable us to employ these technologies effectively.

AR: Any final thoughts?

GF: I still love doing experiments — it's my first love — and several colleagues have offered me space in their labs. So, in the future, you are likely to find me behind a microscope and not at a desk.

Multifaceted

PROFESSIONAL

DEVELOPMENT

Kristin Knouse

became a Whitehead Institute Fellow in June 2018. She received a B.S. from Duke University, a Ph.D. from MIT, and an M.D. from Harvard Medical School. While her clinical education and experiences have given her important insights, she is most strongly driven to understand the mechanisms underlying disease — and to help patients indirectly through important discoveries in basic science. Her goal as a Whitehead Institute Fellow is to leverage and expand the research systems employed during her doctoral work to learn what gives liver cells their unique regenerative capacity. That research plan — and her demonstrated skills and creativity — recently earned Knouse a coveted National Institutes of Health Early Independence Award, which will supplement Whitehead Institute Fellowship funding for the next five years and help expand her research program.

The Whitehead Institute Fellows Program: A POWERFUL ENTRY POINT

Angelika Amon studies cell growth and division, and how errors in this process may contribute to cancer and aging. She has earned recognition as one of the world's best biomedical researchers. And Amon considers her experience as a Whitehead Institute Fellow to have been a cornerstone for her highly accomplished career in science. The Whitehead Institute Fellows Program enables talented recent PhDs to skip traditional postdoctoral fellowships — working in a senior scientist's lab, pursuing that person's research objectives — and undertake their own investigations. It is one of a handful of programs that offer extraordinary young researchers the funding, facilities, and mentoring needed to jump-start their careers in basic biomedical research.

"The discoveries I made as a Whitehead Institute Fellow — and the experience I gained in managing a lab — were fundamental to the career that followed," Amon recalls. "It was, in many ways, the most rewarding experience I've had as a scientist. It reinforced my confidence as a researcher and provided a level of visibility within the scientific community that was a key to my being offered a faculty position at Massachusetts Institute of Technology (MIT).

"Those are supremely important benefits for any emerging scientist — and especially for women, who still face disproportionate challenges in moving up the faculty ranks," Amon observes. "The opportunity to focus wholly on your own research objectives right out of graduate school, and to have research staff working under your direction, provides a powerful entry point to a scientific career."

Whitehead Institute Member **Terry Orr-Weaver** guided the Fellows program for many years. "What makes Whitehead Institute Fellows unique as young scientists," she explains, "is that they have demonstrated both the confidence to independently pursue questions that others dare not, and the capacity to solve major research problems." Orr-Weaver is credited with broadening awareness of the program, and making its selection process more accessible. The Fellows program now welcomes a new director, Whitehead Institute Member **David Sabatini**, who was once a Fellow himself, and is pleased to assume a leadership role within the program.

The newest Fellow is **Kristin Knouse**, who completed the Harvard/MIT M.D.-Ph.D. Program in May 2018. Knouse conducted her doctoral research in Amon's lab and Amon nominated her for a Whitehead Institute Fellowship. In her graduate work, Knouse created tools to identify and characterize large-scale genomic deletions and duplications in individual cells. She also began to focus on hepatocytes, the primary cell type in the liver, which have the unique ability to re-enter the cell cycle and proliferate following liver injury. That work will be the basis for her investigations at Whitehead Institute.

In her Whitehead Institute lab, Knouse is using the mouse liver as a system to study the unique regenerative ability of hepatocytes. She hopes to discover what endows these liver cells with this remarkable regenerative capacity and, ultimately, leverage that knowledge to enable regeneration of other tissues in the setting of disease. Ironically, the exciting work she leads is the result of initially pursuing a hypothesis that proved incorrect. "One of the things I've learned from working with Angelika is that simply by maintaining an open and curious mind you are almost guaranteed to find something interesting regardless of the initial question," Knouse reflects. "And one of the important benefits of being a Whitehead Fellow is having the freedom and resources to go wherever the science takes you."

"Before I began as a Fellow, I expected that the complete independence and pressure to produce would bring about a considerable amount of stress," Knouse says. "But the reality is that walking into my lab every day, working with my team toward a shared vision, is the most exciting and rewarding experience I have ever had. And that thrill overrides much of the potential anxiety."

Angelika Amon

is the Kathleen and Curtis Marble Professor of Cancer Research and Professor of Biology at MIT, a Howard Hughes Medical Institute Investigator, Member of MIT's Koch Institute for Integrative Cancer Research, and Associate Member of the Broad Institute of MIT and Harvard. Her research examines the regulation of exit from mitosis, the regulation of the meiotic cell cycle, and effects of aneuploidy on normal physiology and tumorigenesis. She received a B.S. and Ph.D. from the University of Vienna, then completed a two-year postdoctoral fellowship at Whitehead Institute before becoming a Whitehead Institute Fellow in 1996. She has been a faculty member in the MIT Department of Biology since 1999. An elected member of the U.S. National Academy of Sciences (NAS) and the American Academy of Arts and Sciences, Amon has received (among many honors) the NAS Award in Molecular Biology, the Genetics Society of America Medal, the Ernst Jung Prize for medicine, one of Europe's most prestigious medical awards, as well as the 2019 Breakthrough Prize.

Training Tomorrow's Investigators

For many scientists, a postdoctoral research project lies between earning their graduate degrees and starting their own research program.

While learning new scientific techniques, burnishing their grant and paper writing skills, and taking greater responsibility for their own research projects, Whitehead Institute's postdoctoral researchers comprise much of the backbone of the science performed at Whitehead Institute. Yet the challenges that face these investigators-in-training extend beyond the lab and may range from understanding a new country's culture, to balancing their research with the needs of family and children, to eventually landing that all-important first job. The reasons for undertaking all of the challenges inherent to a postdoc — and for choosing Whitehead Institute as a research home — are as varied as the postdocs themselves. We spoke with several of them recently and asked them about their research, their time at Whitehead Institute, and how the Institute's unique blend of resources, support systems, and lively research culture first attracted them and contributed to their professional development since their arrival.

Jamie Kwasnieski

Jamie Kwasnieski's requirements for a postdoc position were clear: a supportive mentor who is also a fantastic scientist, a close community where she could forge collaborations and relationships, and the opportunity to develop rigorous molecular biology techniques and learn more developmental biology. She checked all of those boxes when she joined Whitehead Institute Member **David Bartel's** lab. Kwasnieski still has a couple of years left in her postdoc, but already the decision of which career path to take has started creeping out of the shadows. As she speaks of her future, the importance of having Bartel as her mentor becomes evident. Kwasnieski would like to run her own lab, but she is considering doing so at a biotechnology company. Although some mentors prefer their postdocs to follow them into academia, Bartel has been supportive of all of her options.

As the head of the Whitehead Institute Postdoc Association (WIPA), the support that Kwasnieski so values is something she also extends to other Whitehead Institute postdocs. During the first half of her two-year term, she already made substantial changes to the organization. In order to foster camaraderie and collaboration among Whitehead Institute postdocs, the WIPA under Kwasnieski has sponsored career development events and social hours. The crown jewel of her inaugural year was the first postdoc retreat, which was held in downtown Boston. At the event, the majority of Whitehead Institute's postdocs shared posters, presented their research, and attended a career development panel discussion featuring scientists from local biotechnology companies. In response to the event's success, Kwasnieski and others involved with WIPA are considering another retreat for the upcoming year.

Laura Blanton

Laura Blanton's path to Whitehead Institute is closely tied to someone who had been a graduate student with her at Washington University in St. Louis, Missouri — Jamie Kwasnieski. Kwasnieski was a friend of Blanton's and a couple of years ahead of her in the same program, so when Blanton started looking into postdocs, she asked Kwasnieski to suggest a genetics lab with top-notch research and a great mentor, as well as a good community and support system. Kwasnieski's answer: Whitehead Institute Member **David Page's** lab.

For the past two years, Blanton has been a member of the Page lab, where she investigates how sex chromosomes affect gene function in immune cells. She says that she has definitely benefited from Page's mentorship style and guidance in creating and shaping her research trajectory. Page gives her the independence and freedom to explore her research, yet she does not feel that she's "out in the wilderness" when issues arise.

Blanton is still relatively new to the Boston area and cherishes the vibrant Kendall community, including the area's pharmaceutical companies, biotechnology start-ups, and Massachusetts Institute of Technology. A cornerstone of Kendall Square, Whitehead Institute — and the Page lab in particular — has become almost a second home to Blanton. Its dynamic research culture and strong community of postdocs have eased her transition to a city she first visited during the interview for her current position.

For prospective postdocs, Blanton emphasizes that one should be interested not only in a lab's research, but also the lab's culture and especially the relationship with one's mentor.

Zak Swartz

As a graduate student at Brown University, Zak Swartz knew Whitehead Institute as a "small and mighty" force in biomedical research. In addition to its reputation for top-notch research, the diverse range of model organisms represented, such as Arabidopsis and other plants, fruit flies, flatworms, and zebrafish, also impressed Swartz, whose research depends on starfish. In particular, one person and his research — Whitehead Institute Member **Iain Cheeseman** — drew Swartz to the Institute.

When he joined the Cheeseman lab three years ago, Swartz installed seawater tanks to support the starfish, which he uses to study meiosis, the specialized cell division that produces sperm and eggs. Starfish are closely enough related to humans that Swartz can adapt the approaches pioneered in human cells by the Cheeseman lab.

Swartz appreciates Whitehead Institute's culture of fearlessness in regards to research. According to him, many places may not have given him the freedom to establish a model organism that is new to that institution. This spirit extends to investigating novel lines of research — even scientifically risky ones. Swartz says he is surrounded by explorers in biology who are generous with their expertise, and he has already established close collaborations with several Whitehead Institute Members.

Swartz likens the postdoc experience to learning to fly a spaceship, because the scientist is developing a new, defined project that he or she can use to launch a career. In addition, postdocs learn new research techniques, hone scientific communication skills, and cultivate contacts, all while trying to get a paper or two published.

Despite the pressures and varied responsibilities tugging him in different directions, Swartz says that after departing Whitehead Institute, he may not know the answer to every question, but he will be equipped and empowered to lead his own lab.

Malkiel Cohen

Stem cells have fascinated Malkiel Cohen since he was a graduate student at Hebrew University in Jerusalem, Israel.

Attaining the best training in stem cell research was the primary factor Cohen considered when selecting where to do his postdoc. Cohen was impressed that former postdocs of Whitehead Institute Founding Member **Rudolf Jaenisch** have made significant contributions to the field and are among the brightest minds in stem cell research. Although he could have applied to any of their labs, Cohen decided to "go to the source" and joined Jaenisch's lab.

Over the past seven years, Cohen has learned much from Jaenisch about how to run a lab, manage people, approach research, and tell its story. Graduate students and postdocs come and go every year, so turnover is a constant in labs. Cohen has absorbed how to maintain continuity of skills, research, and information despite the churn.

He has also learned perseverance. As a graduate student, Cohen says it is hard to imagine how demanding and dynamic postdoc training will be, with very long hours and research triumphs followed by months of foiled experiments. Yet as part of the Whitehead Institute community, and with Jaenisch as his guide, Cohen never had to look far for technical help or answers. Frequently, everything he needs is right here in the building.

Today, Whitehead Institute is home to investigators focused on biology's most fundamental questions. Whitehead Institute scientists run pioneering programs in cancer research, immunology, developmental biology, stem cell research, regenerative medicine, genetics, and genomics.


Committed to
COMMUNITY

Whitehead Institute Welcomes New Member

Ankur Jain, an emerging leader in the study of RNA aggregation, joined Whitehead Institute in September as its newest Member. Jain, who has also been appointed an assistant professor of biology at the Massachusetts Institute of Technology, comes to the Institute from the University of California, San Francisco where he did his postdoctoral work with Ronald Vale.

"Ankur brings an approach grounded in a combination of soft-matter physics and cell biology to help pioneer an important — potentially groundbreaking — way of investigating and understanding RNA aggregation and RNA-DNA interaction," says David Page, Whitehead Institute Director and Member. "His insights are exciting, and the intellectual and scientific creativity he brings to his research is energizing."

Jain discovered that certain RNAs can clump together and form liquid droplets or "gels." This process, known as phase separation, has been widely studied in proteins but not in RNA. He has found that RNA gels occur in, and could possibly contribute to, repeat expansion diseases, a set of neurological diseases including amyotrophic lateral sclerosis (ALS) and Huntington's. Excessive repetition of short sequences of nucleotides, the building blocks of DNA and RNA, is a hallmark of the genes associated with these diseases, and the RNAs containing these sequences are more likely to clump together. These studies may also provide important clues into the mechanisms underlying other neurodegenerative diseases, such as Alzheimer's and Parkinson's.

Jain is investigating the mechanisms by which cells prevent potentially deleterious RNA aggregation, and will search for therapeutic agents that could one day safely dissolve RNA gels in patients.

RNA aggregation may also play a role in normal cellular function. Protein aggregation, a better-studied analogous process, is seen both in neurological disorders as well as in healthy cells. Phase-separated proteins mesh together to form barriers that help cloister and concentrate certain cellular processes. Jain posits that RNA gels may likewise help to compartmentalize cells, and he plans to look for instances of healthy RNA aggregation.

In order to investigate these questions, Jain will use his expertise in quantitative light microscopy to continue developing imaging methods that enable him to study molecules in their natural context.

"Cells are compartmentalized into many small domains with unique environmental characteristics. Which of these domains a biomolecule operates in affects its function. Yet traditional biochemical methods often disregard biomolecules' location as a factor. We need new approaches," Jain says. "I'm very excited to be joining the rich intellectual community of Whitehead Institute as I continue this work."

Economist Paul Joskow Joins Whitehead Institute Board of Directors

"Basic research is the foundation upon which all applied science and clinical advances are built. Whitehead Institute is a trailblazer in basic biomedical research and its Members have made many breakthrough discoveries with far-reaching impact," Joskow says. "I look forward to contributing my expertise to the Institute."

This year, Whitehead Institute was pleased to welcome back an exceptional member to its board of directors, **Paul Joskow**. Joskow, who previously served on the board from 1993 to 2005, is the Elizabeth and James Killian Professor of Economics, Emeritus at the Massachusetts Institute of Technology (MIT). He joined the MIT faculty in 1972, and has served as both the head of the Department of Economics and the director of the MIT Center for Energy and Environmental Policy Research. His research focused on industrial organization, energy and environmental economics, competition policy, and government regulation of industry. Joskow also spent ten years as the president and CEO of the Alfred P. Sloan Foundation, which supports research and education in science, technology, engineering, mathematics, and economics. He brings to the Board a wealth of experience in governance, management, and stewardship from his time at Sloan, where he modernized many of the foundation's practices.

Joskow is known in the foundation world as an innovative leader in the raising and allocation of scientific funding. He was a key player in the creation of the Science Philanthropy Alliance, which advises philanthropists on how best to support basic research.

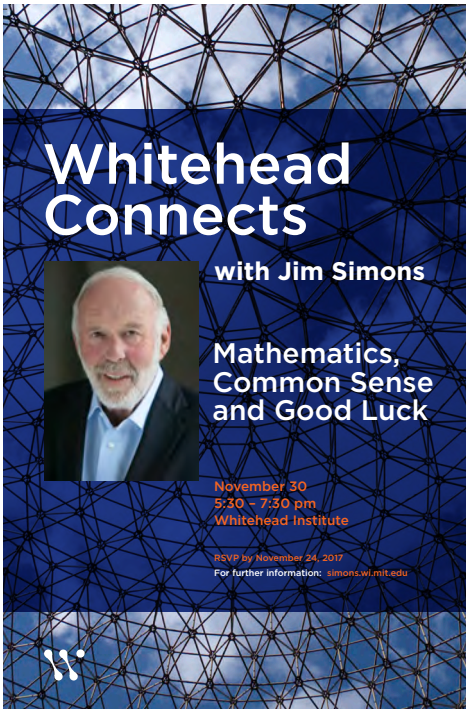
Whitehead Connects: On Orbits and Algorithms

Whitehead Connects, one of the Institute's most popular events, gathers biomedical researchers, the science-savvy, and the curious to hear from a diverse selection of distinguished luminaries. As a world-renowned research institute, Whitehead Institute celebrates its impact as part of the Kendall Square community and is pleased to bring national leaders in their respective fields to the Cambridge community. This year, *Whitehead Connects* featured two outstanding speakers. In September we welcomed NASA Astronaut and Former Whitehead Fellow **Kathleen "Kate" Rubins**, and in November, **James H. Simons**, chairman of the Simons Foundation, an organization dedicated to advancing the frontiers of research in mathematics and the basic sciences.

During Rubins' visit, she recorded a podcast with Whitehead Institute Director David Page that delved into some of the challenges of training for and conducting research in space. After the recording, which was in front a select number of graduate students and postdoctoral researchers, Rubins chatted with the audience and answered questions about her research. Rubins next met with K-12 students, parents, teachers, and even a few children from the Whitehead Day Care Program at Bright Horizons. Whitehead Member Terry Orr-Weaver moderated the discussion with Rubins, during which students asked thoughtful questions about her science and life in space.

Following the student presentation, Rubins spoke to a packed auditorium of guests from the Whitehead Institute and Massachusetts Institute of Technology (MIT) community — including some who worked with Rubins when she was a Fellow almost ten years ago. Whitehead Institute Board of Directors members, Whitehead Institute donors, as well as researchers from the Kendall Square area also attended. **Maria Zuber**, the E.A. Griswold Professor of Geophysics and Vice President for Research at MIT, opened the session with special remarks that highlighted the importance of space exploration

and research, and Whitehead Institute Member Richard Young (one of Rubins' mentors at the Institute) moderated a question and answer segment at the end. To cap the day, the Whitehead Institute community officially welcomed back the returning Fellow with a reception in the Institute's cafeteria.



During the first part of the November *Whitehead Connects* event, entitled "Mathematics, Common Sense, and Good Luck," Simons, who received an undergraduate degree in Mathematics from MIT, conversed with a small group of Whitehead Institute graduate students and postdoctoral researchers about his passion for mathematics, education, and the joys and challenges of research.

After Simons' gathering with trainees, the auditorium doors opened to a capacity audience from the wider community who had come to hear Simons and Institute Director David Page in conversation about Simons' experiences in math, finance, and life.

Simons touched on his pioneering use of mathematical modeling in investment management, his approach to failure, and his fascination with machine learning and the analysis of big data. He also spoke about his philanthropic pursuits, such as the Flatiron Institute, an internal research component of the Simons Foundation focused on using computational approaches to understand science, and Math for America, which supports secondary education in math and science in New York City schools. During the cocktail hour following Simons and Page's conversation, the audience mingled and discussed Simons' insights.

The Simons and Rubins events continue the tradition of previous *Whitehead Connects*. As the new year begins, Whitehead Institute and the greater Kendall community are eagerly anticipating the next installments of this highly popular series.

Whitehead Institute Public Programs Reach out to Area Students and Teachers

As part of its mission, Whitehead Institute strives to inspire, educate, and empower teachers and students about major advances in biomedical research. This year, about 60 teachers from Greater Boston-area high schools, as well as a handful from middle schools and community colleges, participated in Whitehead Institute's Seminar Series for High School Teachers, entitled "How Technology Drives Biology." Held the first Monday of every month from October through June, top minds in biomedical research spoke about their groundbreaking work and the cyclical relationship between tools and techniques and the scientific discoveries that they propel. Speakers selected for this year's program included: Whitehead Institute Founding Member Harvey Lodish speaking about using modified red blood cells to deliver therapeutics; Canan Dagdeviren from MIT Media Lab describing miniaturized neural drug delivery systems; Joanna Buchthal and Jianghong "John" Min from MIT Media Lab and Harvard Medical School explaining how gene drive technology could hamper the spread of Lyme disease; and Whitehead Institute postdoctoral researcher Julien Muffat discussing using brain organoid models to study disease.

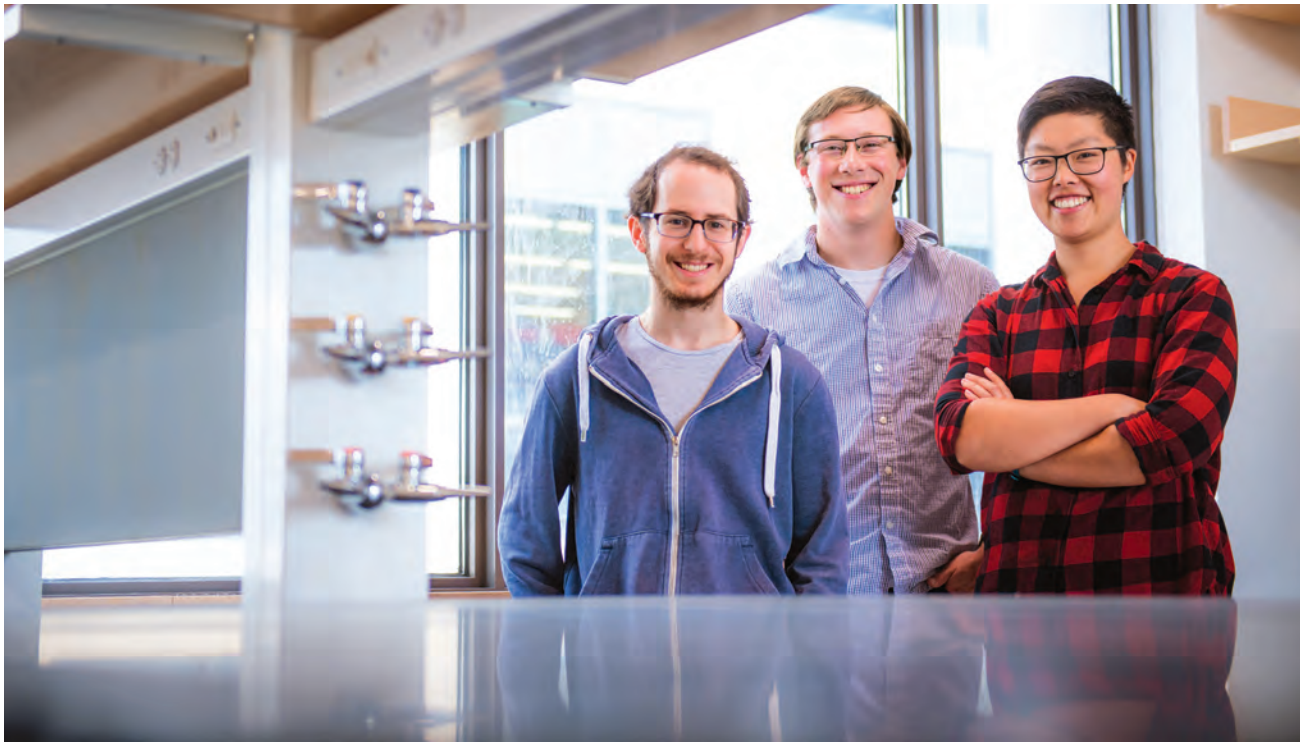
As a part of the program, teachers have a unique opportunity to request a "Whitehead Partner," typically a postdoctoral researcher or a graduate student in one of Whitehead Institute's labs. Following each lecture, teachers and their partners sit down at long tables in the Whitehead Institute cafeteria for dinner, where they can discuss the lecture and any scientific questions the teachers may have. Although the lectures are informative and enlightening, teacher participants point to the partner component for putting the program head and shoulders above its peers. "Whitehead Partners are not your average postdocs or grad students," says Julie Snyder, a 20-year veteran of the program and a biology teacher at Hudson High School in Hudson, Massachusetts. "They are committed to investing in education and getting kids excited about science."

In addition to reaching out to teachers, Whitehead Institute seeks to engage tweens at a critical period of their education and expose them to the world of biomedical research. Expedition: Bio is the Institute's summer course for area middle school students. This year, an expanded two-week iteration of the program teamed instructors with more than 50 years combined public school teaching experience with the award-winning BioBuilder Educational Foundation. Along with exploring the emerging area of synthetic biology at BioBuilder's learning lab at LabCentral in Cambridge, Massachusetts, students gathered biological samples on a field trip to Drumlin Farm Wildlife Sanctuary in Lincoln, Massachusetts. The specimens were analyzed later during modules at Whitehead Institute.

By participating in discussions with scientists and hands-on activities inside and outside the classroom and laboratory, students learned how methods from the fields of ecology, genetics, chemistry, and bioengineering are used to answer some of the most challenging questions in the life sciences today. Over the course of the program, students had the opportunity to do experiments involving DNA extraction, chromatography, gel electrophoresis, PCR, and fruit fly dissection. In addition, students visited the local Kendall Square facilities of the international biotechnology company Amgen® where they ate lunch with Amgen scientists and discussed topics such as therapeutics and drug delivery. Students also participated in an interactive demonstration on manufacturing molecules. The program culminated with a scientific poster session where students shared what they learned at Expedition: Bio with family, friends, program volunteers, and members of the Whitehead Institute community.

Feedback from participants has been resoundingly positive, with many excited about their new scientific skills and looking forward to learning more about biology back in the classroom. "The knowledge the scientists shared with me has inspired me to learn more," says a seventh grader who attended the July session of Expedition: Bio. "It was really interesting and honestly the best summer program I've ever been to." Expedition: Bio is supported by a generous contribution from the Amgen Foundation, with additional scholarship support provided by Sanofi Genzyme.®

National Science Foundation Fellowship



The National Science Foundation (NSF) has awarded 2018 NSF Graduate Research Fellowships to three graduate students who are part of Whitehead Institute laboratories:

Justin Roberts (Sabatini lab) will be investigating how starvation in mammalian cells induces the recycling of protein synthesis machinery and the nucleoside building blocks that comprise them.

Tyler Smith (Lourido lab) will be deciphering the calcium signaling cascade that the *Toxoplasma gondii* parasite uses to invade and egress from its human host cells.

Sophia Xu (Weng Lab) will be developing self-assembly chemistry to cage individual proteins and enzymes and preserve their activity outside of cells.

The Fellowship, which was awarded to 2,000 of the more than 12,000 students that applied, provides three years of financial support.

Remembering Thomas J. Gochberg

The Whitehead Institute community was saddened by the passing of longtime friend **Thomas "Tom" Gochberg** this past May. Tom, along with his wife Letty, were valued members of Whitehead Institute's Board of Associates. Tom held a steadfast belief in the Institute's focus on fundamental biomedical research and he and Letty supported its work through their generosity — including giving their time and effort to host events in New York City where they lived.

Tom grew up in Boston, Massachusetts before moving to New York to attend Columbia University. Over the course of a distinguished career in real estate finance, he was the president and CEO of Smith Barney Real Estate Corporation, co-founder and president of the Pension Real Estate Association, president and CEO of Security Capital Corporation, and co-founder and CEO of TGM Associates L.P. The Whitehead Institute community will miss him greatly and sends his family heartfelt condolences.

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

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

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

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