Annual Report

2020

Whitehead Institute

Contents

The power of the moment

It is an understatement to say that 2020 was tumultuous and challenging.

The pandemic took us all unaware. Like most other members of the Greater Boston community, the people of Whitehead Institute needed to almost immediately change how we work and the way we engage with each other. And like so many others across the nation and around the world, we felt compelled to quickly adapt our skills, knowledge, and capacities to help address the many ways SARS-CoV-2 was affecting humankind.

The pandemic caught most life sciences researchers off guard in other ways too. We were unaccustomed to confronting a disease we knew so little about, and it was unsettling. We'd never before had to shut down labs and then figure out how best to build their operations back up. As challenging as young scientists' career development has become during the past decade, we never before had to confront the impacts — professional, practical, and emotional — of this huge hurdle thrown in their way. And COVID-19's disproportionate impact on minority populations was a powerful reminder that the broad biomedical community is not immune to the effects of institutional bias and inequity.

Now, looking toward 2021, we find ourselves in a unique situation at a unique point in time: still confronting serious challenges, yet energized by our determination to overcome them and to capitalize on the opportunities that challenge and change can bring.

There is power in the moment, and we want to harness it. At Whitehead Institute, the 2020 experience has prompted us to ask new questions and to pursue new directions in our science, to adapt and improve our facilities, and to expand our operations. It's encouraged us to explore new ways of interacting with each other — personally and professionally, as individuals and a community.

But that is just the start of our efforts to harness the power of the moment. We must ensure that Whitehead Institute is a place where scientists are encouraged to think boldly and are empowered to advance our knowledge of the living world. We must maintain a highly effective culture of intellectual risk-taking and excellence. And we must successfully cultivate the value of mutual respect so we can nurture the next generation of biomedical research leaders — offering everyone in our community the opportunity to pursue their full potential.

This annual report offers a glimpse of how we have been pursuing those goals. I invite you to engage with us as we move forward.

Ruth Lehmann
Director

Looking ahead

This past year — my first as board chair, succeeding the inestimable Charley Ellis — was a time of both challenge and renewal.

The global and national challenges we all know too well: pandemic, recession, and reckoning with longstanding bias and inequity. The Whitehead Institute community worked diligently — as scientists, citizens, and members of society — to address those challenges, and our efforts will continue. Going forward, we will learn from this year of challenge, employing those lessons to increase our operational flexibility and resilience and to ensure equal opportunity throughout our community.

This has also been a time of renewal and growth. Ruth Lehmann became the Institute's fifth director in July 2020, succeeding David Page. She brings a distinguished record of scientific achievement and tested leadership to the tasks of steering the organization through near-term challenges and charting its long-term course. Her approach — listening, learning, then acting decisively — is well-calibrated to both these dynamic times and the opportunities that dynamism creates. In addition to Ruth joining the Institute faculty — and David Page returning to his lab full-time — we welcomed two new Members: Jonathan Weissman and Yukiko Yamashita, both world-renowned for innovative and path-breaking biomedical research.

We have also added five extraordinary individuals to the board of directors: Susan Hockfield, Churchill Franklin, Dennis Langer, Robert Satcher, and Seth Alexander. These new board colleagues bring vast leadership expertise, management skill, and financial acumen, as well as deep experience with governance of nonprofit, research, and academic institutions.

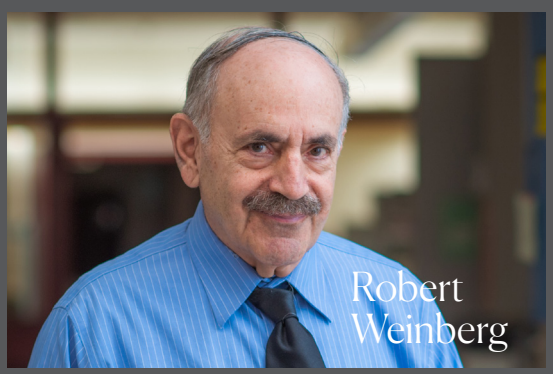
That these highly regarded new board members are willing to invest considerable time and energy in Whitehead Institute makes an important statement: that foundational biomedical research is essential to the healthy and successful future of this nation and that of global society, and the investment we make in pioneering science today will return bountiful dividends in decades to come.

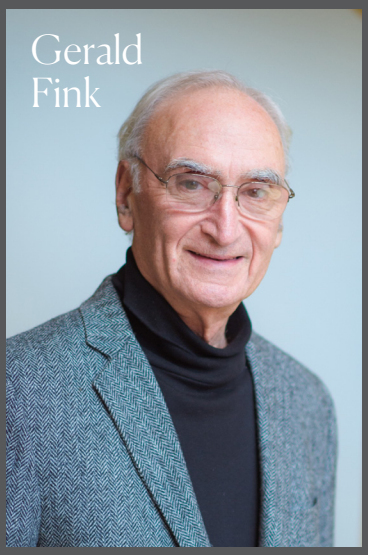
It says, too, that Whitehead Institute's future as an engine of discovery and innovation, as a catalyst for tools and methods that advance research globally, is at least as bright as its storied history.

We welcome you to join us in looking ahead, past these challenging times, to a bright and healthy future.

Sarah Williamson
Chair, Board of Directors

Whitehead Members & Fellows

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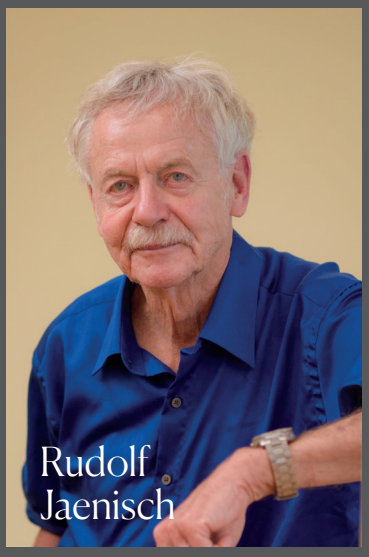
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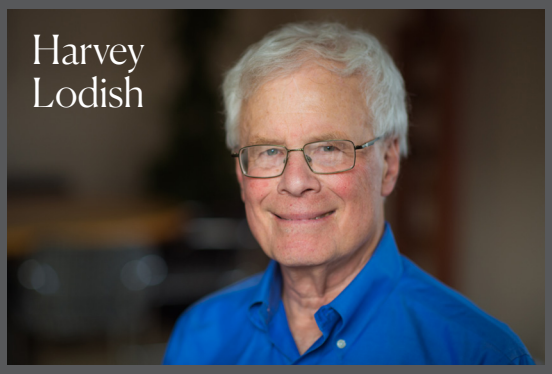
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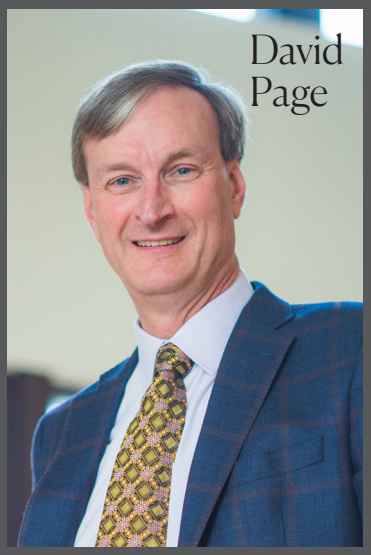
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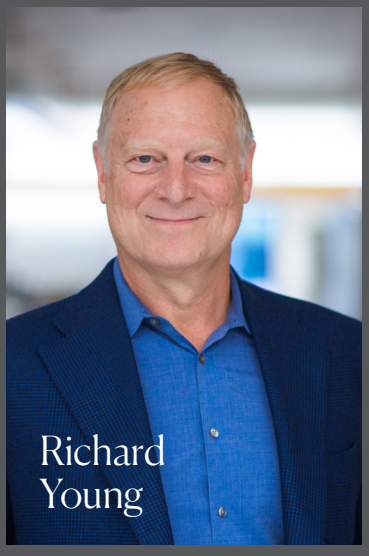
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Whitehead Science

Mother of fields

Hazel Sive

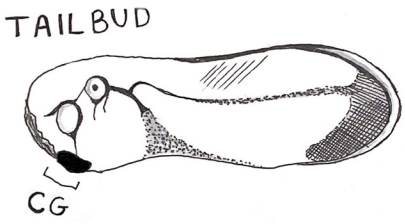
In June 2020 renowned developmental biologist Hazel Sive concluded 28 years as a Whitehead Institute Member and professor of biology at Massachusetts Institute of Technology (MIT). While Sive was a much-lauded teacher and academic leader at MIT — experiences she is now drawing on for her new role as Dean of Northeastern University's College of Science — she is globally recognized for her achievements as a fundamental science researcher. In this piece, she reflects on significant accomplishments in her long, fruitful scientific career at Whitehead Institute.

I have always been drawn to life, to feel part of it in the most spiritual way. And particularly I have spent my career asking, how are vertebrate animals built from cells, so perfectly and intricately? At Whitehead Institute, over the past 28 years, my research group has uncovered profound answers to this question. I am deeply grateful for the opportunity to have been a Whitehead Institute Member, and I am deeply proud of the contributions our research has made. The work of outstanding Sive Lab members has been important and groundbreaking. We have been pioneers in so many areas, I am indeed, the Mother of Fields.

The journey begins

My developmental biology pathway began during an undergraduate project at Wits University in Johannesburg, South Africa. I kept rows of plastic dishes filled with thousands of frog embryos that had all started growing at the same time. As I walked along my rows, I noticed that the embryos were doing exactly the same thing at the same time. When I first noticed, all were composed of eight cells, large enough to see with the naked eye. Hours later they had all become kidney-bean-shaped with a black patch on one end, and at a later point they had all developed eyes and started swimming. It was extraordinary! How, I wondered, did the embryos know what to do and when to do it? There must be a powerful set of instructions connected to some precise timer telling them. Maybe, I thought, I could isolate those instructions and understand this magic. That thought started me on my way.

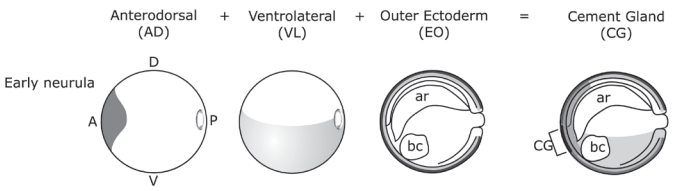
Frogs, and later zebrafish, were what I chose for our studies, because their embryos grow rapidly, and externally in a Petri dish in the lab, and because the embryos are large and easy to observe even at the earliest stages of development. Further, frogs or fish are not so different from people — we all have two eyes, a nose and a mouth, and the same organs. So I figured these animals could teach us something about how people are built.



Frog embryo: The frog Xenopus cement gland (CG) forms at the front of the embryo, and is visible as a dark pigmented patch about a day after development begins (at tailbud stage). We traced its origin back to the early neurula stage, 12 hours earlier. (Drawing by Simone Lassar, adapted from Wardle and Sive, 2003)

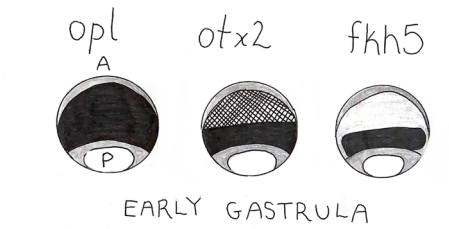
The journey unfolds

I started simple, asking 'HOW does the little patch of black pigment get to the front of the frog embryo?' The patch is called the 'cement gland' and secretes a glue that stops the frog embryo from floating away. No-one had asked this question before, and we had to develop new techniques to isolate the genes involved. Over many ground-breaking publications, we started a field, and found that three separate sets of instructions add together to position the cement gland. Some of the genes we isolated have themselves started entire new fields.



Cement gland patterning: Our work uncovered signals from three regions, Anterodorsal (AD), Ventrolateral (VL) and Outer Ectoderm (EO), that add together to position the future cement gland, many hours before the pigmented region appears. (Wardle and Sive, 2004)

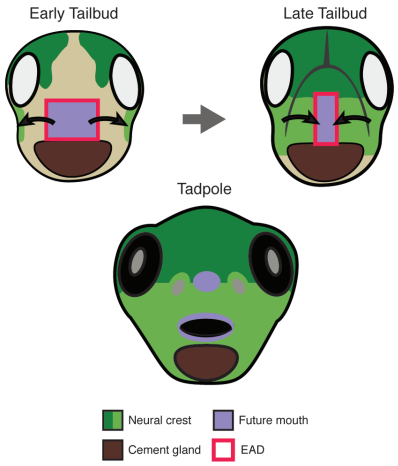
Humans don't have a cement gland, so at the same time we asked: WHEN does the embryo decide to make the brain and spinal cord, organs clearly relevant to people? We identified more than 50 previously unknown genes involved in nervous system formation, including chemical signals and other needed regulators. Amazingly, even when the embryo is just a ball of cells, we showed that it has already decided to make a nervous system and where to place the brain and spinal cord. No one had any idea that these decisions were made so early during development, and our work helped explain how some human birth disorders arise.



Neural patterning: Activities of genes we identified, opl, otx, and fkh5 (black shading) show that regions of the future brain are present at the early gastrula stage, when the embryo is simply a hollow ball of cells. A: anterior or the future head, P: posterior or the future tail. (Drawing by Simone Lassar, adapted from Gamse and Sive, 2000)

Traveling across new frontiers

Another surprising new field came from the cement gland. I realized that a region including the cement gland and lying at the front of the embryo had a special organization of cells, that is present across evolution, including in human embryos. We named this region the Extreme Anterior Domain (EAD). The EAD is important because it becomes the mouth, and we developed a novel facial transplant technique that uncovered the complex, carefully orchestrated mechanisms involved in mouth formation.

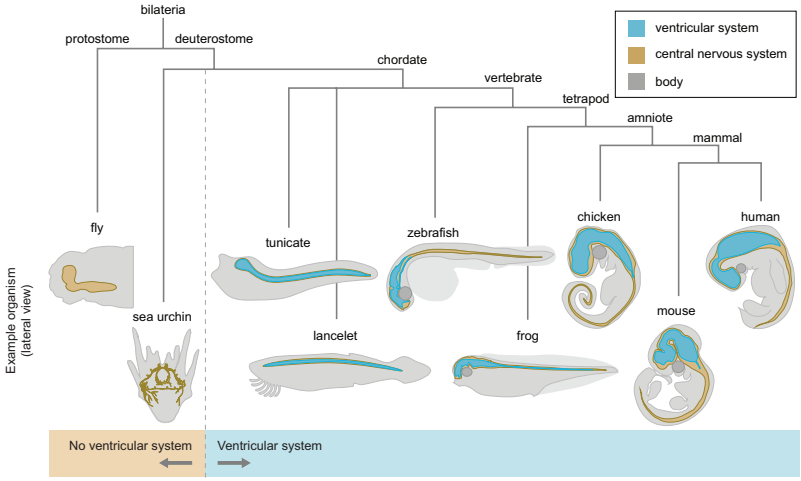


EAD signaling: We defined the Extreme Anterior Domain, and its key role in building the face. During face formation, the EAD (purple) sends signals (arrows) to attract neural crest cells that form cartilage (green), and later, the EAD responds to signals (arrows) leading to mouth formation. (Chen, Jacox et al., 2017)

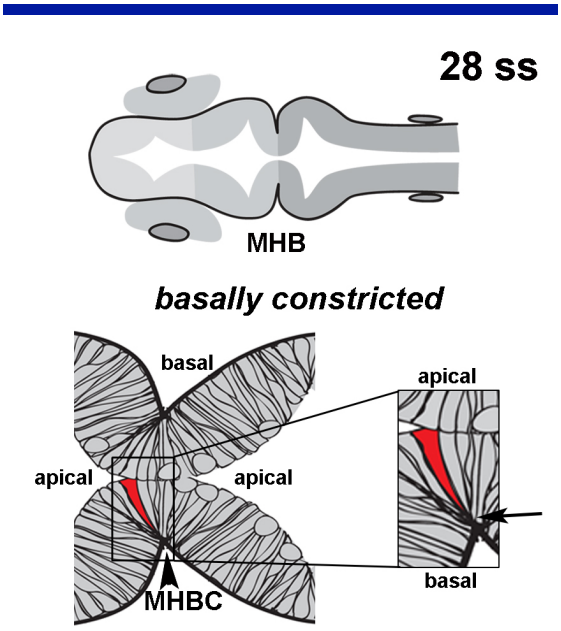
But we discovered something else unexpected — that the EAD produces chemical signals, sending these out to instruct the surrounding cartilages and bones of the face to develop properly. And these signals also instruct the brain to become a certain size, by controlling the number of cells it contains. Wow! From that little patch of black pigment has come an understanding of how the entire head forms, and one way this process may go awry in the devastating birth disorder of microcephaly.

From the very beginnings of the nervous system, our studies moved on to explore later steps. An important direction came from asking 'WHY are the brain and spinal cord tubes?' If the human neural tube (future brain and spinal cord) forms incorrectly, why do catastrophic disorders such as spina bifida and anencephaly arise? We thought it may have to do with the unique cerebrospinal fluid, or CSF that fills the neural tube. In

pioneering studies using the zebrafish, we made the crucial discovery that CSF promotes survival of developing nerve cells and proper brain development. We isolated a CSF factor, RBP4, that increases cell survival. We later uncovered the complex ways that CSF moves through the developing neural tube, carrying a myriad proteins with it. Our contributions included devising several new techniques, and continue to give insight into underlying causes of human neural tube disorders.



CSF: Cerebrospinal fluid within a brain ventricular system is a hallmark of every animal with a complex nervous system. Our work pioneered use of zebrafish to uncover the role of this system in brain development and health. (Fame et al., 2020)



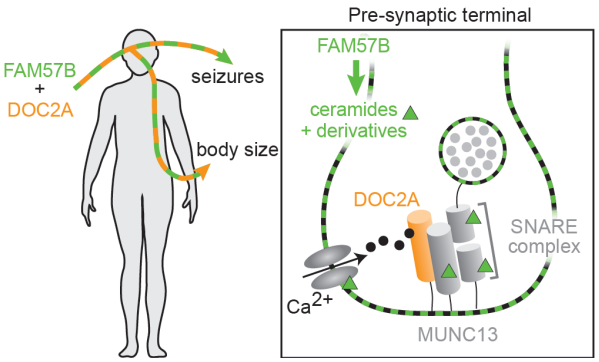
Basal constriction: In the developing zebrafish brain, we discovered a novel change in cell shape, 'basal constriction' (red cell). Basal constriction helps fold the brain for optimal function, and is now known to be widely present during organ formation. (Gutzman, Graeden et al., 2018)

Always thinking hard, we wondered, 'WHY does the brain have its characteristic rounded shape?' since the neural tube starts off long and thin. We thought that a compact brain is less prone to injury than a skinny tube, and set about to understand how the brain acquires its shape. Along the way we made two fundamental discoveries, a cell shape change called 'Basal Constriction' that has started another field, and a 'stretchiness' of cell sheets that we termed 'Epithelial Relaxation', another undescribed process.

Much of our research has been relevant to human disorders; however, some years ago, I decided to actively focus on mental health disorders. These disorders afflict about a quarter of the United States population, but there have been few new treatments for decades. Each disorder involves many genes, whose individual roles are generally not clear.

Our studies pioneered the zebrafish system as a productive tool to analyze genetic contributions, and to uncover possible therapeutic avenues for mental health disorders. We defined gene variants associated with schizophrenia, and gene combinations associated with the severe 16p11.2 deletion

(16pdel) syndrome, a major risk locus for autism and other symptoms. Recently, we showed that the fat (lipid) composition of cells from people affected with 16pdel syndrome is different from that of unaffected people. Likely as a consequence, the synaptic connections between nerve cells, brain activity and behavior are all anomalous in zebrafish models. These novel findings connect metabolism (cellular chemistry) with mental health, and suggest that by correcting lipids, affected people may be significantly helped.



16p11.2 deletion syndrome pathways in mental health: We showed that *FAM57B* and *DOC2A*, genes interrupted in this syndrome, are critical regulators of brain cell connectivity (at the pre-synaptic terminal). *FAM57B* regulates production of certain fats, essential for brain and body health. (McCammon et al., 2017)

What broad travels, since that day I realized that embryos must come with an instruction manual! The important work will continue in my own lab at Northeastern University, and by the scores of talented trainees who were part of my group at Whitehead Institute, and are building their own productive careers.

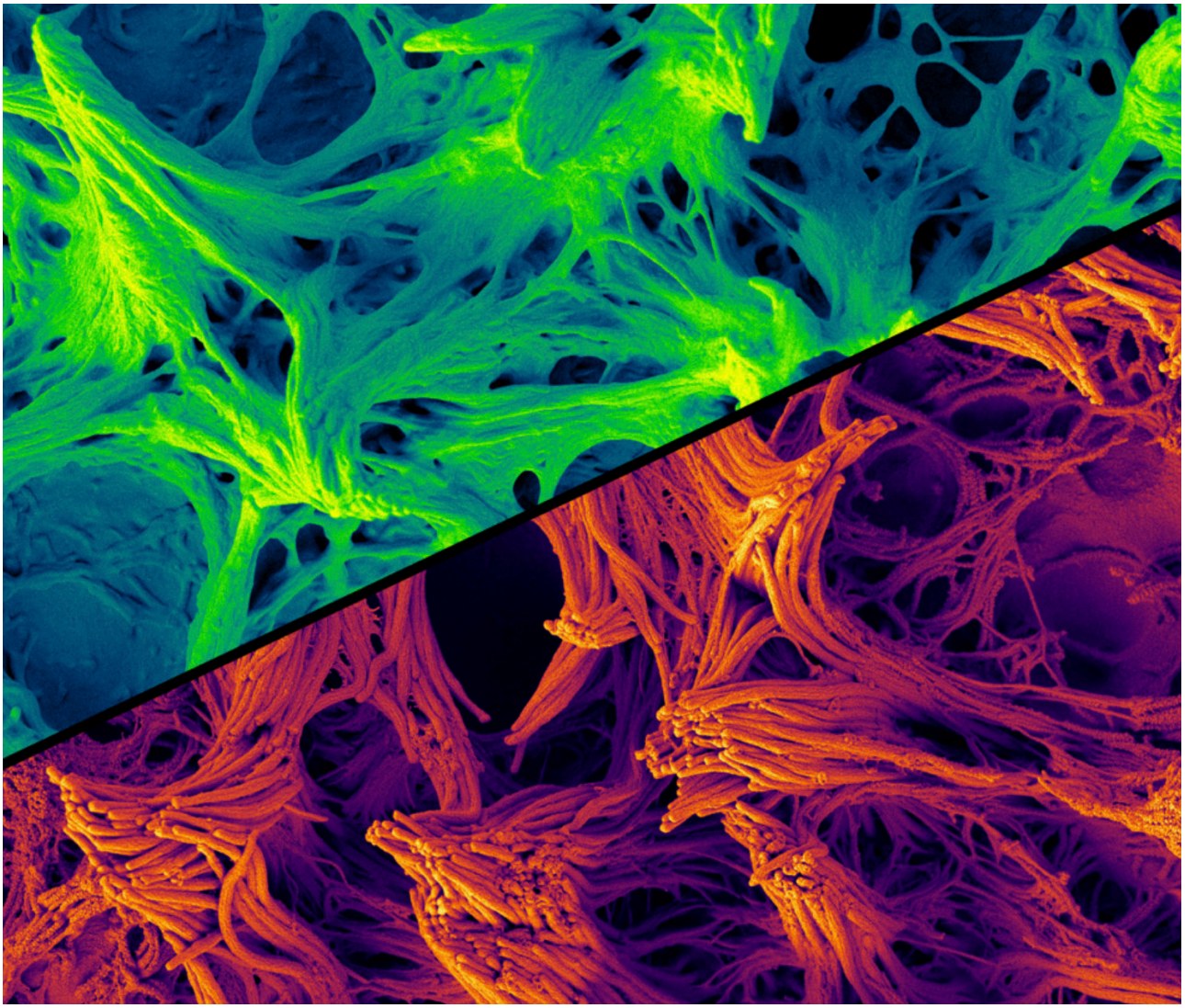
To make this piece succinct, there was much omitted, and I would like to warmly acknowledge the contributions of all Sive Lab members. Our publications are listed at:

https://www.ncbi.nlm.nih.gov/sites/myncbi/hazel.sive.1/bibliography/41155525/public/?sort=date&direction=descending

I am extremely grateful for the funding that has supported our research.

Finally, to the Whitehead Community (Directors, Faculty, Staff, Trainees, and Donors) who helped build the vibrant, effective Institute landscape in which we worked, my most sincere appreciation.

From Bedside to Bench and Back



Postdoctoral researchers are, in many ways, the engines of biomedical science laboratories, helping to drive discovery forward. At Whitehead Institute, these early career investigators rank among the world's most skilled and accomplished. Clinician-scientist Raghu Chivukula, MD, PhD, is representative of this extraordinary group — and of the potent synergies that can emerge when bench research and clinical care work hand-in-hand. Fundamental research is key in understanding the root causes of many diseases; and one of Chivukula's recent clinical cases is a focused example of that principle: he along with other Whitehead Institute researchers helped discover a new genetic lung condition and revealed a gene's previously unknown function.

In 2018, a 31-year-old woman checked into Massachusetts General Hospital (MGH) in Boston with a respiratory infection so bad she had to be placed on oxygen. A trip to the hospital for lung trouble was nothing new for her — several times in the past, recurrent infections required her to stay under a doctor's supervision for days until they blew over. Now, however, it seemed that she would not be leaving the hospital until she received two entirely new lungs.

The woman had had respiratory issues since she was a baby. Her flare-ups usually presented like pneumonia — a nasty, phlegmy cough accompanied by a fever. After years of this, her airways were swollen and inflamed. When her physicians tested for likely causes such as cystic fibrosis, however, the results came back negative. Her case was a total mystery.

Cracking the case study

As she awaited her double lung transplant, the woman met Dr. Raghu Chivukula, at the time a pulmonary and critical care medicine fellow at MGH interested in rare and unusual lung diseases as a consequence of his Ph.D. training in human genetics. During his time spent working with often critically ill patients, "it became clear that there were lots of unanswered questions in lung biology," he said. Chivukula soon realized that the woman's condition was one of these unanswered questions.

Often, when doctors are unable to come to a diagnosis, they end up referring a patient to another hospital or to see a specialist. MGH, with its reputation as one of the top hospitals in America, sees quite a lot of these mysterious cases. In 2016, the hospital created a program called the Pathways Consult Service through which physician-scientists could evaluate these unusual patients to see whether their maladies might be something entirely new to science.

After his initial conversations with the patient, Chivukula reached out to the Pathways program to see whether they could help him further investigate her disease. "We were so excited when Raghu, who is an incredible physician and scientist, came to us with this opportunity to learn about biology from this patient that he was seeing," said Dr. Katrina Armstrong, the chair of the Department of Medicine and physician-in-chief of Massachusetts General Hospital. Chivukula began his investigation by talking to two of the woman's siblings, who were in town to help their sister in the run-up to her operation. This offered Chivukula a clue: respiratory infections ran in the woman's family.

With help from the Pathways program, Chivukula sent blood samples from the woman, her parents, and her two siblings to Dr. Fowzan S. Alkuraya, a geneticist at King Faisal Specialist Hospital and Research Centre in Riyadh, Saudi Arabia.

Alkuraya performed sequencing and sifted through the data looking for mutations that could be playing a role in the family's lung issues. Across all three affected siblings, one common difference stood out: a mutation in a gene called NEK10. "I wrote back to Raghu to tell him how excited I was for having identified this novel gene," Alkuraya said.

Scientists weren't sure what this gene did, although they knew it coded for a kinase — a type of protein involved in signalling by modifying other proteins. Chivukula decided to take on the project as part of his postdoctoral research in David Sabatini's lab at Whitehead Institute, since Sabatini's previous research has included a focus on understanding important protein kinases in cells.

Chivukula had initially begun working with Sabatini on a project about the role of lysosomes in the development of pulmonary fibrosis, and the new mutation seemed like a perfect additional project that bridged his interests in rare pulmonary disease with basic mechanistic research. "I was hopeful that the combination of my own interests in lung biology with David's lab's world-class cell biology expertise and specialized toolkit would allow us to figure out this disease," Chivukula said.

The mystery mutation

To determine whether this mutation was to blame for the woman's condition, Chivukula and Sabatini took a closer look at the mutation itself. The alteration caused the insertion of seven additional amino acids in the NEK10 protein, which Chivukula showed rendered the protein unstable and suggested mutant NEK10 was unable to perform some key job in the woman's lung cells.

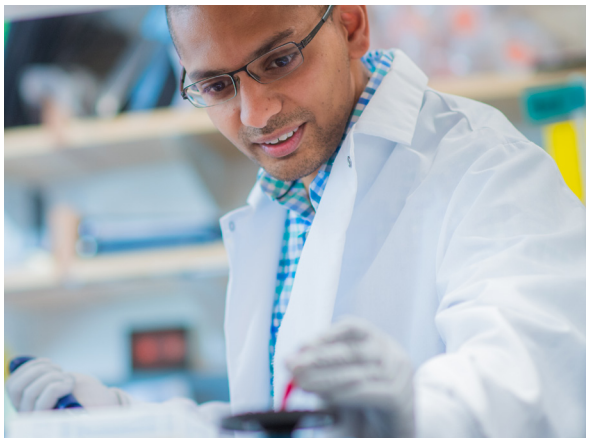
Still, she was only one patient. Was this just a fluke, the scientists wondered, or could NEK10 mutations be to blame in other cases of unexplained respiratory problems?

Chivukula started sending out feelers to other hospitals and research centers around the world, hoping to find patients who shared the mutations the woman and her siblings had in their NEK10 genes. His search eventually turned up six additional patients — including several under the age of 25 — with slightly different mutations in NEK10 and conditions similar to the woman's, marked by pneumonia-like flares and enlarged airways typical of a condition known as bronchiectasis.

Armed with a broader pool of data, Chivukula went back to the lab to find out what exactly NEK10 was doing in cells. Using undifferentiated lung tissue, the researchers used a fluorescent protein to mark the cells expressing NEK10 with a green glow. When they allowed the cells to differentiate, the brightest glowing cells were those that were covered in cilia, indicating that NEK10 likely functions in these specialized cells.

In the lungs, cilia move mucus by wiggling back and forth in tandem with their neighbors. When Chivukula took a closer look at the woman's airway cilia, he found that they still wiggled at the same speed, but that something was off; while normal cilia could transport polystyrene beads on a slithery wave of mucus, her mutated cilia could barely move mucus at all.

Under a microscope, the cilia were strangely clumpy and underdeveloped. The mutation had caused the cilia to be too short to effectively move mucus, leading to a build-up in her airways and increasing her likelihood of respiratory infections. With each infection, her bronchi grew more dilated until she could barely breathe on her own.



A new disease

Chivukula, Sabatini, and coauthors published their findings on the new disease in *Nature Medicine* in February. As for the woman who received the double lung transplant, "She's doing pretty well," said Chivukula. "She doesn't need oxygen and can finally walk around without becoming short of breath. Being sick for 20 years takes its toll like it would for anyone, but she's in a much better state than she was before her transplant."

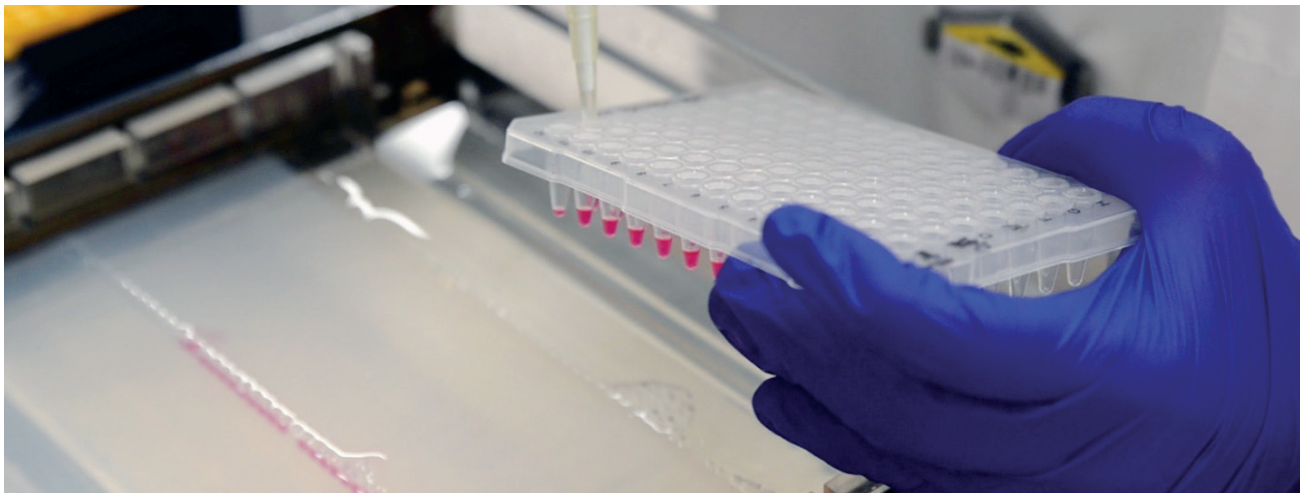
Dr. Armstrong and others at MGH are excited by the potential applications of Chivukula's findings. "It's pretty unusual [for a Pathways case] to have quite as beautiful a story as Raghu was able to put together that quickly," she said.

Maybe in the future, Chivukula said, other patients in the woman's position will be able to be treated before their condition becomes severe enough to need a transplant in the first place. Although much research remains to be done before the condition could be cured, Chivukula believes the potential is there. Cilia, he points out, have been shown to change slightly due to external causes. For example, smokers have slightly shorter cilia than non-smokers.

"We've shown that delivering extra active NEK10 protein actually causes cilia function to be improved, so that does suggest that this condition could be druggable in the future," he said. "We just need to understand the biology a little bit better."

Advancing science during a pandemic

While the institutional challenges presented by COVID-19 have been significant, Whitehead Institute scientists have responded with determination and focused innovation.



In March 2020, a team of Whitehead Institute scientists and administrators planned and implemented something few had ever imagined: a quick ramp down of the Institute's scientific operations to help limit spread of the novel coronavirus in the Boston region. By early summer — when the COVID-19 curve had flattened and Institute labs began, slowly, moving toward fuller operation — the work of every Institute scientific and technical staff member had been affected.

It is an understatement to say that the process of ramping down and then restarting research operations was multifaceted, detailed, challenging, and frustrating. "Scores of researchers had projects slowed in significant ways, and some had projects stopped in their tracks," said Institute Member and former director David Page, who led the pandemic-response processes from March through June when Ruth Lehmann succeeded him as director. "The true impact on scientific discovery — and on the professional growth of our postdocs and early career scientists — will only become clear in coming years. But it certainly feels like we, collectively, have lost momentum on many fronts."

Yet the Whitehead Institute scientific community was able to keep an array of scientific projects moving forward through the difficult spring and early summer months. A special team worked with Page to review projects critical to each lab and, on a case-by-case basis, approved the continuation of specific work. For example, many projects that involved specially developed animal models continued, albeit at a slower pace due to limitations on the number of people who could occupy the lab at any one time. So, too, did work on infectious disease and the Institute's many projects utilizing human stem cells.

Perhaps the most significant ongoing work involved projects where Institute researchers applied their specialized tools and methods to delve deeply into how SARS-CoV-2 functions — and thereby lay the groundwork for potential COVID-19 therapeutics. "This is an important example of the broad application of the foundational science we do," said Lehmann. "Our scientists are directly applying their knowledge, expertise, and technical capacities to the virus."

Moving forward

Taking in a tumultuous 2020, Lehmann observed: "Last spring, everyone was caught off guard by COVID-19. David Page and his team did a great job in making and implementing the decision to substantially ramp down Institute operations to help contain the spread of the novel coronavirus, and then in beginning the process of ramping up again during the summer.

"But looking forward, we need to anticipate facing this kind of situation again and consider how best to address a dual imperative: protecting public health while continuing to advance our research and training programs. We must keep science moving ahead. And we must find ways to prevent monthslong setbacks in our students' and postdocs' careers."

If there is any silver lining to the pandemic's effect on Whitehead Institute, Lehmann said, "It's that we have seen our resilience tested and proven. We've demonstrated our collective capacities for flexibility, creativity, and nimbleness. And we have shown, again, how relevant is the work we do and how useful are the new methods and tools our researchers are continually developing."

Following are prime examples of our investigators applying their expertise to the challenges of the present moment.

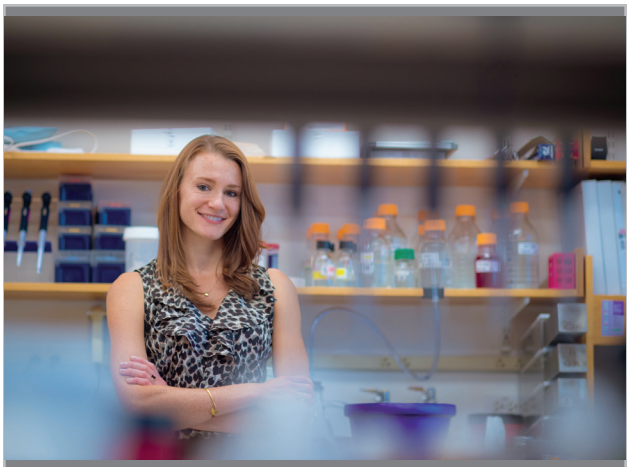
Silvi Rouskin

For the past several years, Whitehead Fellow **Silvi Rouskin's** lab has been developing methods to determine the conformation of RNA viruses such as HIV. In February, as SARS-CoV-2 — an RNA virus — spread around the world, Rouskin recognized that research methods created by her group could be directly applicable to the long-term development of COVID-19 treatments.

"No one knew what the RNA structure of SARS-CoV-2 was," she said. "That's important because understanding the RNA's shape is critical for designing RNA-based therapeutics." Her group undertook to define that shape. When the Institute began ramping down, the lab was already deep into the project. Given its progress and relevance, Rouskin received permission to continue the work. "We were self-contained and self-sufficient; we had all the equipment we needed in our lab." Two months later, they had mapped the virus's RNA structure and made the preprint publication available to the scientific community through the open access repository bioRxiv. Rouskin is now working with collaborators to screen small-molecule drugs capable of incapacitating the viral RNA.

Rudolf Jaenisch

When COVID-19 emerged, Founding Member **Rudolf Jaenisch** recalled, "We decided to use our expertise in stem cells to investigate which cells in the body are directly and indirectly affected by the coronavirus and how different cell types respond." In one project, Jaenisch's group has been inducing embryonic stem cells to differentiate into every type of cell in the body, then screening them to see how they respond to coronavirus infection. Aleksia Richards — a postdoc in Jaenisch's lab who is the only person at Whitehead Institute with safety clearance to work with the virus — transfers the newly differentiated cells to a biosecure facility at the Ragon Institute of MGH, MIT and Harvard; there she infects the cells with the coronavirus and analyzes the results. In a second project, the Jaenisch lab — collaborating with a group at Harvard University that has lung tissue samples from COVID-19 patients — has created lung organoids that comprise all the different cell types of the lung in a 3-D system. "We have found that certain types are infectable and others are not," Jaenisch explained, "and we are trying to understand how to block the infection process."



Looking to the liver

Some animals have an amazing capacity for regeneration — cut off a limb or, for some species, even a head, and it will grow right back — but humans are limited in their bodies' ability to repair extreme damage. Researchers like Whitehead Fellow **Kristin Knouse** seek to understand the regenerative capacities that humans do possess in the hopes that regenerative medicine can build on that knowledge to help people recover from medical events like strokes, heart attacks, and neurodegeneration.

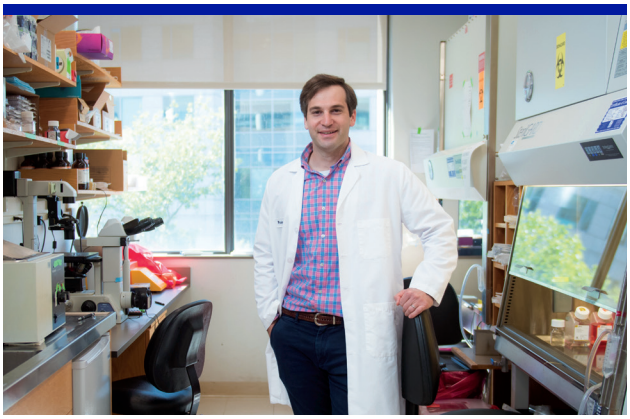
Knouse investigates the liver, an atypical organ that not only can regenerate after significant tissue loss or injury but does so without relying on stem cells, the progenitor cells of differentiated tissue. Differentiated, or mature, liver cells retain the ability to proliferate — to divide and repopulate — that cells usually lose when they mature. Knouse researches liver cells to better understand the factors that allow liver cells to regenerate when other differentiated cell types cannot, as well as what differences there might be within liver cells that affect their regenerative capacity. Over the past year, the lab developed genome-wide screening in the liver in mice, which Knouse expects will provide unprecedented insight into the liver's complex physiology.

Jonathan Weissman

New Institute Member **Jonathan Weissman** has been pursuing two COVID-related projects. The first involves the gene-silencing technique, CRISPR-OFF, which, rather than cutting DNA with CRISPR's molecular scissors, allows researchers to methylate the gene, rendering it inactive but intact. "We are using this, along with technologies that Rudolf Jaenisch pioneered, to try to develop a system that could shut off the lung epithelial cell genes required for coronavirus to infect those cells," Weissman explained. "This could create a sort of immunity that protects against both SARS-CoV-2 and future SARS-like coronaviruses." His lab's second COVID-relevant project has involved a closer look at the specific components of human cells that viruses hijack to replicate their genetic material. Building on other researchers' identification of proteins that SARS-CoV-2 needs to reproduce, Weissman has been studying where in the viral life cycle those proteins are acting. In the long run, he said, "These projects could lead to inhaled RNA-based treatments that go into the respiratory tract and use CRISPR-OFF to shut off key host factors used by the virus."

Kipp Weiskopf

Whitehead Fellow **Kipp Weiskopf's** lab studies interactions between cancer cells and the immune system and is pursuing methods to prompt immune cells called macrophages to fight the disease. When the pandemic hit, he realized that efforts to promote macrophage activity might be repurposed to identify treatments for severe cases of COVID-19. The connection? In some patients, hyperactive macrophages trigger an immune reaction called a cytokine storm, which can cause more damage to organs than the virus itself would.



"We saw an opportunity to use the tools and models our lab had previously created toward a new goal: investigating whether and how drugs that inhibit macrophages may prevent the cytokine storm," Weiskopf explained. His lab received special approval to pursue this work during the spring shutdown. Now they are collaborating with the Broad Institute to screen thousands of existing drugs for their ability to inhibit macrophage activation. "It's a prime example of how research in one area of fundamental biology can have implications for many different diseases," he noted, "and over the coming year, we will begin studying potential drug candidates' effects in animal models and in vitro."

Richard Young

Institute Member **Richard Young** is a pioneer in the emerging field of bimolecular condensates — and in studying condensates' potential role in COVID-19 therapeutics. These membraneless droplets concentrate certain proteins, effectively providing shelter from the broader chaos of the cell and enabling complex functions to take place. Condensates help the cell transcribe its genetic material, produce ribosomes, and splice RNA. "Condensates provide an important new lens on cell biology," Young observed, "and hold the potential for both explaining many mysteries and raising many interesting new questions." Young has been applying his knowledge of these cellular droplets to better understand how viral infection takes place. Currently his lab is investigating how condensates may contribute to the virus's ability to replicate itself in human cells and he and his collaborators — research leaders in biology, chemistry, physics, and artificial intelligence — are using condensates as the basis for a whole new paradigm for drug discovery. "We see increasing evidence that condensates play a significant role in distribution of a therapeutic within a cell and, therefore, in its effectiveness and efficiency," Young explained. "And we have been studying the role that condensates may play in the delivery of drugs that interfere with the coronavirus's function."

Teaching about COVID-19

In parallel with his scientific work on the SARS-CoV-2 virus, Young partnered in developing and leading a special MIT Department of Biology course entitled "SARS-CoV-2, COVID-19 and the Pandemic." The course addressed the pandemic from an array of perspectives, including virology, immunology, epidemiology, public health, and clinical care. It was presented by a who's who of biomedical experts including Anthony Fauci, director of the National Institute of Allergy and Infectious Diseases; Whitehead Institute Founding Director David Baltimore; Bruce Walker, director of the Ragon Institute of MGH, MIT, and Harvard; Arlene Sharpe, chair of the Department of Immunology at Harvard Medical School; and others at the forefront of COVID-19 research and treatment. Co-developed and

co-led by Young's MIT faculty colleague Facundo Batista, who is associate director of Ragon Institute and an expert on immunology and infectious disease, the course was presented through a weekly livestream during MIT's fall semester. Then each lecture was made available to the general public on YouTube. It is estimated that the lectures collectively had tens of thousands of views.

Illuminating mysteries of metastasis

Whitehead Institute Founding Member **Robert Weinberg's** work has helped shape our understanding of cancer for decades. In the late 1970s and early 1980s, his lab discovered the first human oncogene, a gene that, when mutated, causes cancer. His focus has since shifted from how cancer originates to how it spreads, or metastasizes.

Cancer is typically at its most deadly when cancer cells become able to travel from the initial tumor site to other sites in the body, colonize tissues there, and form secondary tumors called metastases. Weinberg's research has provided key insights into what is required in order for a cancer to metastasize. His work has also made clear how inefficient the process of metastasis is, with many cancer cells falling at one of the hurdles designed to prevent the successful forming of metastatic colonies. For example, people diagnosed with metastatic cancer often will have tumor cells disseminated throughout their bodies, but most of these cells fail to thrive in their new tissue environments and instead become dormant, unable to form new tumors. Recently, Weinberg's lab investigated these disseminated tumor cells and identified a signaling pathway — a chain of biochemical reactions operating within a cancer cell — that regulates their dormancy.

The lab's findings on both the role of the pathway, described as the syndecan-mediated ligation of extracellular matrix proteins, and how aggressive cancer cells overcome it could deepen researchers' understanding of how and when metastasis occurs.

Empowering science for today and tomorrow

Whitehead Institute's mission — expanding science's understanding of biology and opening new pathways for preventing and treating disease — is now more relevant than ever. Indeed, the pandemic has shown how fundamental our work is to human well-being, today and in decades to come.

The knowledge and tools being used to fight COVID-19 today are rooted in basic biomedical research discoveries made years ago. Those discoveries enabled scientists and clinicians to quickly begin to understand the new coronavirus's function and develop ways to defeat it. In fact, the key diagnostic test for COVID-19 relies on the discovery of reverse transcriptase made by our founding director David Baltimore decades ago.

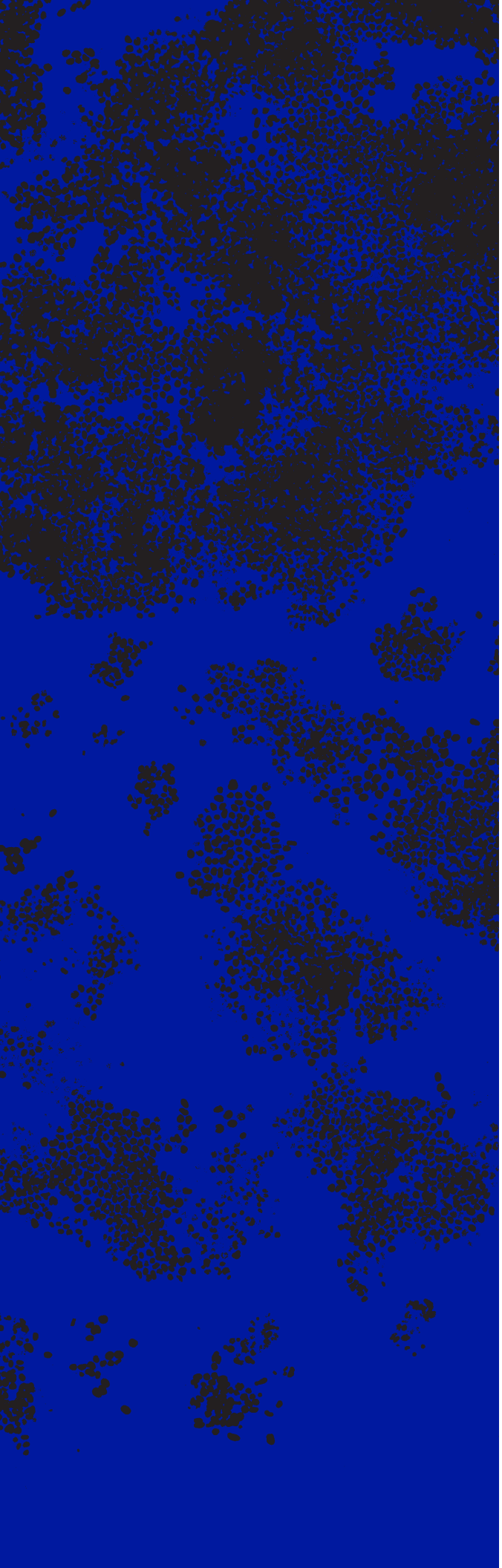
But as the article "Science During the Pandemic" makes clear, our current work holds enormous promise as well. Not only could it lead to new ways to diagnose and treat this coronavirus; it may also position biomedicine to respond, quickly and effectively, the next time a dangerous virus emerges. Moreover, as Ruth Lehmann has observed, our scientists' ability to directly apply their knowledge, expertise, and technical capacities to a new virus is a prime example of the broad application of the foundational science we do.

At Whitehead Institute, we continue to lay the foundation for new ways of addressing a broad range of diseases. We are deepening science's knowledge of the basic biological processes driving cancer, neurodegenerative disease, diabetes, and many other conditions. And the work we are doing right now will help shape the therapies of the future.

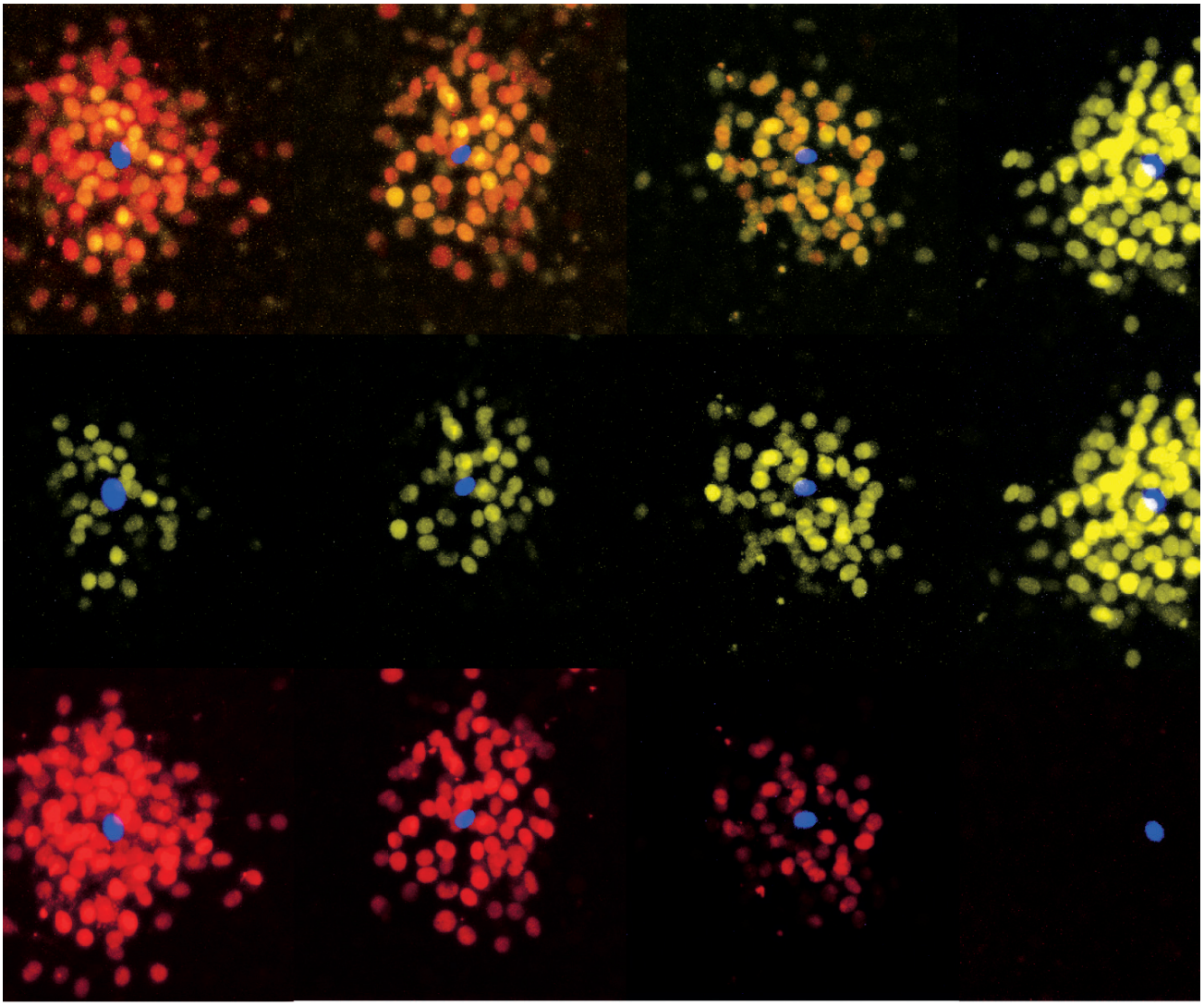
I share Ruth's belief that there is power in the moment. It is a power primed to shape medicine and health care for decades to come.

Our donors help us leverage the power of this unique moment: Their philanthropic support today enables Whitehead Institute to achieve amazing things now and in the future. In this challenging time for us all, I am grateful for their commitment to Whitehead Institute and to our long-term mission of driving basic science research to improve human health.

Sharon Stanczak
Vice President for Institutional Advancement



Conducting the Cell



Our bodies are made up of trillions of cells, and each of those cells is made up of countless biological molecules with specialized functions that keep the cells alive. When those molecules malfunction, it can lead to disease. If we imagine the cell as an orchestra, with many musicians who each have a small part to play, then what conducts all of these musicians and keeps them organized and harmonized as they play a symphony?

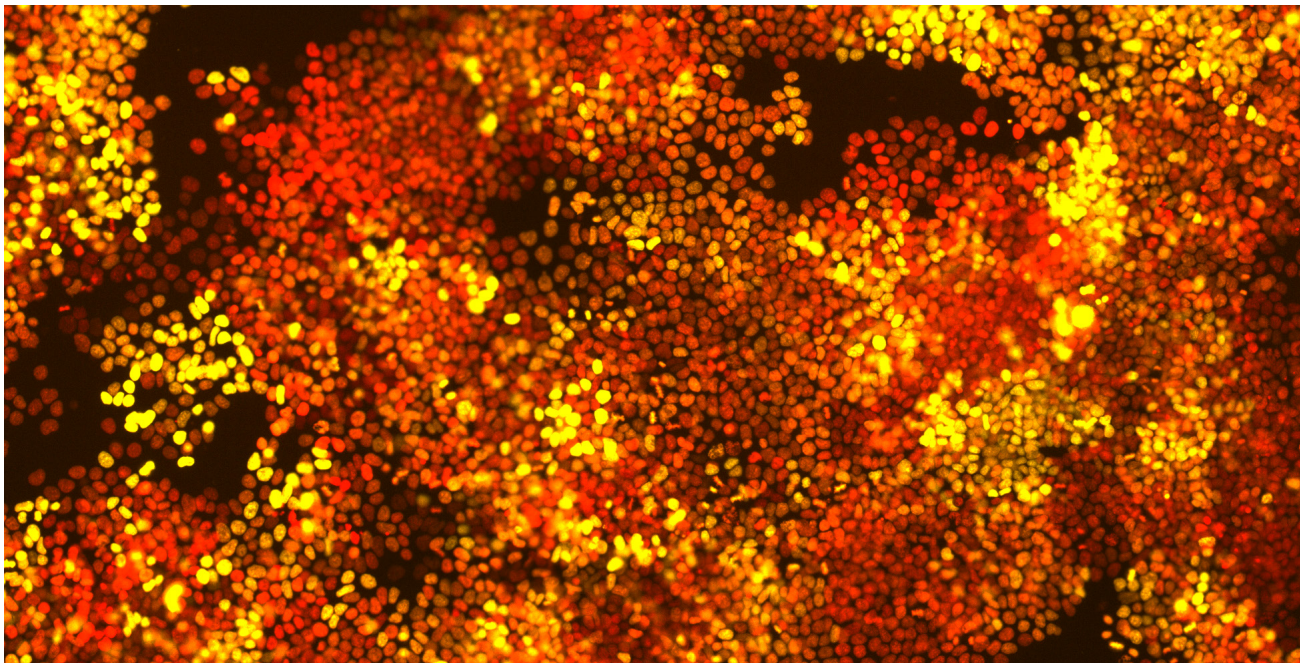
Whitehead Institute researchers are showing that, like a conductor, certain key molecules tune the cell's behavior to the needs of the occasion. The knowledge of how cells give order to complicated processes could prove crucial to learning how to restore healthy function in diseased cells.

Fine-tuning gene activity

While some features of our cells are hard-coded into the sequence of DNA, altering the chemical structure of DNA can change how the cell reads a gene and whether it gets activated. Such modifications of the genome, many of which are heritable, are called epigenetics. They allow a cell to precisely tune its gene activity. Problems with epigenetics are linked to many disorders, including fragile X syndrome and Rett syndrome. Whitehead Institute Member **Mary Gehring** uses the Arabidopsis plant as a model system to study how epigenetics shape gene expression.

In a recent study, Gehring and postdoc Xiao-yu Zheng examined epigenetic changes in the endosperm, which provides nutrition to developing seeds. They focused on chromatin — the way that DNA is packaged in the nucleus. Tightly-packed chromatin can inhibit gene expression. However, mapping chromatin has been difficult in the short-lived endosperm of Arabidopsis. Zheng and Gehring showed how a new technique, CUT&RUN, can efficiently map chromatin modifications for the full Arabidopsis endosperm genome, opening avenues for further research into how chromatin influences gene expression in developing seeds. With discoveries like these, Gehring's lab is identifying the key players that impose order on gene activity.

Gehring is now exploring how to use epigenetics to engineer crops resistant to harsh environments, leading Massachusetts Institute of Technology (MIT) to choose Gehring as a Bose Research Fellow in recognition of highly innovative research. Her lab is beginning to focus on orphan crops — less frequently grown plants that provide a largely untapped source of genetic diversity and often thrive in challenging growing conditions. By linking fundamental mechanisms of gene regulation to real-world problems related to the food supply, Gehring is illustrating the transformative potential of research into how cells control their genome.



The dance of cell division

For bodies to grow, cells need to divide billions of times to build tissues. A cell dividing into two daughter cells has to split its chromosomes evenly between two new nuclei. Cells have to direct this complex dance routine to make sure the chromosomes end up where they are needed. Whitehead Institute Member **Iain Cheeseman** investigates the tools our cells use to divide and what goes wrong in cells that cannot divide or cannot stop dividing.

Carrying out the cell divisions that produce egg cells is essential for fertility. Scientists have wanted to know how immature egg cells — oocytes — retain their ability to divide for years before they become viable eggs. In a study led by postdoc Zachary Swartz, the lab investigated the centromere, the part of a chromosome that anchors rope-like fibers that pull apart chromosomes during cell division. A critical part of the anchor is a protein called CENP-A, without which the cell loses its ability to divide. It was thought that CENP-A remains static in cells that go dormant but later divide. Using sea star oocytes as a model, because of their similarities to human oocytes, Swartz and Cheeseman have shown

that CENP-A is slowly but steadily replenished in oocytes, allowing them to remain dormant for years while retaining the ability to divide.

Cheeseman's lab is now pursuing how to rejuvenate centromeres in aging egg cells. Cheeseman was recently named a scholar of the Global Consortium for Reproductive Longevity & Equality for pursuing a better understanding of how centromeres degrade with age. This research could reveal how to one day engineer egg cells to extend the window of female fertility.

Engineering how cells harmonize

If you know how the cell conducts its symphony, you can try to compose new tunes for the cell to play. Whitehead Institute Member **Pulin Li** studies how cells communicate with each other to form multicellular patterns. She focuses on molecules called morphogens — the primary guide for developing tissues, providing the blueprint for the body. Morphogens guide where an embryo's head and limbs should develop as well as the finer details of organs with many cell types, like the brain.

By growing cells in Petri dishes and genetically engineering them to form patterns, Li hopes to uncover the fundamental rules for tissue formation, which could address longstanding questions about development and potentially prove useful for learning how to regenerate body parts or heal damaged tissues. In recognition of her path-breaking work, Li has been named the Eugene Bell Career Development Professor of Tissue Engineering at MIT.

Li's bottom-up approach begins with a simplified system: sender cells broadcasting a message and cells interpreting the message and responding to it. This Petri-dish approach is inspired by what we know of tissue development, in which cells coordinate with each other to determine cell fate and produce a fully functioning tissue. The music of the individual cell has to harmonize with all those around it. Li's lab seeks to apply the knowledge gained from studying development to engineer cells that communicate to form specific patterns. This could help overcome challenges faced by tissue-engineering approaches that rebuild tissue on top of a synthetic scaffold that directs the cell pattern. Li's goal is to engineer cells to form patterns on their own — a bold new approach to tissue engineering and regenerative medicine.

Directing the cell's metabolism

In order to survive, cells need to adjust their metabolism based on the amount of nutrients available. Disruptions to the control of cell growth and metabolism can lead to diseases such as diabetes and cancer. Whitehead Institute Member **David Sabatini** studies a protein called the mechanistic target of rapamycin (mTOR), a master regulator of cell growth. Sabatini is the co-recipient of the 2020 Sjöberg Prize from the Royal Swedish Academy of Sciences for his role in discovering the mTOR protein and its role in controlling cell metabolism and growth.

Sabatini's lab is studying how new drugs might target mTOR or the proteins that regulate its activity. A study led by postdoc Kacper Rogala described a new structure for mTOR complex 1, a regulatory protein complex that includes the mTOR protein. The study revealed how mTOR complex 1 docks with the lysosome, an organelle that breaks down and recycles materials in the cell. Partner proteins allow the complex to dock only if nutrient levels are high and push it off the lysosome when the cell is starved for nutrients. The docking mechanism is crucial to understanding mTOR complex 1, because the protein complex only activates once on the lysosome. A related study led by former postdoc Kuang Shen and Rogala provided a high-resolution structure for a key mTOR complex 1 activator, FLCN, and a partner protein, FNIP2. Problems with FLCN can lead to tumor formation. These structures are more detailed than any previous work, giving the researchers precise information about how mTOR interacts with its regulatory proteins.

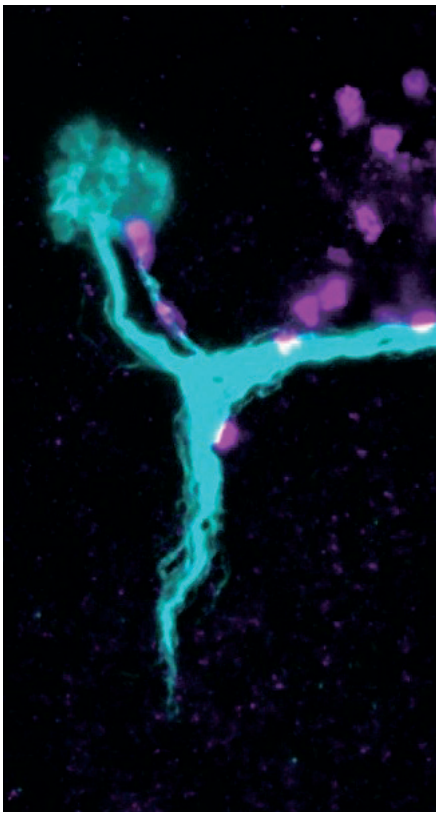
By filling in the gaps of how mTOR senses nutrients and how its partner proteins regulate it, Sabatini's lab moves closer to identifying factors that act on it with high specificity without affecting other important cellular pathways.

Scientific Highlights 2020

A selection of major research findings published by Whitehead Institute investigators

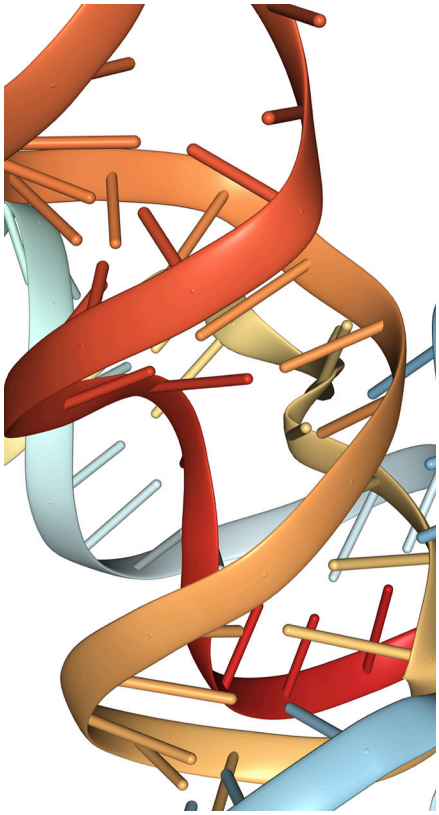
Refining multiple sclerosis genetics

Multiple sclerosis (MS) is a debilitating disease in which the body's own immune system attacks itself. Over time, it can permanently destroy the protective sheaths, or myelin, that insulate nerve cells and facilitate their activity — in turn leading to nerve damage and a wide range of symptoms. Previously, researchers had identified genetic alterations that increase one's risk of developing MS. These genetic alterations were widely believed to only impact the function of immune cells. However, Whitehead Fellow **Olivia Corradin** has developed a new approach to investigate risk factors. With lab member Anna Barbeau and collaborator Daniel Factor, she discovered that immune cells are the primary — but not the only — cell types implicated in the development of MS. Rather, genetic variants that affect cells in the central nervous system — including oligodendrocytes, the brain cells that produce myelin — also appear to contribute. The discovery could provide new avenues for therapies. The researchers also intend to use their approach to identify overlooked secondary cell types involved in other diseases.



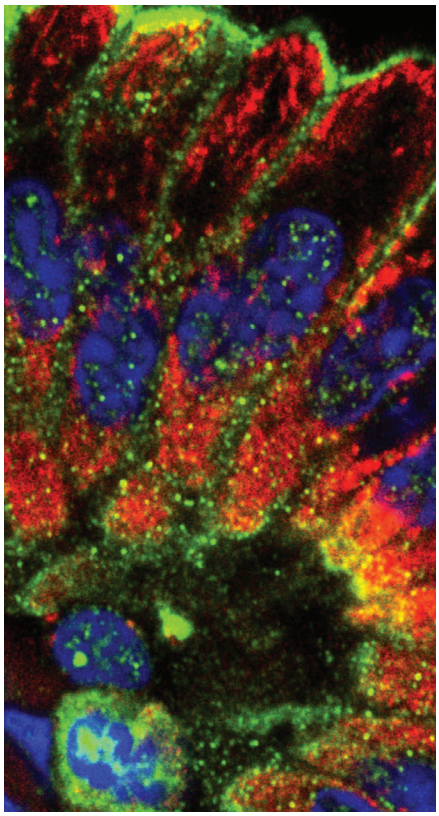
How muscle cells guide eye regeneration

When neural systems develop in embryos, specialized cells called guidepost cells help direct axons along the right paths to form working circuits. In many organisms, these guidepost cells are not maintained after development is complete, posing a challenge to the possibility of nervous system regeneration. The planarian *Schmidtea mediterranea*, a tiny freshwater flatworm, has the potential to regenerate essentially any part of its body. Recent research from Whitehead Institute Member **Peter Reddien** and lab members Lucila Scimone and Kutay Deniz Atabay offers insight into how the worms regrow their eyes, which requires the regenerating visual system to rewire neurons from the eyes to the brain. Reddien's lab found cells behaving as guideposts in adult planarians, helping route axons during eye regeneration. In other organisms, guidepost cells are often neurons or glia, but the guideposts that the researchers found were muscle cells. Reddien's lab has identified important instructive roles for muscle cells in planarian regeneration, and this latest finding adds to their long list of regulatory functions in guiding regeneration outcomes.



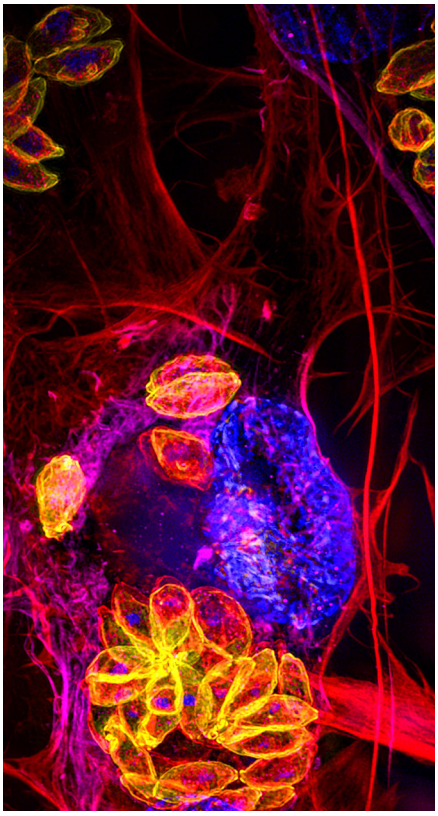
To be long- or short-lived?

Genes are often imagined as binary actors, on or off, but their activity actually runs the gamut from barely perceptible to off the charts. This large range is due in part to molecular controls that determine how long the protein-making instructions corresponding to any given gene — known as messenger RNA — can persist before being destroyed. Whitehead Institute Member **David Bartel** and graduate students Timothy Eisen, Stephen Eichhorn, and Alex Subtelny have taken a deep and systematic look at the dynamics of mRNA decay across thousands of genes. Their analysis — the most extensive to date — reveals surprising variability in the lengths of the ends, or tails, of mRNAs both across genes and for the same gene, as well as in the rate at which the tails are shortened. In addition, the researchers uncovered a link between this rate of shortening and how quickly the short-tailed mRNAs decay. These findings, along with other recent discoveries by the lab, help us understand mRNA decay, which is an important factor in cell identity and function.



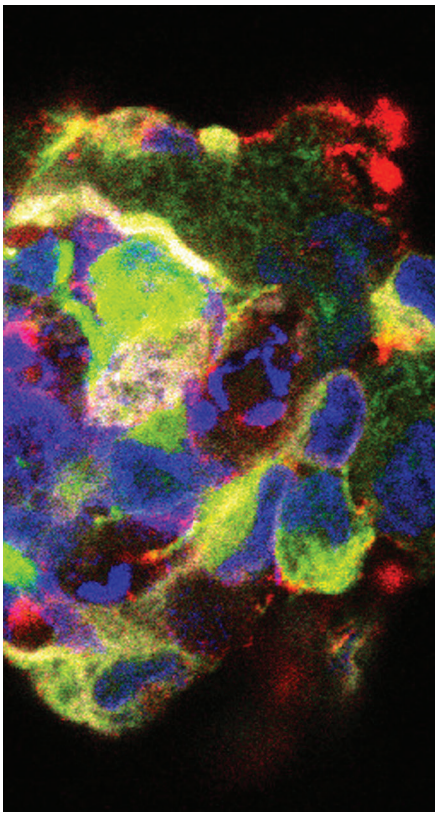
"Good fat" regulator could help fight obesity and diabetes

The white fat in our bodies stores fat and provides insulation, but too much abdominal fat contributes to obesity, diabetes, cardiovascular disease, and other diseases collectively called the metabolic syndrome. The body also has small amounts of brown fat, which is activated by cold and metabolizes fat into heat, burning calories, and so can help fight obesity. Researchers looking to treat obesity and related metabolic conditions have become very interested in ways to both enhance the body's amount of brown fat and prompt some white fat to function more like brown, but the drugs used to achieve this have had limited efficacy and serious side effects. Recently, Whitehead Institute Founding Member **Harvey Lodish** and then-postdoctoral researchers Nai-Jia Huang and Mengxi Jiang identified the enzyme phosphocholine phosphatase-1 (PHOSPHO1) as a negative regulator of brown fat activation. PHOSPHO1 catalyzes a reaction that hydrolyzes the molecule phosphocholine, which the researchers found to be a positive regulator of brown fat activation. When the enzyme PHOSPHO1 is inactivated in mice, or when phosphocholine levels are increased, the mice become more tolerant of cold and more protected against obesity and related symptoms. These results suggest that the PHOSPHO1 pathway may prove useful in the development of therapies for obesity and metabolic syndrome.



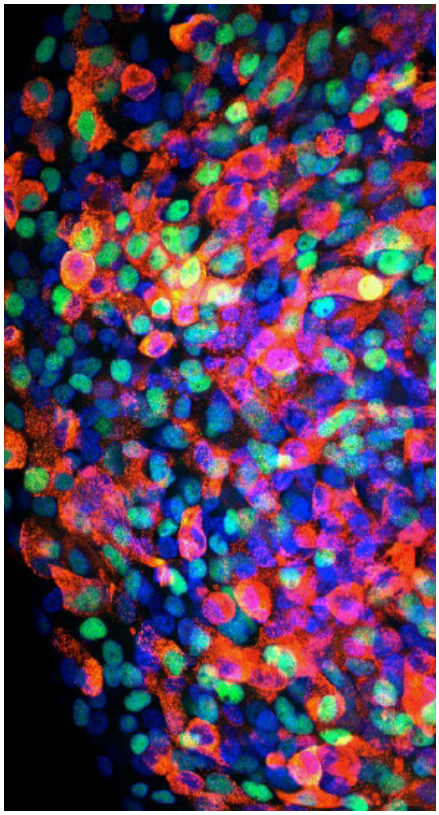
Putting a finger on the switch of chronic parasite infection

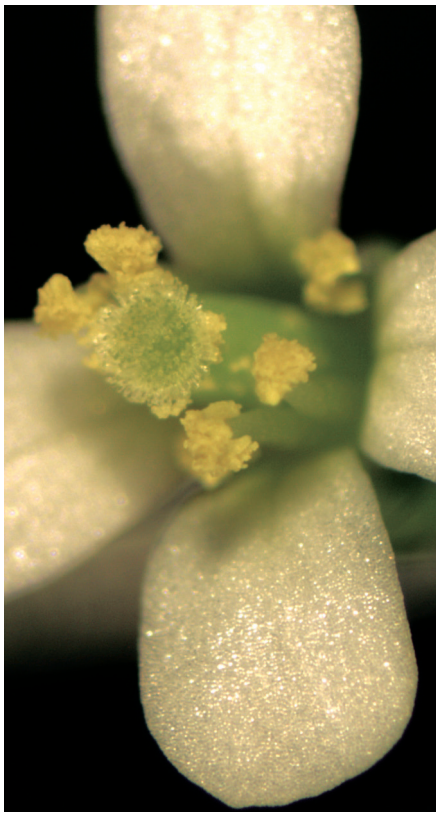
For an infection to spread within a population, it needs to persist long enough in an individual to be transmitted. Pathogens like *Toxoplasma gondii* have mastered this ability, as evidenced by a quarter of the world's population chronically carrying the parasite, which can cause the potentially deadly disease toxoplasmosis. One reason that *T. gondii* is so pervasive is that the parasites can transition from an acute infection stage to a quiescent life cycle stage and effectively barricade themselves inside of host cells. In this protected state, they become impossible to eliminate, leading to long-term infection. Researchers used to think that a combination of genes triggered the parasite's transition into its chronic stage, in part due to the complexity of the process. However, new research from Whitehead Institute Member **Sebastian Lourido** and graduate student Benjamin Waldman has identified a sole gene whose protein product is the master regulator that is both necessary and sufficient for the parasites to make the switch. The finding may prove valuable for treating toxoplasmosis, since preventing the parasites from assuming their chronic form keeps them susceptible to both treatment and elimination by the immune system.



Solving the structure of key metabolism molecules

Whitehead Institute Member **David Sabatini** and postdoctoral fellow Kacper Rogala have described the structure of a key protein complex that helps activate mTORC1, a master growth regulator that enables cells to quickly respond to changing nutrient levels by adjusting their growth rate. This activating complex includes two proteins, FLCN and FNIP2. FLCN functions as a tumor suppressor, and genetic mutations in FLCN are associated with Birt-Hogg-Dubé (BHD) Syndrome, an inherited condition that includes a predisposition to kidney cancer and benign tumors in other parts of the body. The team's findings reveal how FLCN and FNIP2 interact with each other and with other key components of mTORC1 to regulate nutrient and growth signals. This sort of detailed structural knowledge of the complex provides key insights that can help guide future studies, including into how FLCN leads to tumor formation in BHD syndrome and into the mechanics of mTORC1 signaling — a crucial step toward designing drugs that can potently inhibit these signals.



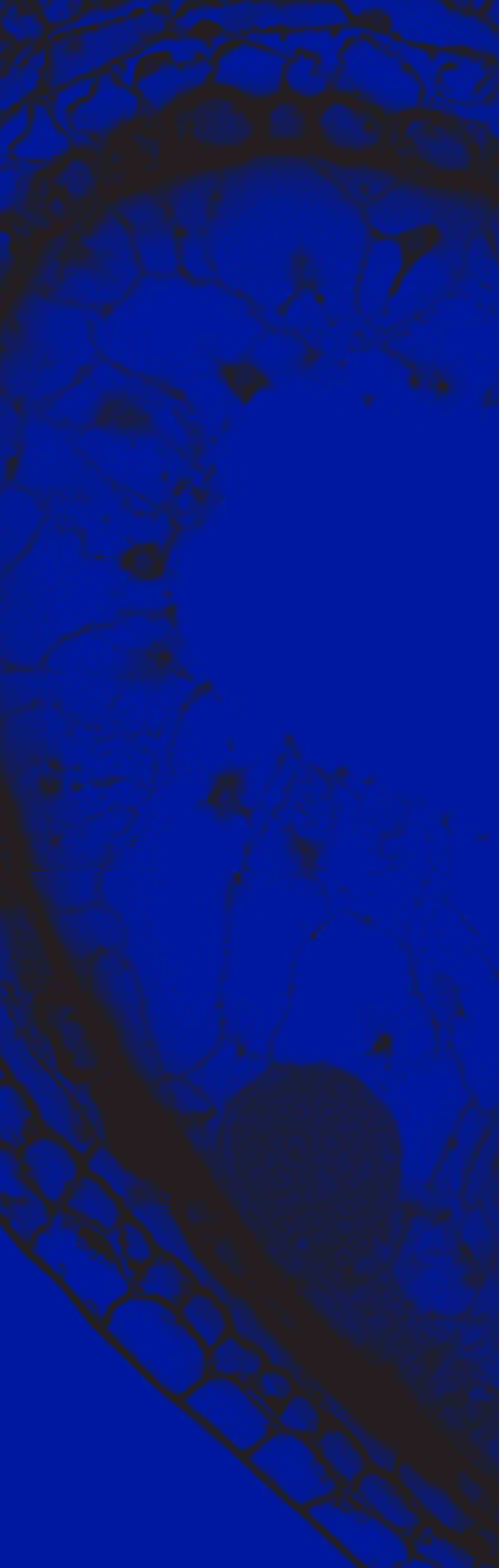


New method to study immune cells in the brain

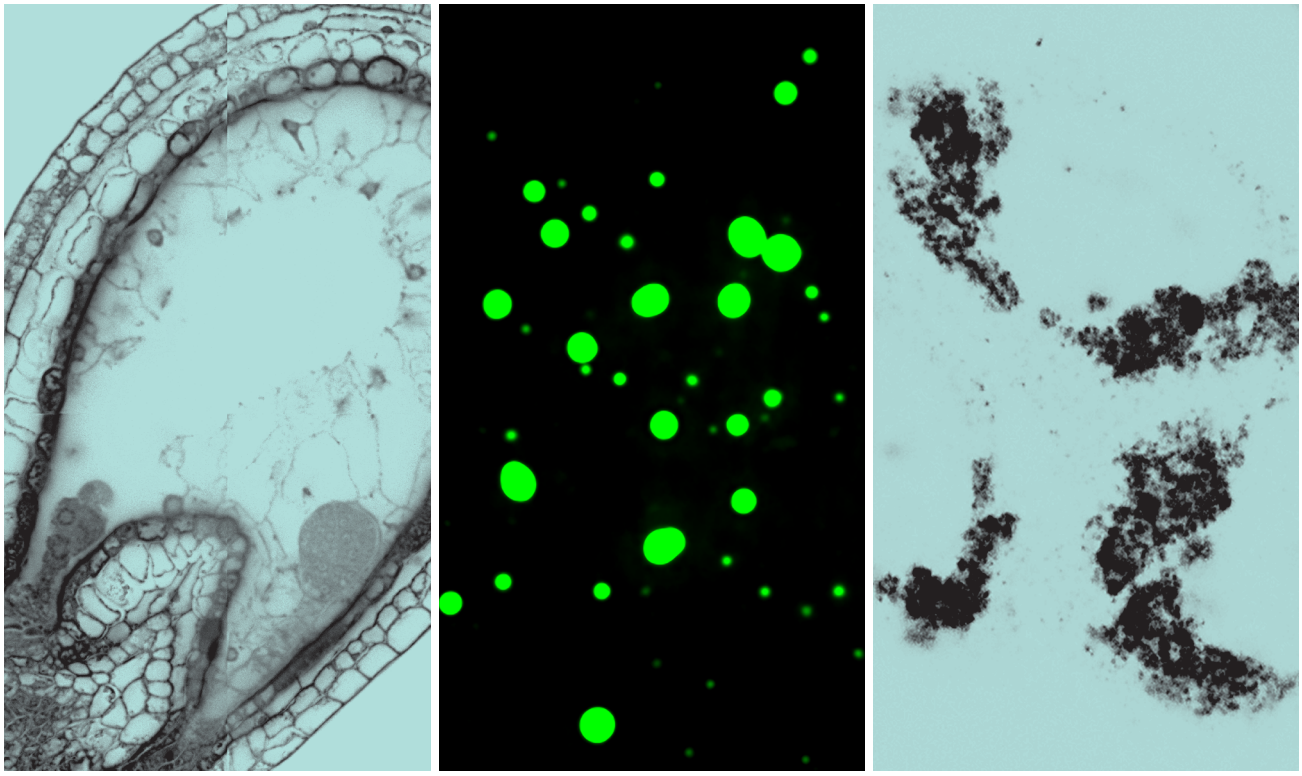
Microglia, the brain's resident immune cells, are increasingly recognized as key for brain health, and their dysregulation has been implicated in neurodegenerative disease. To get a better understanding of the roles these important brain cells play, multiple research teams have recently devised methods to generate microglia using human stem cells and grow them under laboratory conditions that mimic their natural environment. However, this approach has had a fundamental drawback: The cultured cells do not look like microglia, nor do they behave much like them, even though they display the appropriate molecular hallmarks. Now, Whitehead Institute Founding Member **Rudolf Jaenisch** and postdoctoral researcher Devon Svoboda have developed a new experimental platform for generating microglia from human stem cells. Jaenisch uses special strains of mice that carry human genes for certain growth factors, called cytokines, required for microglial development and survival. This new method yields microglial cells that resemble those in the human brain more closely than previous approaches, which could help enable future studies into brain health and neurodegeneration or help inform research into new therapeutic options.

Building a roadmap for salicylic acid

Salicylic acid, which is used as a treatment for skin conditions like acne and warts — and in its modified form as aspirin — is a critical plant hormone involved in growth, development, and regulation of immune defenses. Because plants can't move, they instead defend themselves against bacteria and pathogens chemically, with salicylic acid controlling cascades of other defense responses. Consequently, control of salicylic acid production in agricultural plants could boost crops' resilience to pathogens and insects, thereby reducing the overuse of pesticides. Yet scientists have been missing a key tool necessary for manipulating salicylic acid levels in plants: a full description of the pathway necessary to synthesize the hormone. Now, Whitehead Institute Member **Jing-Ke Weng** and postdoctoral researcher Michael Torrens-Spence have finally uncovered the missing steps in the Arabidopsis plant's salicylic acid pathway, determining the roles played by key enzymes PBS3 and EPS1, and so have provided a roadmap to explore salicylic acid production across plant species.



Mapping the labyrinth of gene expression



Our genes contain instructions for our biology, but neither our development nor the everyday functioning of our cells is based on a straightforward reading of those instructions. Instead, additional layers of contextual information and processes contribute to whether, when, and to what extent genes will be expressed — meaning their instructions will be carried out in the form of protein production — in each cell. Regulators of gene expression are necessary for embryonic development; every cell in a developing organism has identical genes, and it is how the genes are expressed that enables cells to differentiate and form distinct tissues.

Whitehead Institute researchers are investigating regulators of gene expression and the important roles they play in establishing the identity of cells and their behavior throughout our lives. Some are shedding light on previously unknown processes involved in gene transcription — how genes are read into RNA — and the implications for health and disease. Others are focusing on epigenetic mechanisms, heritable modifiers that affect how genes are expressed much as changes in the DNA sequences themselves would.

Seeds find epigenetic balance

Whitehead Institute Member **Mary Gehring** studies epigenetic mechanisms in plants to understand how they affect plant development and growth. She typically focuses on DNA methylation, which regulates gene expression by adding chemical tags to DNA, and on seed development, when epigenetic modifications are most dynamic. Epigenetic modifications in seeds and particularly in the endosperm — the seed equivalent of the placenta and the source of much of our nutrition — can have huge impacts on seed size and the timing and likelihood of a seed reaching maturity, factors that are, in turn, hugely important to agriculture.

Recently, Gehring and postdoctoral researcher Satyaki Rajavasireddy delved into the role of one epigenetic mechanism in seed abortion, when seeds die before they reach maturity, in the common model plant *Arabidopsis thaliana*. Like

human embryos, plant seeds receive different copies of each chromosome from their biological mother and father, but whereas humans receive one copy from each parent, plant endosperm typically receives two copies of the genome from the mother for every one copy from the father. When the number of copies from the father goes above this ratio, the seeds abort.

However, the researchers found that disabling a certain system of epigenetic modification, in which small RNAs direct DNA methylation in the father, corrected the expression of a small set of important genes, leading to viable seeds even with excess paternal gene copies. They also found that the endosperm exhibited some protective buffering against excess paternal gene copies by increasing the expression of maternal copies of genes and decreasing the expression of paternal copies. This research not only provides new insights into how gene expression is regulated in the endosperm; it also may enable the development of new crop strains by allowing breeders more flexibility in which strains they can interbreed without causing seed abortion.

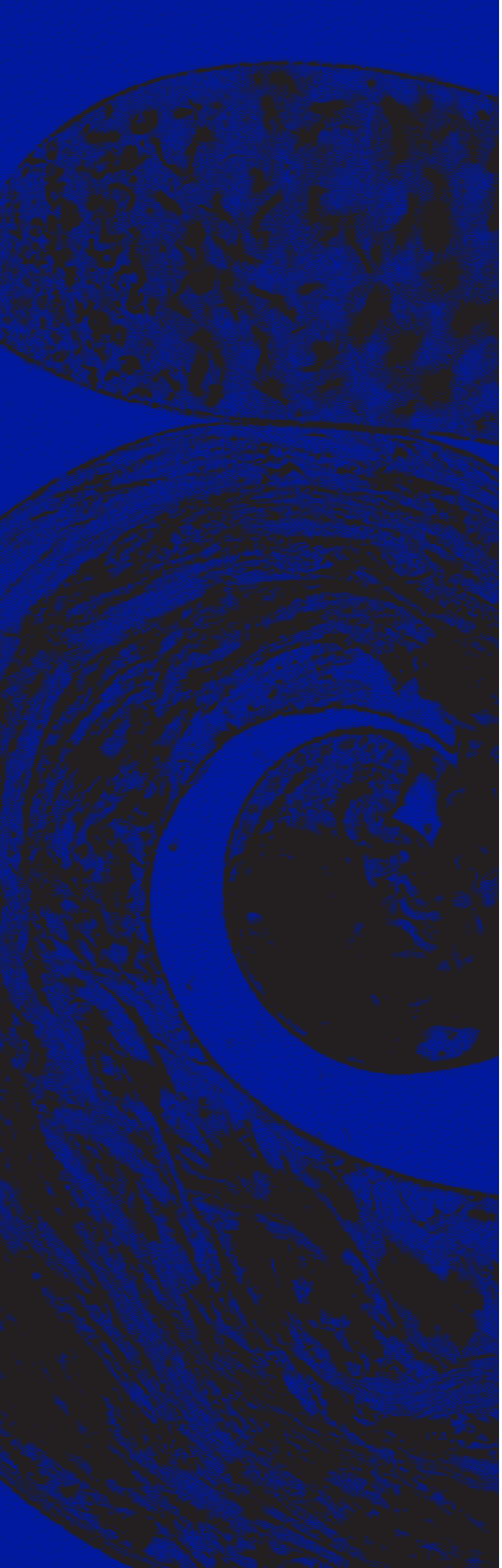
Droplets help organize transcription

Many processes in our cells take place not while floating around the cell but rather in specialized rooms or compartments called organelles, such as our mitochondria, lysosomes, and more. But how do other molecules — such as proteins called transcription factors, the molecules that transcribe DNA — end up in the right place at the right time? Scientists have come to understand that cells use a mechanism called phase separation, in which certain molecules form large droplet-like structures that separate out of their surroundings, like oil refusing to mix with water, to gather molecules without relying on membraned organelles. These droplets, called condensates, help to corral and concentrate molecules at specific locations where they are needed. Whitehead Institute Member **Richard Young's** lab has been investigating the important role of this process in gene transcription.

Recently, Young's lab has shown that droplets are not interchangeable; rather, a given molecule will join only certain droplets and not others. A study led by graduate students Charles Li and Eliot Coffey, in collaboration with Whitehead Institute Founding Member **Rudolf Jaenisch's** lab, observed this when they investigated disruption of transcriptional condensates in the neurodevelopmental disorder Rett syndrome. They found that proteins joined condensates linked either to active or inactive regions of chromosomes but not both. In another study, postdoctoral researchers Ann Boija and Isaac Klein showed how small molecules, including cancer drugs, concentrate in different droplets — a finding that could have implications for developing new cancer therapeutics. If researchers could tailor a chemical to seek out and concentrate in one kind of droplet in particular, it could enhance the delivery efficiency of the drug.

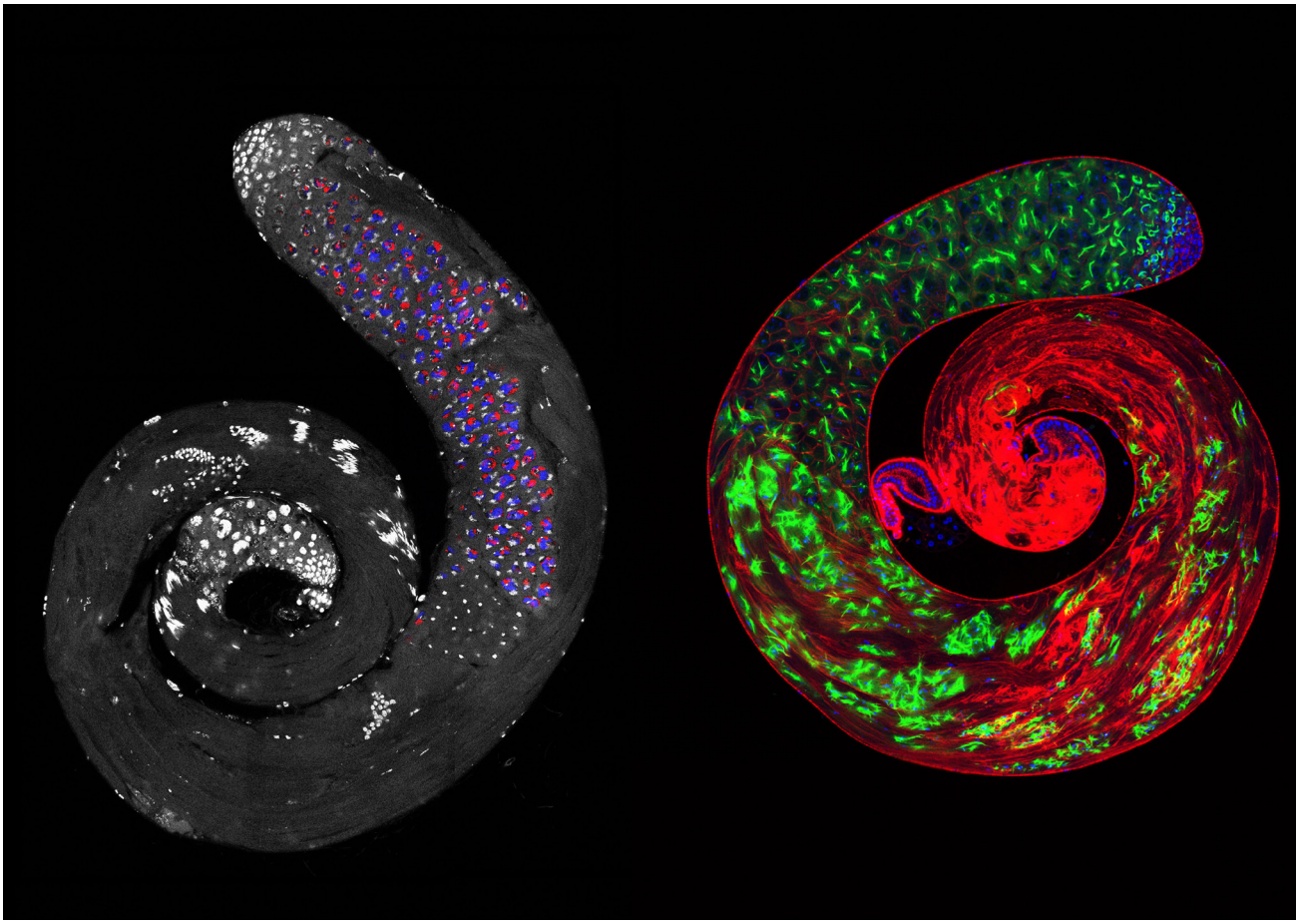
RNA condensates and disease

Whitehead Institute Member **Ankur Jain** also investigates phase separation, but in RNA. Jain is studying whether and how RNA condensates may contribute to neurodegeneration in repeat expansion disorders — a set of disorders that includes Huntington's disease and amyotrophic lateral sclerosis (ALS) in which the disease genes contain excessive repeats of short sequences, like CAG or GGGGCC. The RNA transcribed from this DNA likewise contains long strings of repeats, which make the RNA more likely to stick to itself and to other RNAs in the same way that a long piece of tape is more likely to stick to itself than a short one. The RNA that meshes together in this way can not only form droplets but can condense even further into gels with solid-like properties. Jain has found that these gels occur in repeat expansion disorders and hypothesizes that they could contribute to them. He is also investigating whether phase separation of RNA may have functions in healthy cells, the way that transcriptional condensates contribute to DNA transcription. Jain hopes to understand whether RNA transcribed from the repetitive DNA sequences at the ends of our chromosomes undergoes phase separation.



Intrigued by Immortality

Whitehead Institute scientists investigate germ cells — the cells that never cease to exist



New Whitehead Institute director **Ruth Lehmann** and new Member **Yukiko Yamashita** study opposite sides of the germ cell life cycle. Yamashita's work in male germ cells shows how the cells are formed and maintained; Lehmann studies female germ cells to understand their fates. At the Whitehead Institute, they join Member and former director **David Page** in painting a fuller picture of how these seemingly immortal cell lines pass instructions uninterrupted from generation to generation.

All other cells in the body — neurons, muscle cells, the stem cells that replenish other tissue types — are made anew in each embryo and go away when organisms die. But not the germ cells. "The germ cell passes its DNA to the next generation, then that DNA is used to build up to a new germ cell," says Yamashita. "That means that germ cells never cease to exist."

In this way, an unbroken chain of germ cells stretches back to our most distant ancestor. Scientists study this never-ending link for insights into the fundamentals of biology and evolution. Yamashita began studying germ cells as a model to investigate other questions, but as her research progressed, she grew more and more intrigued by the cells' special properties.

"This is one thing Ruth and I have in common," Yamashita says. "There are many biologists that study germ cells, but not many are acutely interested or fascinated by this immortality. We want to know, where does it come from?"

Yamashita, also an Investigator of the Howard Hughes Medical Institute, joined Whitehead Institute in September. Work in her laboratory at Whitehead Institute will focus on two areas, using the fruit fly *Drosophila melanogaster* as a model. First, she will continue her focus from previous projects on the mechanics of asymmetric cell division using male germline stem cells. These cells, like other stem cells in the body, must undergo a series of asymmetric divisions — instead of simply dividing into two identical daughter cells, the cells must create daughters with different cell fates and programming.

"This balance — maintaining the stem cell number while making some differentiating cells — is considered to be a very important process," she says. "If you end up making too many stem cells, it can become cancerous; but if you commit too much to the differentiation, you lose the stem cell count, and that means you cannot continue sperm production."

A newer project in her lab centers on the long sequences of nucleotides within organisms' genomes that don't code for any genes. They're often nonsensical, gibberish combinations or long strings of certain bases. This "genomic junk" has long been dismissed as meaningless filler between essential genes, but Yamashita proposes that the junk is essential for the overall structure of the genome. Much like the binding of a book holds together its contents in an organized fashion, the genomic junk may provide a blueprint for how genetic material is held together and eventually read.

Ultimately, it is the germline cells that are responsible for maintaining this DNA framework. Yamashita hypothesizes that slow changes in junk DNA could provide some explanation for why different species are reproductively incompatible. "If you look at the chimpanzee genome and the human genome, the protein coding regions are, like, 98 percent, 99 percent identical," she says. "But the junk DNA part is very, very different. We think this divergence might explain what happens when one species splits into two."

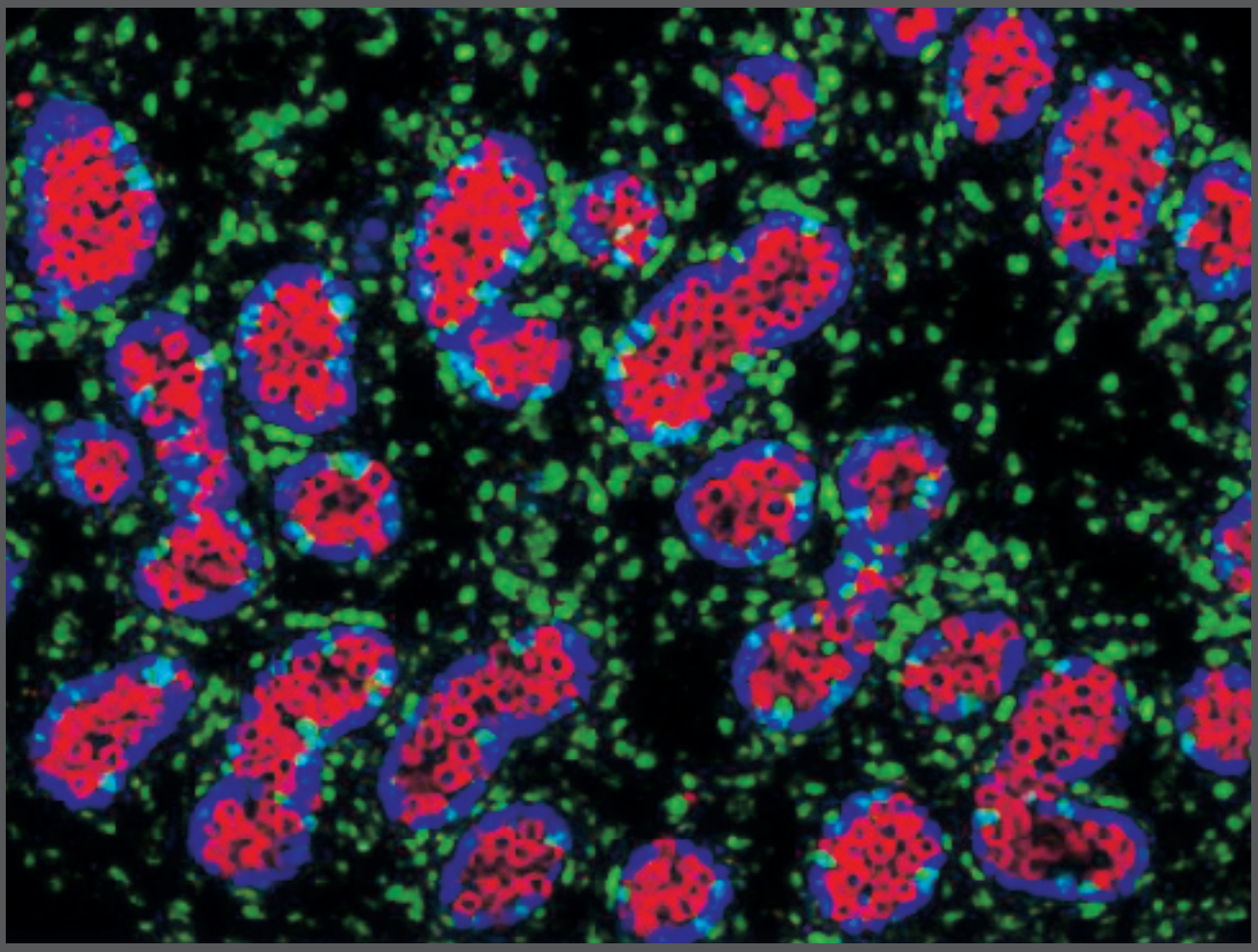
Yamashita's research team will share lab space with Lehmann's group. Both researchers use fruit flies for their experiments, but Lehmann's research focuses on egg cells, not sperm. "Germ cells are special; you don't need them for survival, but you need them to keep the species going," she says. "How are they initially specified and set aside? What makes them different, how are they set aside from somatic cells, and how do they maintain their cell fate?"

One project Lehmann is carrying over from her work at New York University's Skirball Institute of Biomolecular Medicine involves phase transition condensates — small, membraneless granules that bring together the components needed for complex cellular functions. Lehmann studies a specific type of condensate called a germ granule, an aggregation of small RNAs and RNA binding proteins found only in germline cells, which helps determine the cells' fate.

Lehmann is also investigating the female germline cells' role in maternal inheritance. After fertilization, the maternal cell imparts not only its nuclear DNA but also components of its cytoplasm, including mitochondria, RNAs, and even bacteria. "This whole idea of cytoplasmic inheritance and the transgenerational continuum of the cytoplasm is something I'm just starting to think about," she says.

Yamashita and Lehmann share a large open space on the third floor of the Institute, with researchers from each lab integrated throughout. They will also share a fly room and computational room. The researchers hope the communal setup will allow a flow of ideas between their labs. "By sharing this kind of basic space, we are hoping to let our people interact with each other and for discussions to happen," Yamashita says.

"This is a new concept for Whitehead, and we'll see how it works," Lehmann says. "It's an exciting experiment in lab sociology."

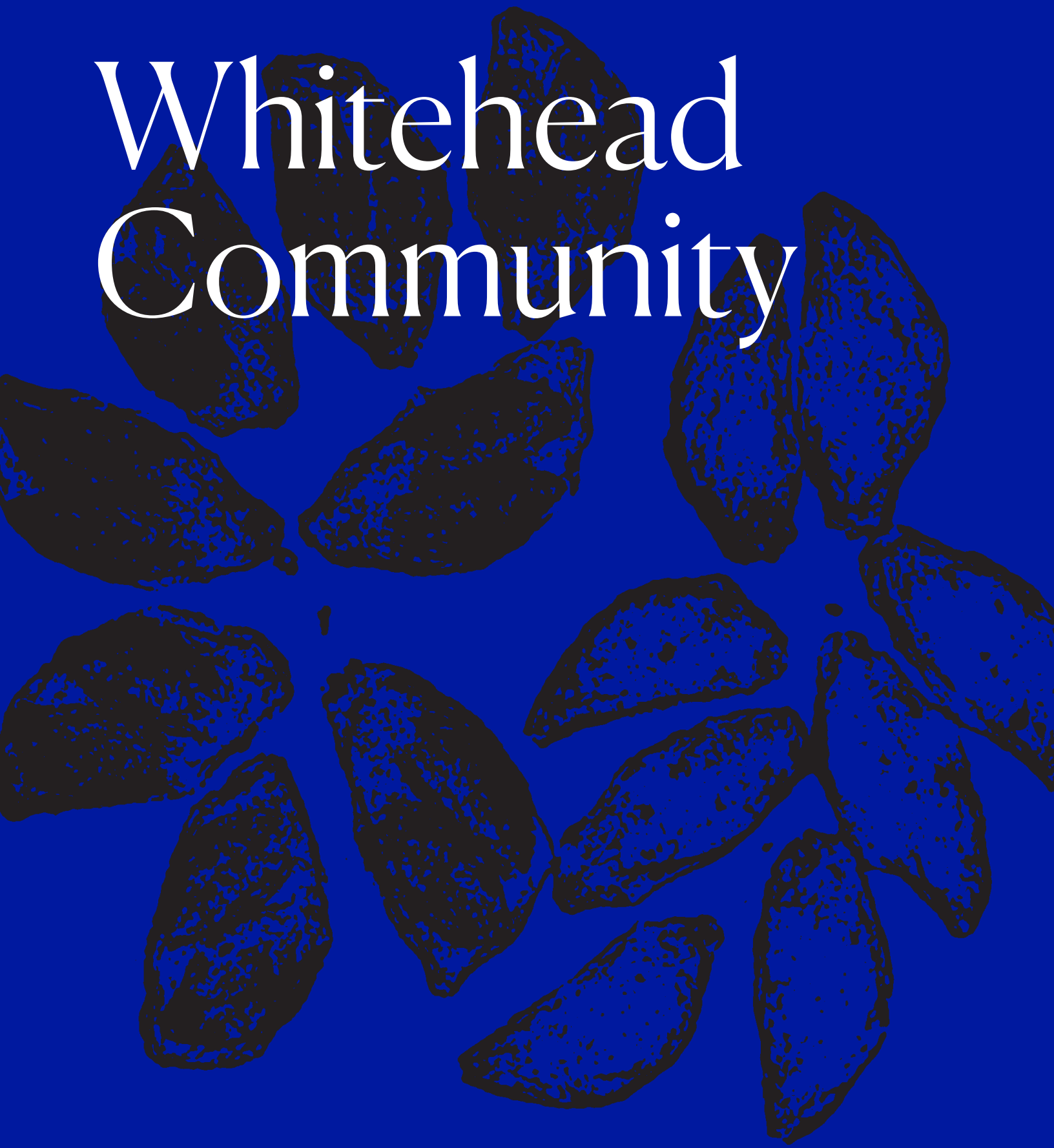


Early in mammalian embryonic development, long before the organism's ultimate form has taken shape, a precious subset of cells are set aside for creating future offspring. Most cells construct the growing body, and their journey begins and ends there. But the cells that are set aside, called primordial germ cells (PGCs), will eventually produce sperm and eggs that will in turn produce a new body.

An embryo's earliest cells are pluripotent, meaning they can develop into many different cell types, but their descendants eventually become committed to producing only one type. Scientists long believed that when PGCs are set aside, they immediately lock in to producing only eggs and sperm. In a recent study, Page and postdoctoral researcher Peter Nicholls discovered that primordial germ cells exhibit signs of pluripotency until they arrive in the gonads.

The researchers also identified a gene, Dazl, that induces the cells to commit to their reproductive fates. In mice with the Dazl gene knocked out, PGCs never differentiated into eggs or sperm and often formed tumors containing other cell types. Page and Nicholls hypothesize that testicular cancer could be the result of a malfunctioning DAZL protein. "Our findings suggest that the cancer has embryonic origins," Page says. "Understanding the nature of primordial germ cells will be important for investigating and addressing this disease."

Whitehead Community



Growth Amid the Tumult

Despite all the challenges of 2020, Whitehead Institute welcomed three new members and a new Whitehead Fellow

T to B: Ruth Lehmann, Jonathan Weissman, Yukiko Yamashita, Kipp Weiskopf.

Ruth Lehmann joined as Institute director and Member. Previously, she was the Laura and Isaac Perlmutter Professor of Cell Biology and chair of the Department of Cell Biology at New York University (NYU), where she also directed the Skirball Institute of Biomolecular Medicine and The Helen L. and Martin S. Kimmel Center for Stem Cell Biology. She was also a Howard Hughes Medical Institute Investigator (HHMI). Lehmann was an Institute Member from 1988 to 1996 before beginning a distinguished 23-year career at NYU. An elected member of the National Academy of Sciences (NAS) and a fellow of the American Academy of Arts and Sciences, Lehmann has made seminal discoveries in developmental and cell biology. For example, her uncovering of the mechanisms needed for proper specification and migration of germ cells has informed the understanding of processes essential for the continuity of life through the generations.

Jonathan Weissman joined as a Member and the Landon T. Clay Professor of Biology at Whitehead Institute. He is also an HHMI Investigator. Previously, Weissman was professor and vice chair of cellular and molecular pharmacology at University of California, San Francisco. An elected member of the NAS, Weissman is renowned for both scientific discovery and building innovative research tools. Among his many scientific achievements, he developed the ribosome profiling approach that has transformed researchers' ability to probe the molecular mechanism of translation in vivo. At Whitehead Institute, he will continue to study the mechanisms used by cells to ensure the correct folding of proteins, develop experimental and analytical tools and approaches to investigate complex biological systems, and work to develop new CRISPR-based tools for controlling gene expression and studying gene function.

Yukiko Yamashita joined the Institute as a Member and the Susan Lindquist Chair for Women in Science at Whitehead Institute. Previously, at the University of Michigan, she was the James Playfair McMurrich Collegiate Professor of the Life Sciences, professor of cell and developmental biology, and research professor in the Life Sciences Institute. Yamashita, who is also an HHMI Investigator, was named a 2011 MacArthur Foundation Fellow and has received both the Keck Foundation and Tsuneko and Reiji Okazaki awards. Known for fearless pursuit of new and unanticipated biological processes uncovered in her scientific investigations, her research has focused on the process by which stem cells are renewed in normal and diseased contexts and how asymmetric cell division maintains tissue homeostasis. At Whitehead Institute, Yamashita's research will also expand into new territories such as functions of satellite DNA, a little-understood constituent of the genome.

Lehmann, Weissman, and Yamashita were each also appointed as a professor of biology at Massachusetts Institute of Technology.

Though not the first Whitehead Fellow to hold both an M.D. and a Ph.D., **Kipp Weiskopf** is just the second to both run an Institute lab and practice medicine. He is completing a clinical fellowship in medical oncology at Dana-Farber Cancer Institute and sees patients in its Center for Immuno-Oncology. Weiskopf earned a B.A. in biology from Amherst College, an M.Phil. in biological sciences as a Winston Churchill Scholar at University of Cambridge, and medical and doctoral degrees at Stanford University. His primary research focus is the interaction between cancer cells and the immune system — notably, the potential for using the myeloid immune cells called macrophages to treat cancer. Some of the therapies developed through Weiskopf's Ph.D. research are currently being tested in phase I clinical trials.

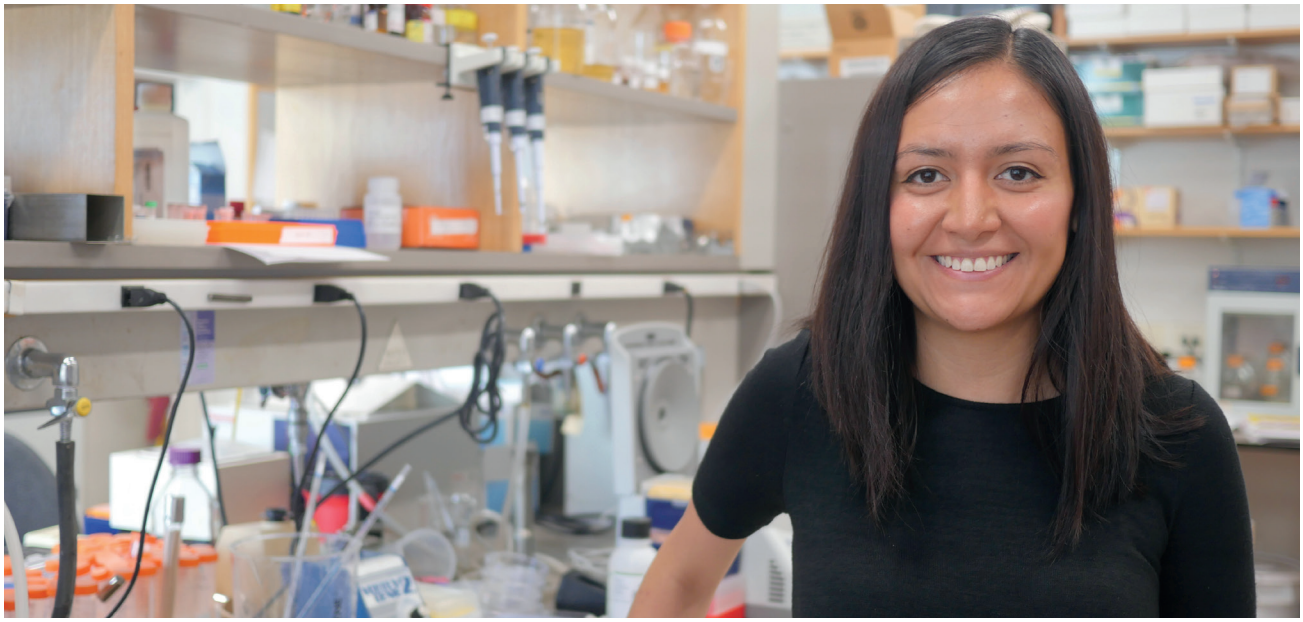
The Path to Science

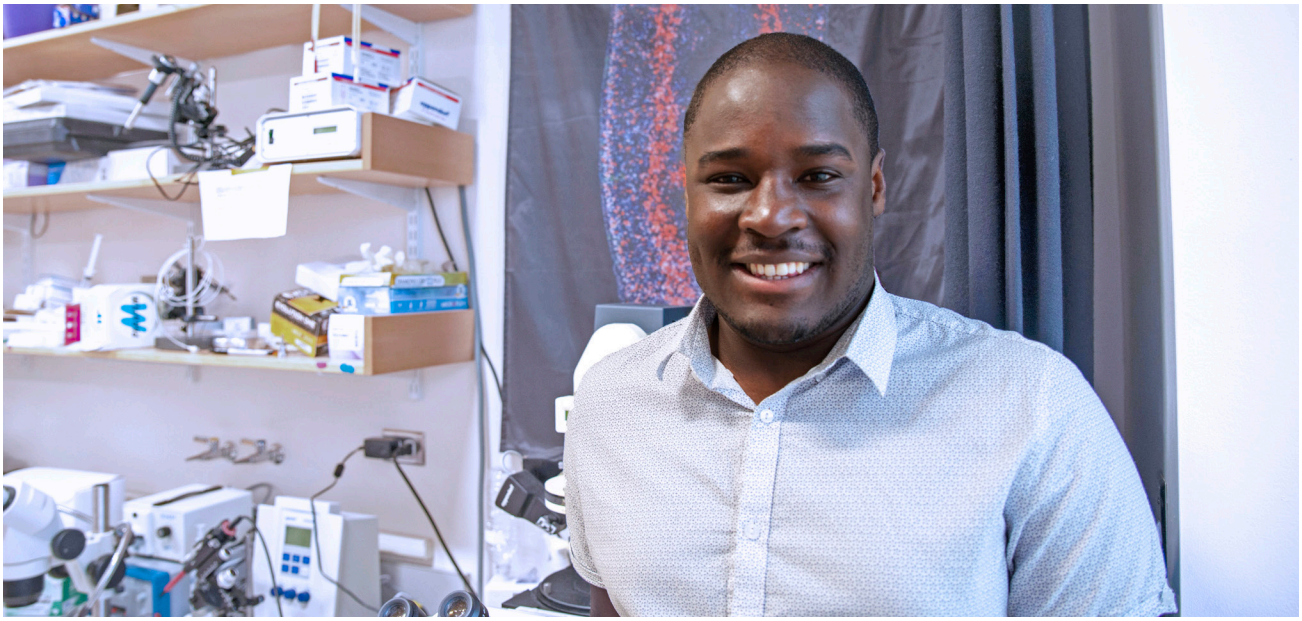
To help prepare the next generation of leaders in biomedical research, our labs welcome talented students eager to investigate fundamental scientific questions. Here are snapshots of two such students and the paths that led them to the Institute.

During a sophomore neurophysiology class at San Diego State University, psychology major Alicia Zamudio had an epiphany. "During a lecture, my professor showed a video of a monkey that had been trained to control a robotic arm using only a device implanted in its brain," she recalls. "I was amazed to learn that something that sounded like science fiction was actual work being conducted at a university." And it started her thinking — perhaps she could be someone who turned sci-fi into reality. Fast forward: Alicia majored in both psychology and biology, engaged in two summer neuroscience research projects at Massachusetts Institute of Technology, and ended up pursuing her Ph.D. in the MIT Department of Biology.

Alicia's undergraduate research had sparked an interest in investigating how DNA is packaged within the cell and how that packaging affects gene expression. When it came time to choose a lab for her doctoral research, there was a natural choice: Whitehead Institute Member Richard Young is one of the leaders in the field. Working with colleagues in the Young lab, Alicia helped create a new way of understanding how genes — including oncogenes — are turned on and off or prompted toward higher or lower rates of expression. Their investigations have helped prompt a major reconception of gene regulation and laid the groundwork for a wholly new approach to drug development for cancer and neurodegenerative diseases.

Earlier this year, Alicia received her Ph.D., then spent six months as a scientist at Dewpoint Therapeutics, a company formed to develop drugs based on that new approach. Recently, she undertook a postdoctoral research fellowship at Genentech, where she continues pursuing her longstanding interest in neuroscience and hopes to one day help develop drugs for neurological diseases for which there are no treatments. She has, it seems, leaped past sci-fi and is helping turn her science dreams into reality.





As a teen, Kwadwo Owusu-Boaitey had set his sights on pro soccer, and he was good enough to join the Olympic Development Team. But as a high school junior, another passion emerged to divert his path from soccer stardom. "I did a research project on steroids and public health," he recalls, "and spent a year learning about what steroids did to your body and how they worked." That experience ignited his interest in medicine. It also prompted a realization: A lot of things that are transformative in medicine really come from basic science, from a researcher's curiosity about how something works. And so, after earning his bachelor's degree at University of Maryland, Baltimore, he decided to pursue a career as a clinician-scientist. Today he is seven years into the M.D./Ph.D. program of MIT and Harvard Medical School.

Kwadwo believes that success often depends not on how smart you are but primarily on being in the right environment. For him, the right research environment is Institute Member Peter Reddien's lab. "Not only is Peter globally respected for his use of the planarian flatworm to understand regenerative biology," he notes, "but from the outset he impressed me with his depth of thought about topics outside of science."

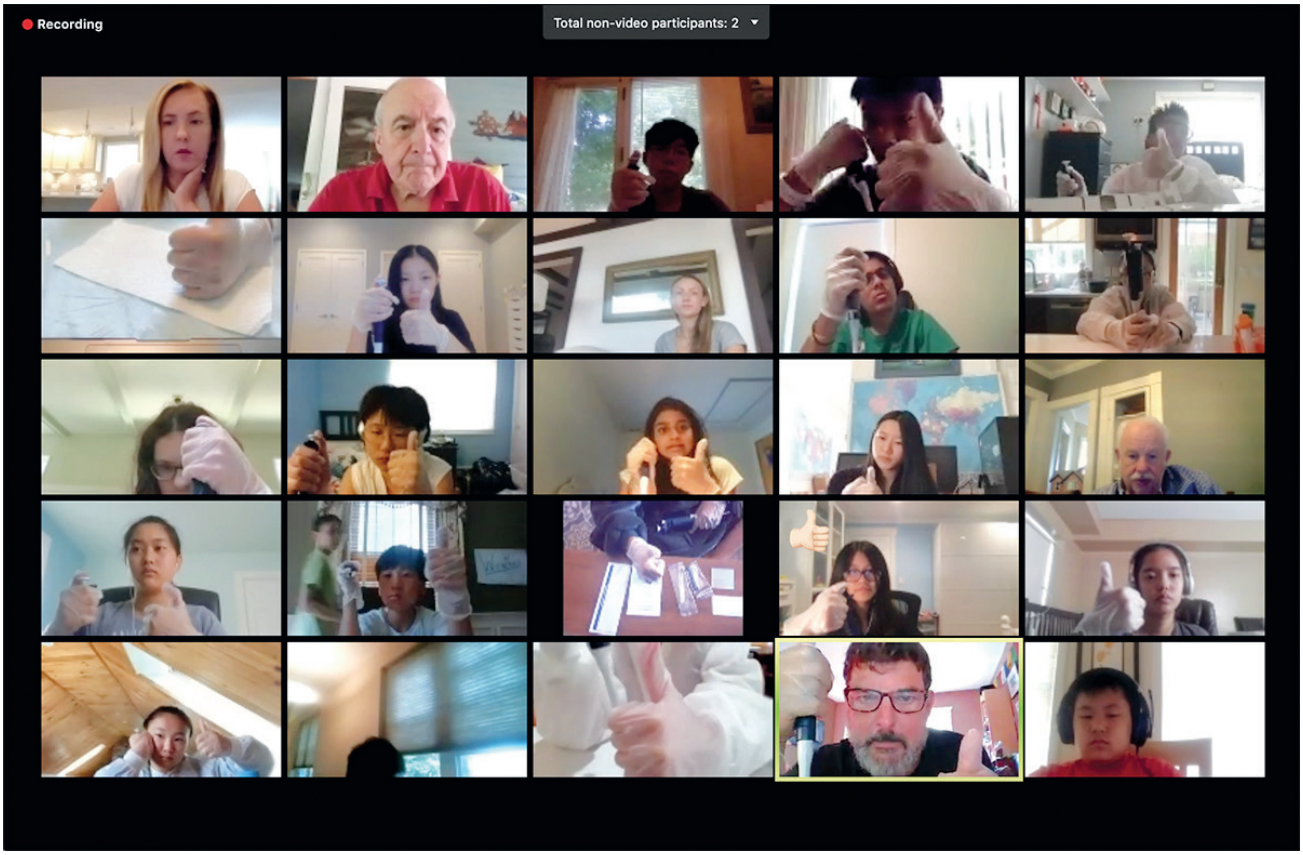
In the lab, Kwadwo is working to understand how the stem cell population in planarians spatially organized — where the various types of stem cells exist and what pattern guides their distribution. His near-term goal is to better understand planarians' ability to regenerate any part of their body. Ultimately, he hopes that his and his lab colleagues' work will shed light on both human development and ways to promote repair from injury or disease. And that very much appeals to the soon-to-be-clinician in him.

Expedition: Bio pivots to online learning

Giving middle schoolers a hands-on science experience at home

For more than five years, Whitehead Institute's **Expedition: Bio** has provided Boston-area middle schoolers with an engaging summer science experience. The program exposes students to varied scientific concepts, experimental procedures, fields, and career paths and they get to use equipment they might not otherwise access until high school or later.

This year's program was no different — except that, with the COVID-19 pandemic, activities took place online and in students' homes, not Institute labs. Rising to the challenge of creating a substitute for face-to-face programming, Public Programs Manager Amy Tremblay and her team devised creative solutions for running hands-on science sessions remotely. Before the program began, participating students received a lab kit with everything they would need for two weeks of experiments. The hardware ranged from a micropipette to a foldscope microscope (made mostly of cardboard) to a mortar and pestle to gummy bears. Those materials were used in activities that included extracting DNA from smashed strawberries, observing osmosis swell gummy bears to frightening proportions, assembling and using



the microscope to see items at 140x magnification, and grinding leaves and pipetting the residue to see how chlorophyll fluoresces when extracted.

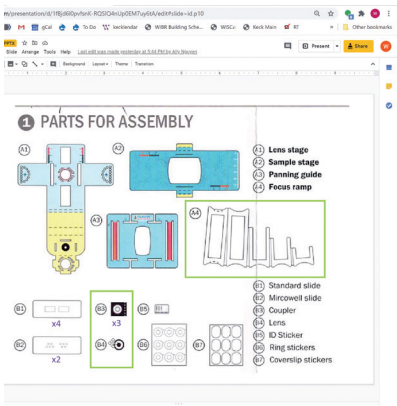
The students used video conferencing to attend sessions led by Whitehead Institute scientists including Member Jing-Ke Weng, Lab Manager Valentina Carballo, Microscopy Facility Manager Wendy Salmon, and postdoctoral researchers Mary Jane Tsang and Ally Nguyen. The sessions included a synthetic biology course, during which students learned the basic steps of developing a biosynthetic product and debated the ethics and marketability of synthetic biology prod-

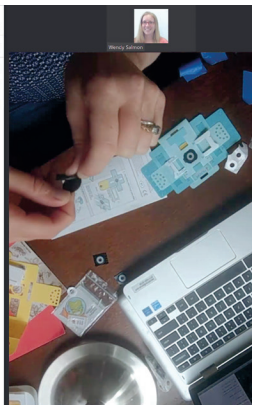
ucts such as vanilla-producing yeast and lab-grown meat. Students also participated in nature journaling, discussed drug discovery with a biotech company scientist, and had a virtual visit to a farm to observe pond life and learn about life cycles, evolutionary adaptations, and food webs.

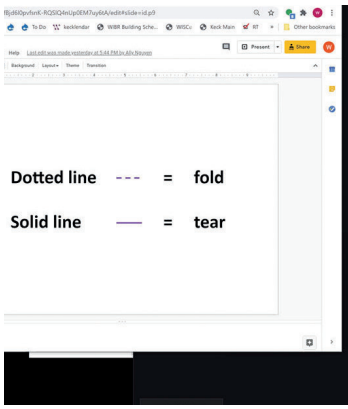
"One advantage of doing the program virtually is that the kids learned how accessible science can be," explains Julia Kautz, a Northeastern University undergraduate who has been a teaching assistant during Expedition: Bio for three years. "Although getting access to the labs and equipment at Whitehead Institute is usually an exciting part of the experience, there's something to be said for discovering that you can do cool science in your kitchen."

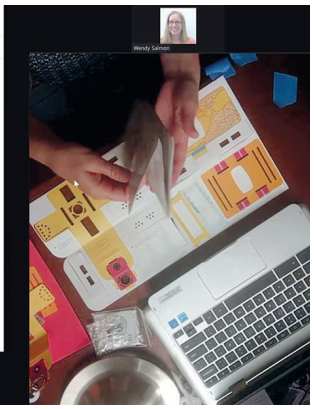
"The program's primary goal is to give all our students a deeper understanding of and appreciation for science," Tremblay says. "And we believe that, for some students, it will be an early step in a STEM career."

The program is supported by a generous contribution from the Amgen Foundation, with additional scholarship support provided by Sanofi Genzyme. This year's program was offered to participants for free.









Whitehead Connects

Whitehead Connects — Whitehead Institute's signature speaker series — invites renowned industry leaders to share lessons learned during their distinguished careers. It also enables members of the broader Whitehead Institute community to engage in a dynamic networking opportunity with accomplished professionals in corporate, academic, and scientific organizations. This year's speakers included a deeply experienced biotech leader and a globally recognized health sciences investor.

Our October 2019 speaker was **John Maraganore**, who has served as CEO and director of Alnylam Pharmaceuticals since 2002. Previously, he was a senior executive with Millennium Pharmaceuticals, Biogen, and Agios Pharmaceuticals and has served as chair of the Biotechnology Industry Organization. Much of the early science underpinning Alnylam emerged from the lab of Institute Member David Bartel, a pioneer in RNA science. Maraganore's talk, entitled "Bringing RNAi from Basic Science to Patients," offered a strategic overview of Alnylam's development of RNA interference treatments, which include a growing array of drugs that are FDA-approved or are moving through advanced clinical trials.

John Maraganore (L) and Pablo Legorreta (R) engaged with the Whitehead Institute community through Whitehead Connects

Pablo Legorreta is the founder and CEO of Royalty Pharma, one of the world's largest dedicated life sciences investors. He serves on the board of institutions including Epizyme, the New York Academy of Sciences, Rockefeller University, Brown University, the Hospital for Special Surgery, and the Pasteur Foundation. In his March 2020 Whitehead Connects talk, Legorreta discussed his company's approach to transforming life sciences funding through collaborative capital. He also shared previous experiences as an investment banker in Paris and New York and as founder of a nonprofit dedicated to enhancing the quality of health care in Latin America.

Whitehead Institute adds five distinguished leaders to its Board of Directors

They include an oncologist/former NASA astronaut and a former president of Massachusetts Institute of Technology

L to R: Robert Satcher, Susan Hockfield, Churchill G. Franklin, Seth Alexander, Dennis H. Langer

The Whitehead Institute Board of Directors has elected five new, highly accomplished members for six-year terms. These individuals collectively bring vast leadership skill, scientific insight, and management acumen, as well as a deep understanding of governance of non-profit, research, and academic institutions.

"We are very pleased to have this group of seasoned leaders join our governance team," says board Chair Sarah Keohane Williamson. "They bring extraordinary knowledge and expertise in their respective fields and substantial experience working with academic research institutions."

Former NASA astronaut **Robert Satcher** earned bachelor's and Ph.D. degrees in chemical engineering from MIT and an M.D. from Harvard Medical School. He is an associate professor of orthopaedic oncology at the University of Texas MD Anderson Cancer Center in Houston, where he specializes in the treatment of skeletal metastatic disease and soft tissue sarcoma and in development of tools and approaches to improve surgical outcomes. His translational research is focused on tumor-bone cell interactions during bone metastasis progression. In addition, he is working with MDACC and other partners to develop a cancer center in sub-Saharan Africa, co-founded the eHealth Research Institute to improve access to specialized health care, and has performed medical missions in underserved countries in Africa and Central America as a member of Doctors United in Medical Missions. In 2009, Satcher participated in an 11-day mission to the International Space Station, during which he took two spacewalks and was the crew's medical doctor. Previously, he served on the faculty of Northwestern University's Feinberg School of Medicine and held an adjunct appointment in Northeastern University's biomedical engineering department. Earlier in his career, he was a Schweitzer Fellow at the Albert Schweitzer Hospital in Gabon and completed fellowships at University of California, Berkeley, and University of Florida. Satcher serves on the board's leadership advisory committee.

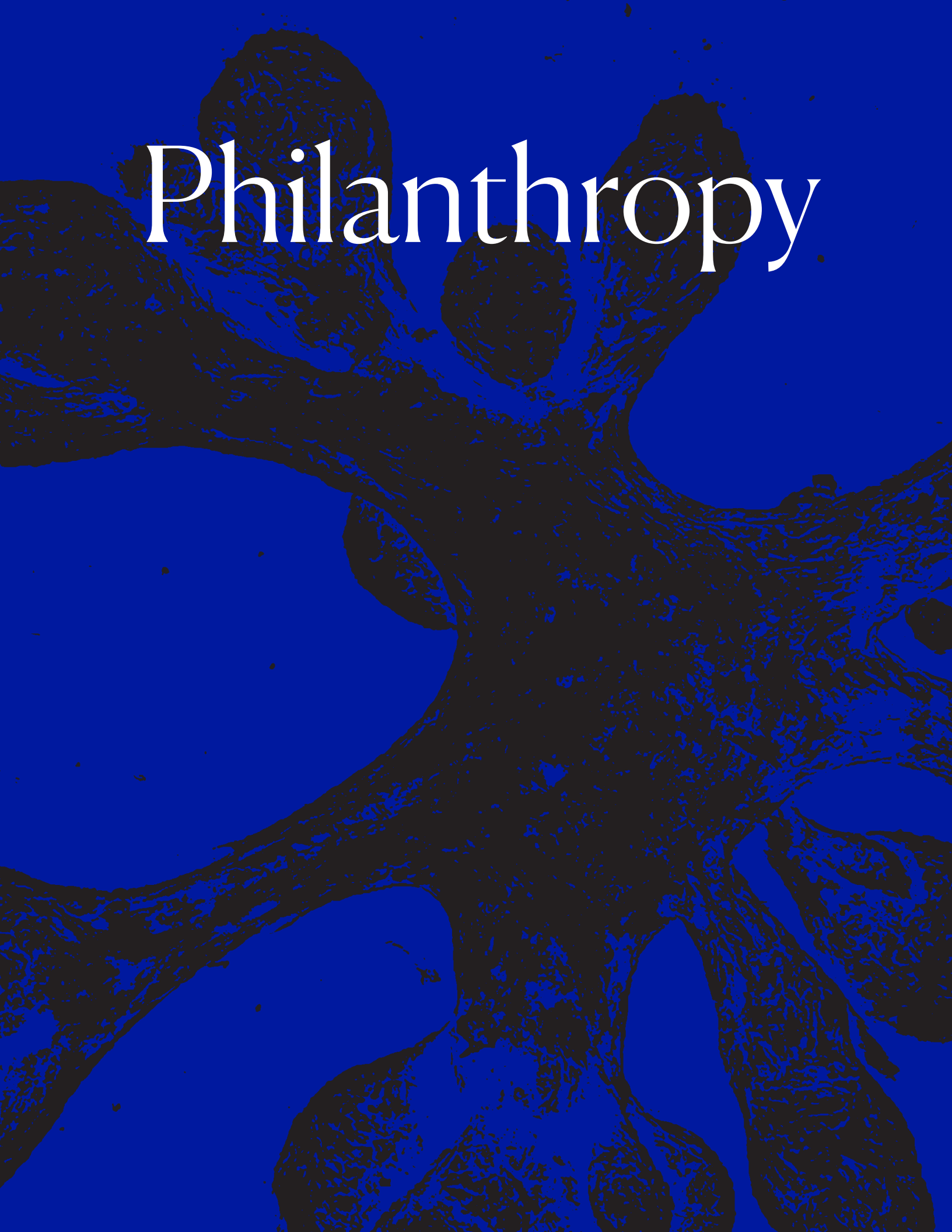
Susan Hockfield, PhD, is president emerita and professor of neuroscience at Massachusetts Institute of Technology (MIT) and served as the sixteenth president of MIT. There, as the first life scientist to lead the institution, she championed breakthroughs emerging from the convergence of the life, engineering, and physical sciences; and she oversaw the founding of the MIT Energy Initiative, the David H. Koch Institute for Integrative Cancer Research, the Institute for Medical Engineering and Science, and the Ragon Institute of MGH, MIT and Harvard. Formerly at Yale University, Hockfield served as provost, dean of the Graduate School of Arts and Sciences, and William Edward Gilbert Professor of Neurobiology. Last year, Hockfield chaired the search committee that recruited Ruth Lehmann to become Whitehead Institute's fifth director. In 2019, Hockfield published The Age of Living Machines, a book that explores the role scientific convergence could play in overcoming major humanitarian, medical, and environmental challenges. She chairs the board's nominating committee and is a member of the leadership advisory committee.

Churchill G. Franklin is chairman and former CEO of Acadian Asset Management, a $100 billion institutional asset management firm that he co-founded in 1986. Before joining Acadian, Franklin was assistant treasurer of Thermo Electron Corporation (now Thermo Fisher Scientific, a Fortune 500 company), where he managed all aspects of the treasury function. A graduate of Middlebury College—from which he received an Honorary Doctor of Humane Letters degree in 2008—Franklin chaired the College's board from 2000 to 2004 and is now a member of the investment committee for its $1 billion endowment. He is also a Boston board member of The Posse Foundation—which recruits students from diverse backgrounds with extraordinary leadership potential, trains them to pursue consensus solutions to complex social problems and sends them to some of the country's most competitive colleges—and is a past president of the Concord (MA) Museum. Prior to joining the Institute's board, Franklin served on its investment committee. He currently chairs the development committee and serves on the investment committee.

Since 2006, **Seth Alexander** has been president of the MIT Investment Management Company (MITIMCO), which manages the university's endowment, and oversees investment of its current funds, pension assets, and other institutional assets. Between 2006 and 2019, the MIT endowment grew from approximately $10 billion to approximately $17.6 billion. Prior to joining MITIMCO, Alexander was a director at the Yale University Investments Office, where he worked for 10 years. He also served as a Management Fellow at the Yale School of Management and co-taught a class on endowment management. Alexander earned a BS in biology from Yale in 1995. For 12 years prior to joining the Institute board, he served as a member of its investment committee and continues to do so; he also serves on the finance committee.

For more than three decades, **Dennis H. Langer**, MD, JD, has held executive, operating, and governance roles for both start-up and established biotechnology and pharmaceutical companies. Under his leadership, those organizations developed and/or commercialized more than 60 products. Having begun as a clinician—serving as chief resident at Yale University School of Medicine and a clinical fellow at Harvard Medical School and the National Institutes of Health—Langer went on to hold significant R&D and marketing roles at Eli Lilly, Abbott, Searle, and GlaxoSmithKline (where he was a senior vice president for research and development), and to be a managing partner of Phoenix IP Ventures. He has also been a clinical professor of psychiatry at Georgetown University School of Medicine since 2003. In addition, Langer has served on more than two dozen company boards and been a member of governance or advisory boards at Columbia University, Georgetown University, and Harvard Law School. Before joining the Institute's board, he was a member of its finance committee. He is currently a member of the leadership advisory and finance committees.

Philanthropy



Continuing a legacy of philanthropy

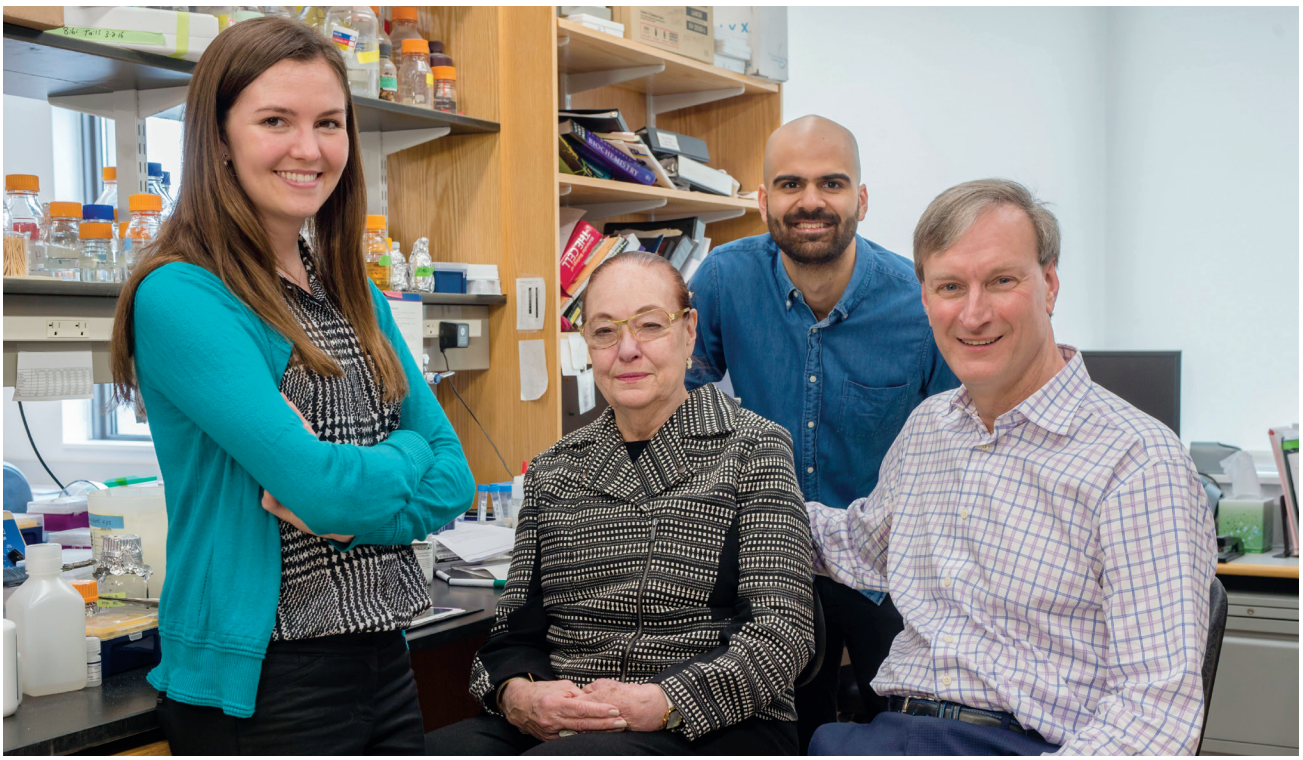
While 2020 was, in many ways, a time of uncertainty, for Whitehead Institute it was also a year of carefully planned and smoothly implemented leadership transition.

Ruth Lehmann became director; Sarah Keohane Williamson became chair of the board of directors. From the outset, they each articulated an intention to be both stewards and change agents: to move the organization forward even as it meets the pressing challenges and uncertainties of the present moment. And both are committed to strengthening our legacy of philanthropy by supporting the activities that define Whitehead Institute: conducting pioneering science and preparing the next generation of scientific leaders.

The new development committee chair is Churchill Franklin. (He is joined on the committee by Nobel laureate and MIT professor Phillip Sharp and John Whitehead, son of Institute founder Jack Whitehead.) Churchill is a proven leader in both the corporate and nonprofit sectors as co-founder, chairman, and former CEO of the $100 billion firm Acadian Asset Management and former chair of Middlebury College's board of trustees. His knowledge, experience, and dedication are important assets as the Institute seeks to increase support for its path-breaking research.

The year included another transition of note for Whitehead Institute's fundraising program. For a decade, Jonathan M. Goldstein served, with distinction, as chair of the board's development committee; he completed his service in that role in September. Jono has been part of the Whitehead Institute community for many years: As an undergraduate researcher in Founding Director David Baltimore's lab, a Massachusetts Institute of Technology (MIT) biochemistry graduate student, and then as a private equity investor, he saw the Institute grow in stature and spark the transformation of Kendall Square into a premier research and innovation community. He joined the board in 2008 and, two years later, became development committee chair. Since then, the Institute has benefited greatly from his commitment to building a culture of philanthropy at Whitehead Institute as well as from his professional expertise and passion for the life sciences.

Generous donors fuel courageous science



Brit Jepson d'Arbeloff Center on Women's Health

Men and women often experience health and disease in very different ways. But science knows little about why those differences occur. The Institute's Initiative on Sex Differences in Health and Disease aims to help fill that knowledge gap. Its working hypothesis is that males and females read all of their chromosomes in very different ways — spurring individual genes to be expressed at different levels and causing differences in cellular function. In 2020, the Initiative created the Brit Jepson d'Arbeloff Center on Women's Health to drive research on how the female and male genome, transcriptome, epigenome, proteome, microbiome, and metabolome differ. D'Arbeloff has described the Initiative as an imperative biomedical quest. "I cannot make a more important investment in the health of my grandchildren and their children," she said when announcing her $10 million gift to the Center. Former Institute director David Page, who leads the Initiative, believes that discovering how females and males differently read our shared genome will transform biomedical research and, ultimately, medical practice.

Endowed professorships

Endowed professorships provide recognition and tangible support for the work of pioneering researchers. These positions are also a boon in recruiting and retaining talented scientists. In 2020, three endowed Whitehead Institute professorships were awarded for the first time.

Jonathan Weissman, who became an Institute Member this year, is the **Landon T. Clay Professor of Biology**. Previously a professor and vice chair of cellular and molecular pharmacology at University of California, San Francisco, Weissman is a Howard Hughes Medical Institute Investigator renowned for both scientific discovery and building innovative research tools. At Whitehead Institute, he will continue to study protein-folding mechanisms, develop tools and approaches to better understand complex biological systems, and develop new ways to use CRISPR-Cas9 gene editing for research and development.

Yukiko Yamashita, who also became an Institute Member in 2020, holds the **Susan Lindquist Chair for Women in Science**. Previously the James Playfair McMurrich Collegiate Professor of the Life Sciences and professor of cell and developmental biology at University of Michigan, she is an HHMI Investigator and a 2011 MacArthur Foundation Fellow. Widely recognized for her bold and productive approach to science, Yamashita will continue investigating the mechanisms underlying asymmetric stem cell division while expanding into new territories such as satellite DNA, a little-understood constituent of the genome.

Institute Member Mary Gehring has been appointed the **Landon T. Clay Career Development Chair**. An emerging superstar in plant biology and a respected leader within the Institute community, Gehring focuses on plant epigenetics — the heritable information that influences cellular function but is not encoded in the DNA. By studying epigenetic differences between generations of plants, Gehring seeks to learn if epigenetic responses to environmental factors can cause evolutionary changes. Her work has implications for addressing food security during climate change.

Also this year, a prestigious professorship passed to a new scientific leader: Institute Member Iain Cheeseman received the **Margaret and Herman Sokol Chair in Biomedical Research**, succeeding Member and former director Gerald Fink in the role. Cheeseman's research focuses on the kinetochore, a central player in directing chromosome segregation. He has helped identify dozens of the kinetochore's molecular components and their specific roles.

L to R: Jonathan Weissman, Yukiko Yamashita, Mary Gehring, Iain Cheeseman.

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

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

FACULTY ACHIEVEMENTS
Whitehead Institute's world-renowned faculty include the recipient of the 2011 National Medal of Science (Rudolf Jaenisch); the recipient of the 1997 National Medal of Science (Robert A. Weinberg); ten Members of the National Academy of Sciences (David Bartel, Gerald R. Fink, Jaenisch, Ruth Lehmann, Harvey F. Lodish, David C. Page, David Sabatini, Weinberg, Jonathan Weissman, and Richard A. Young); six members of the National Academy of Medicine (Fink, Jaenisch, Page, Weinberg, Weissman, Young); and six Fellows of the American Academy of Arts and Sciences (Fink, Jaenisch, Lehmann, Lodish, Page, and Weinberg). In addition, two Members — David C. Page and Yukiko Yamashita — have been named MacArthur Foundation Fellows.

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