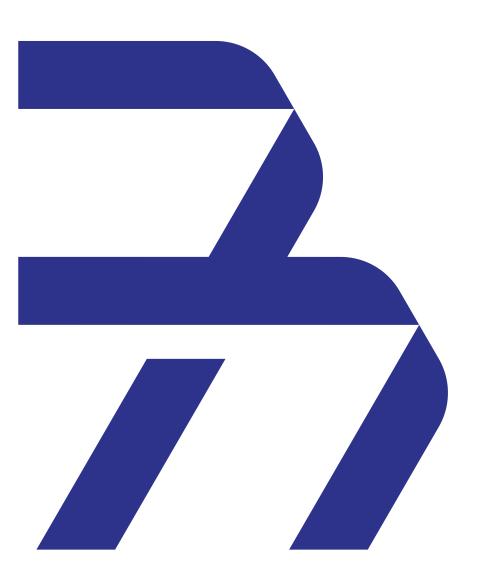
Whitehead Institute 2021 Annual Report



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A message from Ruth Lehmann

I'm pleased to introduce you to our annual report for 2021. This was my first year as director. It was, to say the least, eventful — marked by the continuing COVID-19 pandemic and by the nation's ongoing struggle with injustice and inequity. Through it all, Whitehead Institute carried on its mission of uncovering the most fundamental aspects of biology and human health.

For example, Olivia Corradin created an approach for defining epigenetic variation in some individuals with opioid use disorder. This will help researchers identify genes associated with the disorder, and could open a path to new therapeutics. Yukiko Yamashita extended her pioneering discoveries on satellite DNA — which has long been regarded as "genomic junk," but which, Yukiko shows, is essential for keeping individual chromosomes together in a single nucleus. Jonathan Weissman and his colleagues developed a new gene editing technology called CRISPRoff which allows researchers to control gene expression while leaving the DNA sequence unchanged. These are a small sample of the extraordinary research being done across the Institute.

Building on our knowledge and capabilities, we began an ambitious initiative on the biology and health impacts of climate change. We believe that climate change represents an existential crisis for humanity. We're determined to bring our expertise, passion, and resources to bear in helping mitigate its negative effects on human health and wellbeing.

This year, we also focused on the vibrancy of the Whitehead Institute community itself. Pioneering science requires having some of the world's smartest, most creative, skilled, and intellectually courageous researchers. It demands that we develop new ideas and consider new perspectives in a safe and supportive environment. That's why we're pursuing a comprehensive plan to enhance diversity, equity, and inclusion at Whitehead Institute.

Creating a truly diverse and inclusive community takes focus and hard work. But the end result will be an even stronger, more resilient organization: one that is ready to meet the extraordinary challenges the future holds — and that's well-positioned for our next 40 years of achievement.

I hope that you'll explore the richness of this annual report. I think you'll be impressed by all we're doing to advance biomedical science and human health.

Sincerely, Ruth Lehmann.

Rto 6 cm

Our Science

Our Science

Our research mission is to be a trailblazer for fundamental discoveries in science. We encourage our scientists to take risks, take on difficult problems and explore big open questions to reveal new biology for the benefit of global health. In this section of the Annual Report, enjoy a selection of news stories and multimedia features on Whitehead Institute science in 2021.

Meet the researchers

Whitehead Institute has a world-renowned faculty consisting of 22 Members and Fellows



David Bartel



Iain Cheeseman



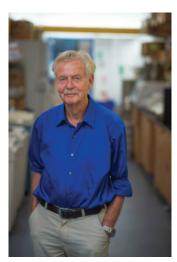
Olivia Corradin MEMBER, WHITEHEAD INSTITUTE



Gerald R. Fink



Mary Gehring



Rudolf Jaenisch



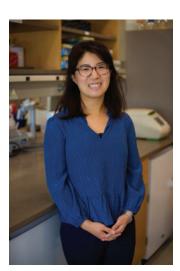
Ankur Jain MEMBER, WHITEHEAD INSTITUTE



Kristin Knouse



Ruth Lehmann DIRECTOR, MEMBER, WHITEHEAD INSTITUTE



Pulin Li member, whitehead institute



Harvey Lodish



Sebastian Lourido



Tobiloba Oni



David C. Page



Peter W. Reddien



Silvia Rouskin



Robert A. Weinberg



Kipp Weiskopf



Jonathan Weissman



Jing-Ke Weng MEMBER, WHITEHEAD INSTITUTE



Yukiko Yamashita Member, whitehead institute



Richard A. Young

Climate change initiative



Confronting an existential crisis

Whitehead Institute establishes Initiative on Biology, Health, and Climate Change

Earth's average surface temperature has increased more than 1.18 degrees Celsius over the past two centuries. The resulting climate change is contributing to more intense hurricanes, extreme flooding, and rampaging wildfires - and to slower-moving crises such as drought, food insecurity, deadly high temperatures, extinction of many species, and spreading infectious diseases.

Those are just the effects we can see. What biological effects of climate change are not yet apparent? What impacts will it have on human health and well-being in coming decades? Right now, science has limited knowledge about how to mitigate the negative effects of increased temperature on biology, and society lacks biotechnological tools to begin addressing detrimental impacts. Huge segments of the world's population will be at risk if scientists and engineers cannot develop methods for anticipating, understanding, and ameliorating climate change's effects on human health.

"Whitehead Institute believes that climate change is an existential crisis for humanity; further, that we must help create the fundamental scientific knowledge and biotech tools necessary to protect human health in the face of the emerging challenges," says Institute director Ruth Lehmann. "We are establishing the Initiative on Biology, Health, and Climate Change (IBHCC) to explore the biological impacts of increased global temperatures and their implications for human health; and to spark new biomedical and biotech interventions to prevent or treat detrimental impacts on health and mitigate negative effects on agriculture and other essential natural systems."

Initially, the IBHCC is pursuing work in:

Plant Biology - including projects seeking to create seed-producing plant varieties that are more nutritious, have a higher yield, and are adapted to climate change; and develop methods to synthesize or make more environmentally sustainable the availability of medicines and industrial products that originate in plants.

Infectious Disease - including exploration of climate change's effects on development of infectious organisms and the robustness of the hosts that transmit them; and development of one-time, bioengineering-based interventions that prevent vector-based disease transmission. Temperature Sensitive Cellular Processes - including exploration of the molecular mechanisms by which organisms adapt to extreme environmental conditions; and investigation of the effects of temperature increase on cellular proteins, cell function, and organism reproduction.

Across those scientific thrusts, the IBHCC will also generate new tools and methods to help drive research and development forward; initiate scientific collaborations and institutional partnerships; and help inform the public and train future generations of researchers and policymakers.

"Whitehead Institute has long been a pioneer in foundational biological research," Lehmann says. "Today, we are passionately committed to applying the Institute's knowledge, tools, and capacity for innovation to protect human health from emerging climate challenges.

"... we must help create the fundamental scientific knowledge and biotech tools necessary to protect human health in the face of the emerging challenges," says Institute director Ruth Lehmann.

> "As traumatic as the COVID-19 pandemic has been, it enabled scientists to demonstrate both the practical value of discovery research and our collective ability to quickly uncover, translate, and apply new knowledge," Lehmann observes. "Overcoming climate change's threats to human health will require an even larger scientific effort. And it will demand a similar willingness by funders to make up-front investments in research and development."

Selected science stories Browse research stories from 2021



How sea stars get their symmetry

In a *Current Biology* paper published in November 2021, Whitehead Institute postdoctoral researcher Zak Swartz and collaborators delve into the origins of the initial polarity in an animal's first cell, which establishes an axis of symmetry for the developing organism and underlies the first steps of development.

Their research reveals how a specific protein, called Dishevelled, localizes in a cell to help create this polarity. "Sea stars, and a huge diversity of other animals, have an incredibly complex body plan, none of which is possible without the polarity of the initial cell," said Whitehead Institute Member Iain Cheeseman. "This work shows how the polarity originates as early as the meiotic divisions in the developing oocyte through an unexpected strategy to break its symmetry and achieve the asymmetric distribution of developmental factors."

All in the timing

Researchers in Whitehead Institute Director Ruth Lehmann's lab wanted to better understand the different groups of cells involved in creating the gonads—the reproductive organs—and in guiding development of the germ cells, the set of cells that become eggs and sperm. In work published in *Developmental Cell* in June 2021, Lehmann lab postdoc Torsten Banisch showed that an unexpected type of cell, the swarm cells, relay a hormone signal to the germ cell precursors, known as primordial germ cells, which prompts them to differentiate and give rise to the eggs. Swarm cells were first identified almost two decades ago, but until now their function has been unknown.

A "tail" of two RNA regulatory systems

Messenger RNAs (mRNAs) are our cells' intermediaries as genes become proteins. Usually, mRNAs are short lived, constantly being created and degraded to help regulate how much protein is made from a gene at any given time. However, in the earliest stages of development, before the embryo can make enough of its own mRNAs, they are a limited resource and the embryo cannot afford to destroy them. In research published in eLife in July 2021, Whitehead Institute Member David Bartel, postdoc Kehui Xiang and collaborators have now discovered how cells establish this early gene regulatory regime and what conditions prompt a switch as the embryos mature. The researchers have observed the same regulatory switch in fish, frogs, and flies, and because the switch occurs across the animal kingdom, they would expect to see that the mechanism applies in other species including mammals.

New approaches from Whitehead Institute researchers

Tool and method development at Whitehead Institute

Scientists at Whitehead Institute are in relentless pursuit of discoveries that change and deepen our understanding of the biological world. Often, they pose ambitious questions that cannot be answered with the tools and methods that currently exist, but that does not deter them. When our researchers hit a wall, they invent what they need to scale it. In this series, we explore some of the tools and methods, both experimental and computational, that Whitehead Institute researchers have created in order to answer otherwise unsolvable questions. Read on to learn about these tools and methods, what the researchers have discovered with them, and how what they have created can be widely applied in other research — or visit our digital Annual Report at https://annualreport.wi.mit.edu/ for the full multimedia experience.



Top left: Rebecca Povilus/ Whitehead Institute Top right: Kathleen Mazza-Curll/Mansi Srivastava/Whitehead Institute Bottom right: *Arabidopsis thaliana* 2019-04-27 2246 by Salicyna is licensed under CC BY-SA 4.0 Bottom left: Gerald Fink/ Whitehead Institute

Making a model

Some of the most important tools in researchers' toolkits are the model organisms they use to study biological questions. While some organisms have wings and others have tails, all species share a common ancestry and much of the same DNA. Because of this, researchers can often study a biological process in one species to learn about how that process may work in related species. Using model organisms, rather than studying biology in each species individually, allows biologists to ask their questions in organisms with traits that are amenable to research, such as a short generation time, easy-to-manipulate genetics, and the ability to grow and propagate in the lab.

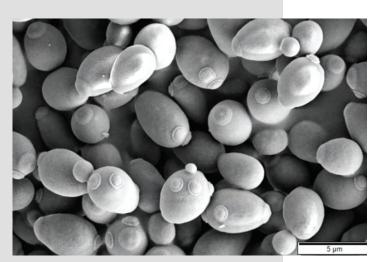
How do researchers decide which species, out of the millions that exist, to develop as models? Whitehead Institute researchers have had a hand in establishing and promoting the use of several model organisms over the years. Read on to learn what drew them to those species and how they helped shape them into powerful models to study fundamental biological questions.



Credit: Gerald Fink / Whitehead Institute

Baker's yeast (Saccharomyces cerevisiae) grows everywhere around us. This tiny powerhouse has long been a diet staple in both bread and beer, and over the past half-century it has also become a staple in biological research. However, when Whitehead Institute Founding Member and Former Director Gerald Fink started working with baker's yeast as a graduate student in the 1960s, he was told that it was a difficult organism to manipulate and was warned against it.

Nevertheless, Fink stuck with yeast and helped turn it into one of the premier model organisms in biology. One of his key contributions was figuring out how to insert any gene, from any organism, into yeast cells. This lets researchers study genetics in yeast, and enables yeast to be used as a biological factory. If researchers or companies know the genes that produce a desired molecule, they can insert those genes into yeast, and the yeast will start pumping out that molecule. Thanks to this innovation, yeast has been used to mass produce many vaccines, such as for hepatitis B, and medicines—perhaps most famously, insulin—as well as biofuels and other products.



Credit: *Saccharomyces cerevisiae*, SEM image by Mogana Das Murtey and Patchamuthu Ramasamy, licensed under CC BY-SA 3.0

Yeast is a go-to model to discover key insights into the biology of most life on Earth because it has fundamental machinery common to all species whose cells contain a nucleus, which includes all animals and plants. It is readily available, easy to maintain in the lab, and now, with the tools that Fink and others have developed, it is widely used in research labs throughout the world. Work in yeast has helped shape our understanding of the cell division cycle and gene regulation. It is often the first organism researchers use to study diseases, test out potential medicines, and engineer biofuels. As researchers develop new tools and approaches for research in yeast, the possibilities—like freshly kneaded dough—continue to rise.



Credit: Arabidopsis thaliana 2019-04-27 2246 by Salicyna, licensed under CC BY-SA 4.0

Mouse-ear cress or Arabidopsis (*Arabidopsis thaliana*), a small flowering plant, is typically considered a weed when found in the wild. Yet, in research institutes around the world, researchers are cultivating Arabidopsis by the trayful. The plant is not much to look at in a garden, but it does not take up much space, is simple to grow, reproduces quickly, and has a small and easy-to-manipulate genome. In other words, it's an ideal model organism, and so it has become a go-to model for plant research.

Gerald Fink, whose work was instrumental in making baker's yeast a premier model organism, also helped to cement Arabidopsis as a model. Fink supported Arabidopsis' promotion to the rank of model organisms; he wrote a piece in the journal Genetics in 1998 stating as much, in which he also explained the factors that made the plant such a successful system. Around the same time, Fink figured out how to engineer Arabidopsis to become more tolerant of salt and drought. This research could be applied to help protect crop plants, like wheat and rice, from the effects of climate change, such as more frequent droughts and seawater incursions into fields.



Credit: Conor Gearin/ Whitehead Institute

Arabidopsis is still plentiful in the Whitehead Institute greenhouse today. Whitehead Institute Members and plant biologists Mary Gehring and Jing-Ke Weng both use it. Gehring, in particular, does much of her research in Arabidopsis. Her lab uses the plants to investigate epigenetics, which is the study of heritable changes, often caused by chemical tags on the DNA, that affect how genes are expressed. Epigenetic markers can modulate whether genes are turned off or on and how strongly the genes are active. Plants including Arabidopsis use epigenetic mechanisms to control everything from seed size to the time it takes to reach maturity – traits that are important in our staple food crops.



Credit: Kathleen Mazza-Curll/Mansi Srivastava/Whitehead Institute

The three-banded panther worm (Hofstenia miamia) is an unassuming creature with a small, simple sausage-shaped body, but its biology may contain key insights into wound healing and regeneration. The species is able to regenerate any part of its body: cut off its head and the head will grow a new body, while the old body grows a new head. Whitehead Institute Member Peter Reddien and Mansi Srivastava, then a postdoc in his lab and now a professor at Harvard University, introduced the species as a model for regeneration research after they collected specimens from a pond in Bermuda. The researchers found three-banded panther worms to be a robust model for regeneration. Reddien relies on them, and Srivastava now uses them as the primary model organism in her lab. The insights that researchers gain into how these animals heal could lead to advances in the field of regenerative medicine.



Credit: Conor Gearin/Whitehead Institute

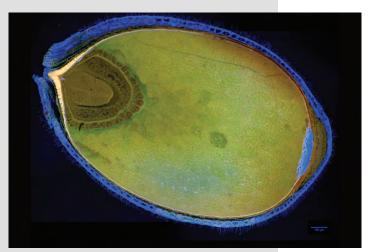
Reddien studies regeneration primarily in another species, the planarian (Schmidtea mediterranea), a small flatworm that has the same incredible regenerative capabilities as the three-banded panther worm and, on the surface, looks quite similar to it (in the images above, the planarian is to the right). But though the species may resemble each other, they are actually only very distantly related: their last common ancestor lived about 550 million years ago. Scientists often compare the biology of such distantly related species. The things they have in common have likely been conserved across time and through speciation events, and so may provide insight into the biology of other species with the same common ancestor. Reddien and Srivastava found that planarians and three-banded panther worms rely on some of the same signaling pathways to control regeneration, which suggests that their common ancestor-which is also the ancestor of most animals-may have used the same pathways. Later work from Reddien and then-postdoc Amelie Raz confirmed another similarity: the panther worms, like planarians, rely on muscle tissue to send the signals that help guide regeneration. The fact that three-banded panther worms diverged from most other animals so long ago makes them a particularly potent tool for understanding the evolution of regeneration and related biological processes.



Credit: Rebecca Povilus/ Whitehead Institute

Flowering plants are a cornerstone of our ecosystems and our diets, yet mysteries remain about how they evolved and quickly became the dominant plant species. Arabidopsis can help to answer many of those questions, but not all of them. Rebecca Povilus, a postdoctoral researcher in Whitehead Institute Member Mary Gehring's lab, wanted to explore the biology of a species that branched out from the flowering plant family tree early on, and has evolved separately since, to gain insights into how reproductive traits in flowering plants have evolved across species with distinct histories over time. The water lilies, a group that split from the other flowering plants long ago, seemed like a good group to study, but most water lilies are too large and they grow and reproduce too slowly to be suitable for use in the lab.

However, Povilus was in luck. As a graduate student, she came across *Nymphaea thermarum* (*N. thermarum*), a tiny water lily—possibly the world's smallest—with quick generation time and a relatively small genome, both good traits for research. Povilus is now breeding *N. thermarum* at Whitehead Institute and using the specimens in her research, but this model-in-the-making almost disappeared before it reached biologists' radar.



In this image of an N. thermarum seed, the embryo and surrounding endosperm are on the left in brown. Credit: Rebecca Povilus/ Whitehead Institute

A German botanist, Eberhard Fischer, discovered the water lily species growing around a hot spring in Rwanda in the 1980s. No *N. thermarum* were found growing anywhere else, and by 2009 the species had become extinct in the wild. Fortunately, Fischer had collected specimens. After some trial and error, horticulturists like Carlos Magdalena at the Royal Botanic Gardens, Kew figured out how to get the specimens to grow and flower in captivity. Without their efforts, Povilus would not have found her perfect research subject.

Currently, Povilus is using the lilies to study how genes are regulated in a tissue called endosperm, which controls nutrient supply to the developing seed. Much of our diet consists of endosperm: the seeds of rice, corn, wheat, and other cereal crops mostly consist of endosperm, so building a better understanding of how this tissue develops may have important implications for new agricultural advancements. Looking ahead, Povilus hopes that *N. thermarum* will become a widely used research model.

Tool and Method Development at Whitehead Institute

Where there's a will, there might need to be a new scientific way.

If Cells Could Talk

Whitehead Institute Member **Rudolf Jaenisch** has used pluripotent stem cells to generate numerous cell types and to create organoids, as well as chimeric mice with human cells that may model cancer better than cells in a dish. In the late 2010s, he turned his toolset to a condition called Rett syndrome, creating a reporter system to allow human neurons to relay how much of an important gene product is being expressed when treated with different drug compounds. Cells are constantly sending and receiving information to keep the body running smoothly. Researchers at Whitehead Institute are finding new ways to listen in on these communications, or even to tap into cells' biology and induce them to "report" to researchers about what is going on in the body.

Whitehead Institute Member **Jonathan Weissman** has engineered cells to provide researchers with a different kind of information: instead of reporting on the amount of a particular gene product, Weissman has created cells that record their family history in their DNA. Researchers can then "read" this history and use it to track instances of metastasis in cancer — the moment when cancer cells jump from a primary tumor to a secondary location in the body.

New ways to work in the lab

Deniz Atabay and colleagues in the lab of Whitehead Institute Member **Peter Reddien** developed a technique to give a planarian a new eye. The technique makes it possible to study growing photoreceptor cell axons in as controlled a situation as possible. "[With this method] you can take an eye from one animal and transplant it into another animal — with or without an eye — and the axonal projections from that eye will correctly wire themselves into the brain," he said.

Whitehead Institute Member **Jing-Ke Weng**, working in collaboration with Makoto Fujita at the University of Tokyo, has helped develop a method to figure out the molecular structure of plant natural products with a minuscule amount of material. The researchers call the technique the "crystalline sponge method." The method uses a material made of two complexes of macromolecules which form a lattice — the sponge — that can absorb and envelop molecules of different sizes.

Much of biology now takes place in the computational world, but the core research at Whitehead Institute still lies in the lab, where researchers conduct experiments using cells and reagents, interact directly with research organisms, and use a variety of hands-on methods to answer their questions. Sometimes, Whitehead Institute researchers encounter a question for which the right method does not exist yet. When this occurs, rather than being stymied, they tackle the challenge head-on and look to create a new technique to accomplish their goal. Read on to learn about new lab methods developed at the Institute in recent years that are helping researchers study the behavior of elusive axons, create biofuels from agricultural waste, solve the structure of mystery molecules, and reversibly edit the human genome.

In an effort to diminish greenhouse-gas emissions, it is possible to replace petroleum derived fuels with biofuels. For the creation of these cleaner fuels, you have fermentation microorganisms to thank. The lab of Whitehead Institute Founding Member **Gerald Fink** has developed a method to help these microorganisms create clean fuels from discarded plant matter, opening the door for a new source of renewable energy.

Whitehead Institute Member **Jonathan Weissman's** lab has created a new gene editing system: "We have developed an approach we call CRISPRoff that lets you direct CRISPR to a particular gene," Weissman said. "And instead of changing the DNA by cutting it, which is irreversible and has some toxicity, we can silence the gene [without changing the sequence]."

Scaling a mountain of data requires new computational tools

When Whitehead Institute researchers have found themselves asking questions that require making sense of large or complex datasets, often they have needed to develop the computational tools to do so themselves, or in collaboration with computer scientists. These include a variety of powerful algorithms and machine learning tools created in order to answer ambitious questions that otherwise could not be addressed. The problems they have tackled range from how cancer cells evolve and spread, to how RNA viruses shapeshift their genomes, to a number of questions in between.

Whitehead Institute Member **Jonathan Weissman** wanted a way to track cancer as it spreads and record the moments of change towards metastasis. The crux of the approach is a CRISPR-based tool developed by then-postdoctoral researcher in the lab Michelle Chan that barcodes cells with a "DNA scratchpad" to which the cells add new marks each time they divide, so that new generations of cells are marked differently than their predecessors. In this way, cells contain a record of their lineage in their DNA that can then be teased apart via complex computational methods. The tiny HIV genome has only nine genes, and yet it uses these to create fifteen proteins with which it can invade cells and reproduce. Former Whitehead Institute Fellow **Silvia Rouskin**, now a faculty member at Harvard Medical School, suspected that the virus was able to create so many different proteins by folding its RNA genome into different shapes, each of which left different sections of the genome available to be read and used to create proteins. In recent research Rouskin and collaborators showed that the conformation, or shape, of the RNA molecules is indeed behind this genetic flexibility. They introduced a new algorithm that can effectively identify and sort RNA molecules by shape.

Whitehead Institute Member David Bartel has

developed a tool that predicts the targets of microRNAs and the success with which each microRNA will regulate each target, based on research from his lab that revealed patterns in how microRNAs target messenger RNAs. The tool, called TargetScan, is co-run by the Whitehead Institute Bioinformatics and Research Computing group and has been made available online for any researcher. In order to better study complex diseases such as multiple sclerosis, former Whitehead Fellow and current Whitehead Institute Member **Olivia Corradin** developed the outside variant approach, a model that can determine which cell types different disease-associated genetic variants are acting in, potentially revealing unrecognized disease pathways.

Our People

Our People

At the heart of Whitehead Institute are the scientists, trainees, and technical experts who drive our research forward. Read on to learn about the achievements and perspectives of individual members of our community, and about our efforts to ensure that each person at Whitehead Institute can pursue their full potential within an equitable and inclusive "One Whitehead" environment.

New Whitehead Institute Members



Whitehead Institute Member Olivia Corradin Credit: Gretchen Ertl/Whitehead Institute



Whitehead Institute Member Siniša Hrvatin Credit: Gretchen Ertl/Whitehead Institute

Whitehead Institute appoints two new Members *Two dynamic scientists join the Institute*

Olivia Corradin, a Whitehead Fellow since 2016, became a Member in July 2021. Siniša Hrvatin, an instructor and postdoctoral fellow at Harvard Medical School through December 2021, joins the Institute in January 2022.

"Olivia and Siniša are creative, collaborative, and highly accomplished early-career scientists," says Institute director Ruth Lehmann. "Each has impressed us with their drive, intellect, and their scientific vision. We look forward to their contributions — as researchers, educators, and colleagues for many years to come."

Corradin, also an assistant professor of biology at Massachusetts Institute of Technology (MIT), investigates genetic variants - small differences in DNA sequence, which can prompt disease-causing changes in gene regulation. During her five years as a Whitehead Fellow, her lab defined the concept of "outside variants," which help to explain how genetic variants increase one's likelihood of developing disease. She also developed a method to identify the cell type affected by a specific disease-linked variant, and then used it to single out oligodendrocytes as one type of brain cell involved in multiple sclerosis. Most recently, Corradin created an approach for defining epigenetic variation - which is caused by factors other than DNA sequence changes - in some individuals with opioid use disorder; this will help researchers identify genes associated with the disorder. Corradin earned a PhD at Case Western Reserve University,

where she researched genetic and epigenetic dysregulation in human disease and pioneered approaches to predict gene targets of regulatory DNA sequences associated with variants.

"I'm incredibly excited to be stepping into this new stage at Whitehead Institute and MIT," Corradin says. "I look forward to continued collaboration and to becoming a part of the rich history that shapes our Institute."

Hrvatin investigates how organisms enter torpor and hibernation and how their cells adapt and survive in these states. As a postdoctoral research fellow at Harvard University, he established an experimental paradigm for studying hibernation-like behavior in mice and discovered the neurons that control entry into this state. He also pioneered the Paralleled Enhancer Single Cell Assay platform to generate cell-type-specific AAV vectors for targeted human gene therapy and to control defined neuronal cell types across species. Previously, as a postdoctoral associate at MIT, he investigated approaches for targeted siRNA delivery to pancreatic beta cells. He also founded ReadCube, a startup that provides access to scientific literature and develops reference management tools. He earned a PhD in stem cell and regenerative medicine from Harvard University, studying directed differentiation from human embryonic stem cells to pancreatic beta cells.

"I look forward to continued collaboration and to becoming a part of the rich history that shapes our Institute," Corradin says. "I've always been inspired by the exceptional scientists, educators, pioneers, and visionaries at Whitehead Institute and MIT Biology," says Hrvatin, who will also become an assistant professor of biology at MIT in January 2022. "I am absolutely thrilled for the opportunity to learn from and become a part of this extraordinary community."

Whitehead Fellows Program



Tobiloba Oni Credit: Gretchen Ertl/Whitehead Institute

Whitehead Fellows Program: Transitions

The Whitehead Fellows program is renowned for preparing emerging leaders in biomedical research and education. This past year has been filled with positive change for the early career investigators who have led independent labs at Whitehead Institute.



Olivia Corradin becomes a Whitehead Institute Member and assistant professor of biology at MIT



Silvia Rouskin becomes an assistant professor at the Harvard Medical School department of microbiology

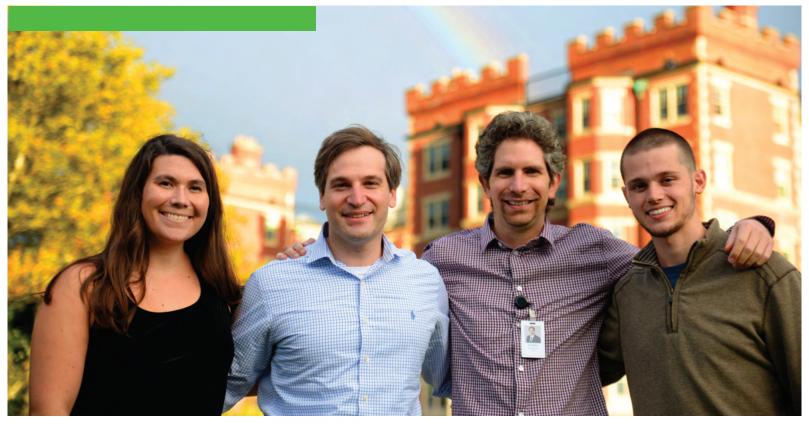


Kristin Knouse

becomes an assistant professor of biology at MIT and a member of MIT's Koch Institute for Integrative Cancer Research



Tobiloba Oni joins the Institute as a Valhalla Fellow



Weiskopf Lab members at the Whitehead Institute Annual Retreat. Credit: Madeleine Turner/Whitehead Institute

Diversity, equity and inclusion at Whitehead Institute

Continuously striving to be better

An action plan for diversity, equity, and inclusion

Ideally, our nation would have learned to appreciate and accept people's differences; the scientific community would have implemented ways to ensure equity of opportunity; and our organization would not need a plan for creating a fully fair, open, and inclusive culture.

"But neither is the case," notes Institute director Ruth Lehmann, "and Whitehead Institute must no longer simply accept the ways that people are treated unfairly. We must continuously strive to be better—fairer, more open, and more equitable."

In July 2021, the Institute introduced its Strategic Action Plan for Diversity, Equity, and Inclusion (DEI) to guide that effort. The Plan has its roots in the decision that Lehmann made, soon after she became director, to hire the DEI consulting firm Jones Diversity, Inc. To clarify the Institute's DEI challenges, the firm conducted an online survey and interviews with 100 employees. Having evaluated that data, Jones Diversity made a series of specific recommendations for action. The Plan, which was developed in full consultation with Institute faculty, incorporates all of those recommendations.

"It is imperative that we achieve real, meaningful change," says Lehmann, "and this Plan will help us do that. The faculty and I are fully committed to it. I have great confidence that, if each member of our community strives toward the goal of realizing a fair and open culture, we will succeed."



Cheeseman Lab members at the Whitehead Institute Annual Retreat Credit: Madeleine Turner/Whitehead Institute

Postdoctoral program

Ready, set, ... repeat: ups and downs of the scientific process

Scientists look to discover the unknown. Exploring uncharted territory means that researchers can hit a lot of unexpected roadblocks, and even dead ends, en route to their findings. Learning to deal with these setbacks is an important part of becoming a scientist. Below, a few of Whitehead Institute's postdoctoral researchers respond to questions about how they have handled research failures and navigated other common challenges of research life.



Rebecca Povilus (Gehring lab)

What's the biggest disaster you've ever had in the lab?

I was doing a procedure called an in situ hybridization. With the particular types of samples I was working on, this was maybe a four-day protocol. This time I had changed to using a new type of sample holder for some of the last steps. What I hadn't realized was that the plastic they were made of would be dissolved by one of the solutions I was using. So near the end of the procedure, I put in this solution, and I immediately see the plastic wells dissolving. After four days of work I watched my samples become encased by plastic goop and get completely ruined. I remember telling myself that I'm going to clean this up, and then I'm going to go get myself a candy bar. Of course, sometimes you can learn just as much from failed experiments as you can from successful ones. Sometimes they can be more informative, if you take the time to try and figure out why the experiment failed. I'll admit that there wasn't a lot to learn from the dissolving-plastics incident, but I do pay a lot more attention to "best practice" notes for handling materials now.



Jason Matos (Weng lab)

How do you approach those moments when your experiment does not go as expected?

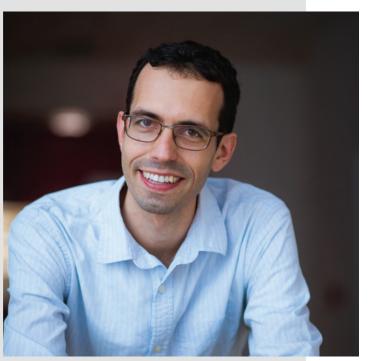
Almost every project I've been involved in has not turned out how we first envisioned it, and things that were problems have actually been signs of something interesting. Initially, you're frustrated and you want the problem to go away, but as it persists, you accept it and pursue the mysterious, and sometimes good things happen. Of course, when people talk about how a mistake or a confusion led to great results, this is true, but it may also be overly romanticized. After you get the great result, you feel exhilarated, but in the beginning, you're so frustrated that you consider quitting. These situations always look better in hindsight.



Whitney Henry (Weinberg lab)

In spite of your successes thus far as a scientist, do you still experience imposter syndrome?

All the time. I've gotten better at recovering, though. It was worse in grad school, with the transition to Harvard from a small HBCU (historically black college or university) in rural Louisiana. With this move came many insecurities, so I think I faced imposter syndrome almost every day. I remember feeling scared about my technical skills at the start of grad school: What if I didn't know something I should have? What if I asked a stupid question? Now, when I feel imposter syndrome coming on, I use logic to deal with it. I tell myself, this may be how you feel, but look at the facts, at your record and accomplishments; there's no way this was all an accident.



Evgeni Frenkel (Sabatini lab alumnus)

How do you balance the demands of postdoc life with your outside life?

In 2019, my wife and I welcomed our son, and this year we welcomed our daughter. They are a blessing, but also a huge responsibility. My wife is a surgeon and a scientist, which are demanding jobs. Life is full of choices and challenges. We simplified our commutes by living close to work for both of us. We have a wonderful nanny and do a lot of tapping in, tapping out with baby care. She comes home, I go back to the lab, vice versa. We love seeing our kids grow and making sure they are happy and learning. It is hard to describe the wonderment of a child seeing every aspect of the world for the first time.

Whitehead Institute Board of Directors Update



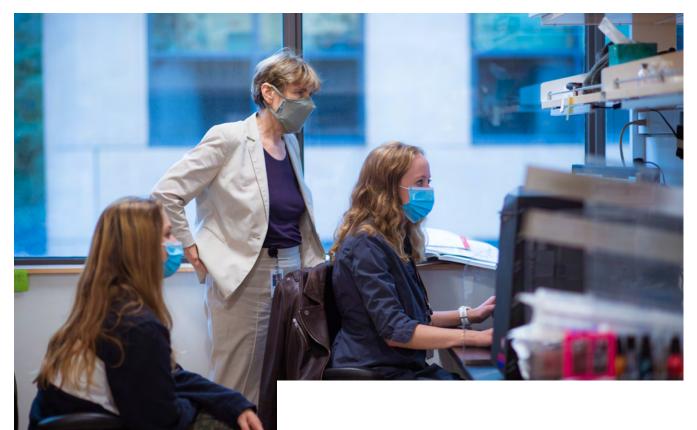
Boston Children's Hospital president and CEO Kevin Churchwell joins Whitehead Institute Board of Directors

At its June 9, 2021 meeting, the Whitehead Institute Board of Directors elected Kevin B. Churchwell, MD, president and chief executive officer (CEO) of Boston Children's Hospital, to a six-year term.

Churchwell, who previously served as the hospital's executive vice president of health affairs and chief operating officer, is also an associate professor of anesthesia and of pediatric anesthesia at Harvard Medical School.

Prior to joining Boston Children's, he was CEO of the Nemours/Alfred I. duPont Hospital for Children in Wilmington, Delaware and of Monroe Carell Jr. Children's Hospital at the Vanderbilt University Medical Center in Nashville. A graduate of MIT and Vanderbilt Medical School in Nashville, Churchwell completed both his residency and clinical fellowship at Boston Children's Hospital. During a recent Director's Dialogue conversation with Ruth Lehmann, Churchwell spoke about the relationship between fundamental science and clinical care, his priorities for Boston Children's Hospital, and his hopes for Whitehead Institute. Visit annualreport.wi.mit.edu to view a clip from that conversation where Churchwell touches on the importance of the Institute's curiosity-driven work.

Our Impact



Our Impact

Whitehead Institute's accomplishments reflect both the exceptional talent it attracts and its unique spirit that fosters connections inside Whitehead and beyond. In a supportive, collaborative, and collegial environment, our researchers are driving major discoveries, creating important new research tools and methods, and spurring translation of their work into new therapeutics. Here are a few snapshots of our impact this year and our plans going forward.



Ruth Lehmann Credit: Gretchen Ertl / Whitehead Institute



Sarah Williamson Credit: Courtesy of Sarah Williamson

Year one reflections

Institute director and president Ruth Lehmann and board chair Sarah Keohane Williamson first undertook their roles on July 1, 2020. Their initial year was one of unprecedented challenge, but also of significant accomplishment. Williamson and Lehmann sat down to discuss some of the year's notable achievements. **Sarah Keohane Williamson:** Although 2021 brought plenty of challenges, it was a year in which Whitehead Institute also had significant successes.

Ruth Lehmann: I agree. And I think the events of the past year have reaffirmed the importance of our mission to be a trailblazer in science.

SKW: For you, what does it mean to be a trailblazer in science?

RL: I believe it has three parts. First, investing in new biology: Supporting curiosity-driven, investigator-initiated research, and encouraging scientists to think big, to take on significant, difficult problems. Second, creating strong connections: Fostering innovative science through collaboration beyond traditional boundaries; partnering to apply knowledge we've created; and disseminating new, enabling technologies. Third, building a "One Whitehead" community: Creating an inclusive, respectful and diverse culture that inspires individuals to achieve their full potential; and training the next generation for careers in science as researchers, inventors, mentors, and educators.

SKW: I've been really impressed by how much Whitehead has accomplished this year against this mission. What stands out most clearly to you?

RL: Most notably, we've continued to invest in new biology despite the challenges of COVID-19 and we've overcome most of the pandemic-created hurdles. Ninety-nine percent of our people are vaccinated; our labs are fully operational; and our investigators are pursuing COVID-related projects investigating the basic mechanisms of infection and identifying new therapeutic strategies. In addition, this fall, we were able to hold our annual scientific retreat for all of our researchers. It's such a significant part of our collaborative culture and — despite the fact that we were all wearing masks and keeping our distance — there was a palpable sense of joy in the room.

This year, we've also launched our Initiative on the Biology and Health of Climate Change. The world knows that climate change is driving intense fires, hurricanes, and floods. But what are its biological effects — and how will they impact human health? We are both exploring that question and beginning to build the foundations for biomedical and biotech interventions to address those developing problems. The Initiative is a great example of how we're encouraging scientists to think big and how we're fostering innovative science through new kinds of collaboration.

SKW: This initiative is very exciting and its potential benefits — from ensuring adequate food supplies to halting the spread of emerging infectious diseases — are extraordinary. What's fascinating is that working on these very practical challenges is a natural extension of the fundamental biological research that Whitehead Institute has excelled at for nearly 40 years.

RL: One other significant accomplishment in 2021 has been our work toward having an inclusive, respectful and diverse culture that inspires individuals to achieve their full potential. We have developed and are implementing a comprehensive strategy for ensuring that the Whitehead Institute community is diverse, equitable, and inclusive. This has been and will continue to be one of my top objectives as director.

SKW: For our part, the board brings dynamic and diverse voices to our governance; and we are completely in sync with the strategy you are pursuing. We also fully support the difficult decisions that are sometimes necessary. For example, the Institute parted ways with an accomplished senior scientist this past summer — but doing so made clear how committed we all are to maintaining a truly equitable and inclusive culture.

RL: Having a strong culture is essential if we are to continue being a world-class scientific organization that attracts the best and brightest scientists. I'm really pleased about the three new primary investigators we hired in 2021. Siniša Hrvatin, who joins us from Harvard, studies the biological mechanisms underlying hibernation. Olivia Corradin, who has been a Whitehead Fellow and now joins as a Member, develops computational methods for understanding the genetic origins of disease. And Tobiloba Oni, our newest Whitehead Fellow, develops ways to prompt the immune system to fight cancer. Each of them is skilled, committed, collaborative, and creative. They really represent what the Institute is all about. **SKW:** That fact — and the continuing flow of new discoveries and new research tools that Whitehead Institute produces—is what makes my work as board chair so fulfilling. Beyond the board's ongoing governance and oversight work, our job is to empower Whitehead science for the long term. In particular, that means ensuring that these fantastic scientists have the resources and facilities necessary to perform world-class research over time.

Philanthropy at Whitehead Institute

Our bold objectives

A letter from Churchill Franklin, chair, Whitehead Institute Board of Directors' Development Committee

This past year made clear the impact that foundational biological research can have on the wellbeing of virtually every person on this planet. And it's exciting to be part of an organization that pushes back the frontiers of biomedical discovery.

It has been energizing, too, to experience the leadership offered by Ruth Lehmann as Institute director and Sarah Keohane Williamson as board chair. They are offering a clear vision of how Whitehead Institute will move forward as an inclusive and cohesive research community that is well positioned to meet the scientific challenges of the coming decade. They are, as well, meeting head-on the important decisions that define both the Institute's culture and its capacities.

The cornerstone for those decisions is a sharpened articulation of the Institute's mission-based objectives. Those objectives will include investing in cutting-edge and innovative science that impacts global health, building research collaborations beyond traditional boundaries, and nurturing a culture that inspires and empowers individuals to achieve their full potential.

The purpose of the board's Development Committee is to help ensure that Whitehead Institute scientists have the long-term financial and technical resources necessary to achieve those objectives. In other words, enabling them to build on the Whitehead tradition of excellence.

RL: I have to say, I'm very excited about 2022 and beyond.

SKW: I am too, and I hope everyone will stay tuned to the important developments coming in the year ahead.



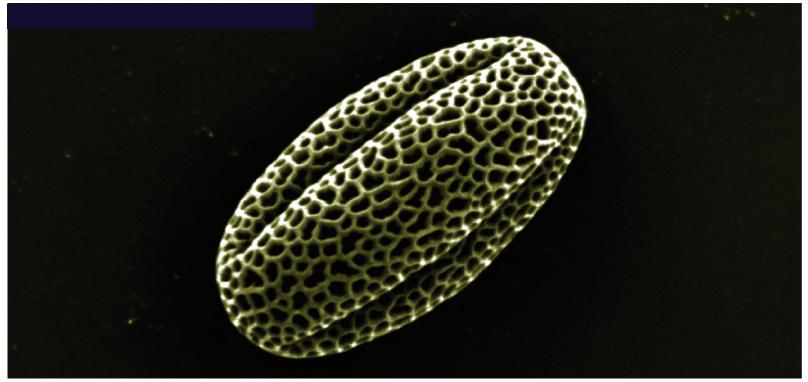
Fundraising since the outset of FY 2021 has been very successful, with strong annual giving and a series of seven-figure major gifts, grants, and pledges supporting both our scientists and our high-impact research programs.

In the next few years, we aim to maintain and build on that strong foundation: cultivating the significant contributions necessary to ensure the Institute's continuing ability to provide the facilities and research technologies our pioneering scientists require. Such strategic-level support will enable Whitehead Institute to continue providing state-of-the-art spaces for principal investigators' and trainees' research; turn our core facilities into robust innovation centers; create common spaces with enhanced capacities for multi-site collaboration and synergistic encounters; and make our operations both more sustainable and more resilient to future pandemics.

In other words, in coming years we aim to take our fundraising to new heights — and invite you to join us in this bold endeavor.

Churchill Franklin

Annual Report



Pollen grain. Credit: Joseph Jacobowitz/Whitehead Institute

Foundation support

Grantham Foundation underwrites ambitious carbon-sequestration project at Whitehead Institute

A pioneering effort to develop decay-resistant plants

Plants are highly effective at capturing atmospheric carbon, one of the major contributors to the temperature increase driving global climate change. But when plants die and decay, much of that carbon is again released into the atmosphere.

Whitehead Institute Member Jing-Ke Weng has conceived a way to bioengineer plants to keep a significant portion of their carbon locked up, essentially permanently. If successful, the approach could be translated into practical applications that help reverse the increase in carbon that has prompted rising atmospheric temperatures.

Seeing great potential in Weng's concept, the Grantham Foundation for the Protection of the Environment is underwriting a pioneering, three-year proof-of-principle project designed to produce prototype plants. The Foundation was established in 1997 by Jeremy and Hannelore Grantham. Jeremy is co-founder and chairman of investment management firm GMO, LLC, and an elected member of the American Academy of Arts and Sciences. In 2016, he was appointed Commander of the Order of the British Empire (CBE) for leadership in climate change activities; and, with Hannelore, received the Carnegie Medal for Philanthropy in 2017. "This project is an example of the high-risk/high-reward work that needs to be done to mitigate the negative effects of climate change," says Institute director Ruth Lehmann.

"This project is an example of the high-risk/high-reward work that needs to be done to mitigate the negative effects of climate change," says Institute director Ruth Lehmann. "The Grantham Foundation's support represents the kind of up-front investments in foundational and translational research that philanthropists must make now if we, collectively, are to meaningfully reduce the threats posed by increasing atmospheric temperature."

Weng, who is also an associate professor of biology at MIT, explains that, "Globally, the emission rate of carbon due to natural decomposition of woody biomass is estimated to be eight times that of fossil fuel consumption. Thus, while it is an extraordinarily ambitious goal, if humanity can plant new forests and crops bioengineered to accumulate decay-resistant biomass equivalent to 15 percent of the current global woody vegetation, we will be able to achieve negative carbon emission."

The carbon fixed in plants is primarily stored in the form of two biopolymers (polysaccharides and lignin) that are subject to decay. However, plants also produce a small quantity of other biopolymers that are naturally more resistant to degradation — and that could be bioengineered to sequester greater amounts of carbon. Sporopollenin is one such polymer; its extreme inertness makes it an attractive target for engineering plants as a permanent carbon sink.

In natural plants, sporopollenin accounts for just a tiny fraction of the total biomass. But the Grantham-funded project aims to bioengineer plants that hyperaccumulate sporopollenin.

Compared to other carbon sequestration technologies, Weng says, "Plant-based carbon fixation technologies can be scalable with very minimum inputs and maintenance. Plus, the resulting decay-resistant biomass could be buried in place or used for industrial purposes such as building material or other products."



Awards and recognitions

Ruth Lehmann

Francis Amory Prize in Reproductive Medicine and Reproductive Physiology, Genetics Society of America's Thomas Hunt Morgan Medal, Vilcek Prize for Excellence in Biomedical Science

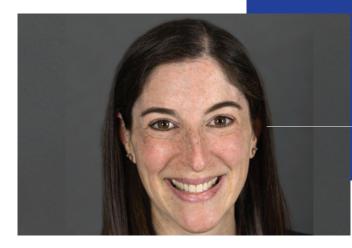
Ruth Lehmann received the Genetics Society of America's Thomas Hunt Morgan Medal for lifetime contributions to the field of genetics. The Morgan Medal, one of the most prestigious awards for career achievement in genetics, was bestowed in recognition for Lehmann's groundbreaking work revealing the unique biology of the specialized cells that give rise to egg and sperm, known as germ cells. She also received the 2021 Vilcek Prize for Excellence in Biomedical Science for unraveling the molecular basis by which germ cells are formed. The award is made by the Vilcek Foundation to honor the outstanding contributions of immigrants to biomedical science. Lehmann, who was born and educated in Germany, was also honored with inclusion in the Carnegie Corporation's 2021 list of Great Immigrants, Great Americans-which celebrates the lifetime and career contributions of "naturalized citizens who live their lives in service to society." Those honored were featured in a full-page spread in the New York Times on July 4, 2021. Lehmann was also awarded the Francis Amory Prize in Reproductive Medicine and Reproductive Physiology by the American Academy of Arts and Sciences. Lehmann shared the prize with longtime friend and colleague Gertrud M. Schüpbach, emeritus professor at Princeton University. They were recognized for their contributions to areas including DNA repair, embryonic development, RNA regulation, and stem cell research.



Deniz Atabay

John Hatch Memorial Prize from the Genes in Space program

Postdoctoral researcher Deniz Atabay received the 2021 John Hatch Memorial Prize from the Genes in Space program. The prize recognizes Atabay, a member of Peter Reddien's lab, as a veteran mentor in the program, which challenges middle- and high-school students to design molecular biology experiments addressing obstacles in space exploration. The program's overarching goal is to inspire young minds to solve real-world problems in the biological sciences while expanding research capabilities on the International Space Station and beyond.



Awards and recognitions

Rebecca Harris

NIH Building Interdisciplinary Research Careers in Women's Health award

Postdoctoral research fellow Rebecca Harris received an award from the NIH's Building Interdisciplinary Research Careers in Women's Health program. The NIH program supports the work of high-achieving early-career researchers investigating women's health and sex differences in health and disease. A physician-scientist, Harris divides her time between Boston Children's Hospital and the Institute's Brit J. d'Arbeloff Center for Women's Health. As an endocrinologist, she works primarily with children, adolescents, and young adults undergoing gender transition. As a researcher in the lab of David Page, she examines gene expression in white blood cells, seeking clues to why diseases differ between women and men.



Sebastian Lourido

Burroughs Wellcome Fund 2021 Investigator

Sebastian Lourido was named a Burroughs Wellcome Fund 2021 Investigator in the Pathogenesis of Infectious Disease. The award supports higher-risk research projects that could significantly advance knowledge on infectious diseases. It provides researchers an opportunity to explore how human and pathogens interact and evolve, potentially leading to new ways to treat—or even prevent—major infectious diseases. Lourido's project will begin to map the many ways that the parasite *Toxoplasma gondii* interacts with its host's genes. The ultimate goal is defining how genetic diversity affects an individual's susceptibility to infection and how virulent the resulting disease will be.



Awards and recognitions

Harvey Lodish

Wallace H. Coulter Award for Lifetime Achievement in Hematology, Foreign Member of the Royal Academy of Medicine of Belgium, MITx Prize for Teaching and Learning in MOOCs

Harvey Lodish received the American Society of Hematology's highest honor, the Wallace H. Coulter Award for Lifetime Achievement in Hematology. The award recognizes an individual who has demonstrated a lasting commitment to the field of hematology through outstanding contributions to education, research, and practice. Lodish is being honored for his mentorship of more than 200 students and fellows, as well as his six decades of key contributions which have provided important insights into several red blood cell diseases. He was also elected as a Foreign Member of the Royal Academy of Medicine of Belgium in recognition of his pioneering role in the field of molecular cell biology, his seminal contributions to understanding protein translation and protein traffic processes, and his discovery and cloning of cell surface receptors for many hormones and cytokines. Finally, Lodish and colleagues earned the 2021 MITx Prize for Teaching and Learning in MOOCs for creating the globally available online course, The Science and Business of Biotechnology, a multidisciplinary exploration of the complexities of developing and marketing new biotech products.



Robert Weinberg

Japan Prize Foundation award

Robert Weinberg received a Japan Prize Foundation award for his cancer research. The Foundation cited his contributions to the development of a multi-step model of how cancer begins and progresses, and the application of that model to improve cancer treatments and outcomes. His work, the Foundation observed, has led to the identification of critical genes for cancer development, which have subsequently become targets of new therapies that saved thousands of lives. He is also credited with major contributions to the development of new areas of cancer research and to the broader field of precision medicine.

Whitehead Institute by the numbers

Whitehead Institute is a powerhouse of biomedical science, with a record of achievements belying its size. Our faculty is, per capita, one of the most honored groups of scientists in the world. Our record of discovery and innovation is unparalleled. The impact of our intellectual property far exceeds the expected returns of our research expenditures: with dozens of pharma and biotech companies catalyzed and an increasing stream of therapeutics developed, in clinical trials, or on the market. Below are a few of the metrics demonstrating Whitehead Institute's extraordinary performance.

Patents issued $32^{in 2020-21}$

2 National Medal of Science recipients

Investigators of the
 Howard Hughes
 Medical Institute

2 MacArthur Fellows IP revenue in 2020, in millions of dollars 12.9

Active companies founded by Whitehead Institute faculty 15 +

> National Academy of Sciences members

> > Searle Scholars 6

Outreach programs

Public programs at Whitehead Institute

For almost three decades, Whitehead Institute has maintained a steadfast commitment to science education and outreach by providing learning opportunities designed to enhance science teaching and literacy for the entire community.

With a variety of programs ranging in scope from lectures and workshops for teachers and students to special events for non-scientists, Whitehead Institute offers its participants first-hand exposure to state-of-the-art research. Through the Institute's K-12 programming, students are inspired to pursue their interest in science, technology, engineering, and math (STEM) and further explore scientific careers. Given the nation's increasing commitment to STEM, Whitehead Institute believes hands-on scientific programs are crucial for developing critically thinking young adults and cultivating the next generation of scientists.

Below is a sample of our offerings:

Seminar Series for High School Teachers

This monthly program offers educators the opportunity to explore topics at the forefront of biomedical research. Interested educators are paired with Whitehead Partners—Whitehead scientists who serve as a resource during the school year. Partners are eager to answer questions, discuss their fields of expertise, and even visit schools to meet with students. The series, which attracts 50-60 high school teachers each year, begins in October and lectures are held the first Monday of every month through June.

The 2021-2022 virtual lecture series, Advances in Agricultural Biotechnology: Emerging tools and methods for climate remediation, will explore how researchers in a range of fields are applying new approaches and techniques to the problems of climate change and sustainability.

Designed as a two-week exploration into the amazing biology that thrives in the world around us, this summer science program for rising 7th and 8th grade students provides immersion in laboratory experiments, hands-on activities that take students both inside and outside the classroom, and discussions with scientists. It allows students to learn first-hand how researchers are answering some of biology's most challenging questions—and have an awful lot of fun doing it!

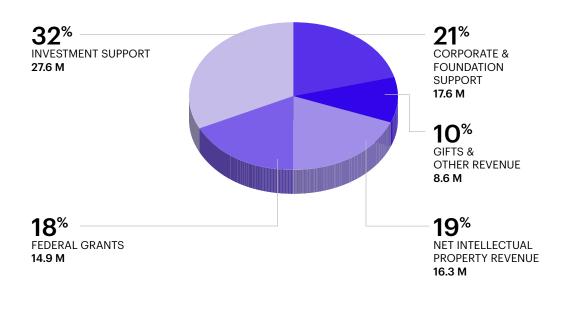
High School Student Program	This program offers students an opportunity to learn about cutting edge topics in biomedical research. The three-day program, held over spring vacation, features lectures from leading scientific experts, hands-on laboratory sessions, visits to local biotech companies, and opportu- nities to meet with young Whitehead scientists. The 2021 series, Nature's Library: Biodiversity in Biological Research, explored how scientists are working to push our understanding of the natu- ral world further, learning all we can from biodi- versity and why it's more important than ever to conserve it.
BioNook	BioNook is Whitehead Institute's online biology resource, offering exciting learning enrichment for students, parents and teachers. Find videos, podcasts and stories on Whitehead Institute science, as well as virtual workshop opportuni- ties, through BioNook's After School Science Club, and ideas for nature-based activities.

Financial Summary



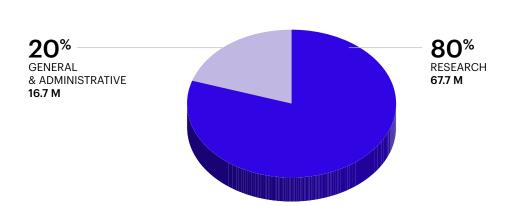
Revenues & Support

2021 TOTAL **\$85.0 M**



Operating Expenses

2021 TOTAL **\$84.4 M**



2020

Investment Support 24.5 M [33%]

Corporate & Foundation Support 13.8 M [19%]

Gifts & Other Revenue 12.9 M [17%]

Net Intellectual Property Revenue **9.0 M [12%]**

Federal Grants **14.1 M [19%]**

TOTAL \$74.3 m [100%]

2020

Research 58.8 M [81%]

General & Administrative **14.2 M [19%]**

TOTAL \$73.0 m [100%]

Whitehead Institute Leadership

DIRECTOR

Ruth Lehmann

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