Whitehead Institute

Annual Report

2022

Thriving in the pursuit of excellence

Whitehead Institute is a special place — the atmosphere is energetic and exciting, the culture synergistic and collaborative, the community diverse and inclusive.

Our principal investigators are among the world's most talented and accomplished researchers — with intelligence, creativity, and scientific passion that is off-the-charts. Along with our postdoctoral researchers and staff scientists, they are creating knowledge that improves human wellbeing: catalyzing new ways to address conditions from cancer and diabetes to neurodegenerative and infectious diseases; working to improve food crop production; and striving to understand how cells and tissues rejuvenate.

They are also furthering the conduct of biomedical research by creating highly effective tools and methods that are used by scientists around the world — advancements ranging from CRISPR-based methods for regulating gene expression to mechanisms for understanding how cells organize into tissues and organs.

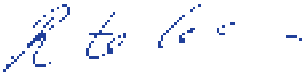
This Annual Report offers a retrospective snapshot of the scientific questions the Institute has been pursuing and the many achievements it has realized. But it also provides a lens on where we are going, scientifically, and on the community we are becoming:

Whitehead Institute is forging new frontiers in science and making paradigm-shifting discoveries — asking big, ambitious questions and figuring out how to answer them.

We are becoming a model biomedical research community: a collaborative, inclusive organization that empowers everyone within it to thrive in the pursuit of excellence.

These are brief articulations of the overarching mission and the values to which Whitehead Institute is committing itself. I encourage you to read the full statement of our mission and values in this report.

Please view this Annual Report as an introduction to who we are and what we have accomplished over this past year — and to what we can accomplish in pursuing our bold mission into the future.



Ruth Lehmann
President and Director

Our Mission and Values

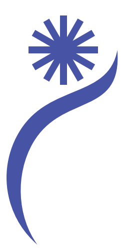
Since its founding in 1982, Whitehead Institute has been renowned for pioneering discoveries in fundamental biomedical science. In 2022, looking forward, Institute director Ruth Lehmann asked the community to consider the overarching objectives and culture that would best empower bold, creative scientists to address the biology-based challenges humanity will face in coming decades.

That process—which engaged principal investigators, staff scientists, trainees, administrative staff, and the board of directors—resulted in a contemporary restatement of our long-standing mission: It specifically articulates our purpose, who we are, what we do, and how we do it. We are excited to present this restatement of Whitehead Institute's mission and the values we deem essential to our success.

Whitehead Institute's mission is to forge new frontiers in science, uncovering insights today that unlock the potential of tomorrow.

We are a biological research institute dedicated to making paradigm-shifting insights into the fundamental principles of life. Our advances in genetics and genomics are now enabling us to tackle the complexities of life with unprecedented depth and breadth. We do this work to benefit society—addressing challenges of global scope from disease to climate change. We cultivate a diverse, open community and foster a deeply curious and collaborative culture in which high-potential ideas are given the space to take shape.

These are our Values



Ingenuity

We are problem solvers. We seek to identify novel approaches and inventive solutions. We are proactive and nimble, unafraid to shift priorities and resources to face new challenges.

Belonging

We empower everyone in our community to thrive. We strive to create a welcoming and familial environment, believing in reciprocity over competition. We treat others with dignity and respect—taking ownership over our individual actions and their impact. We embrace a diversity of people and ideas and encourage everyone's voice to be heard.

Courage

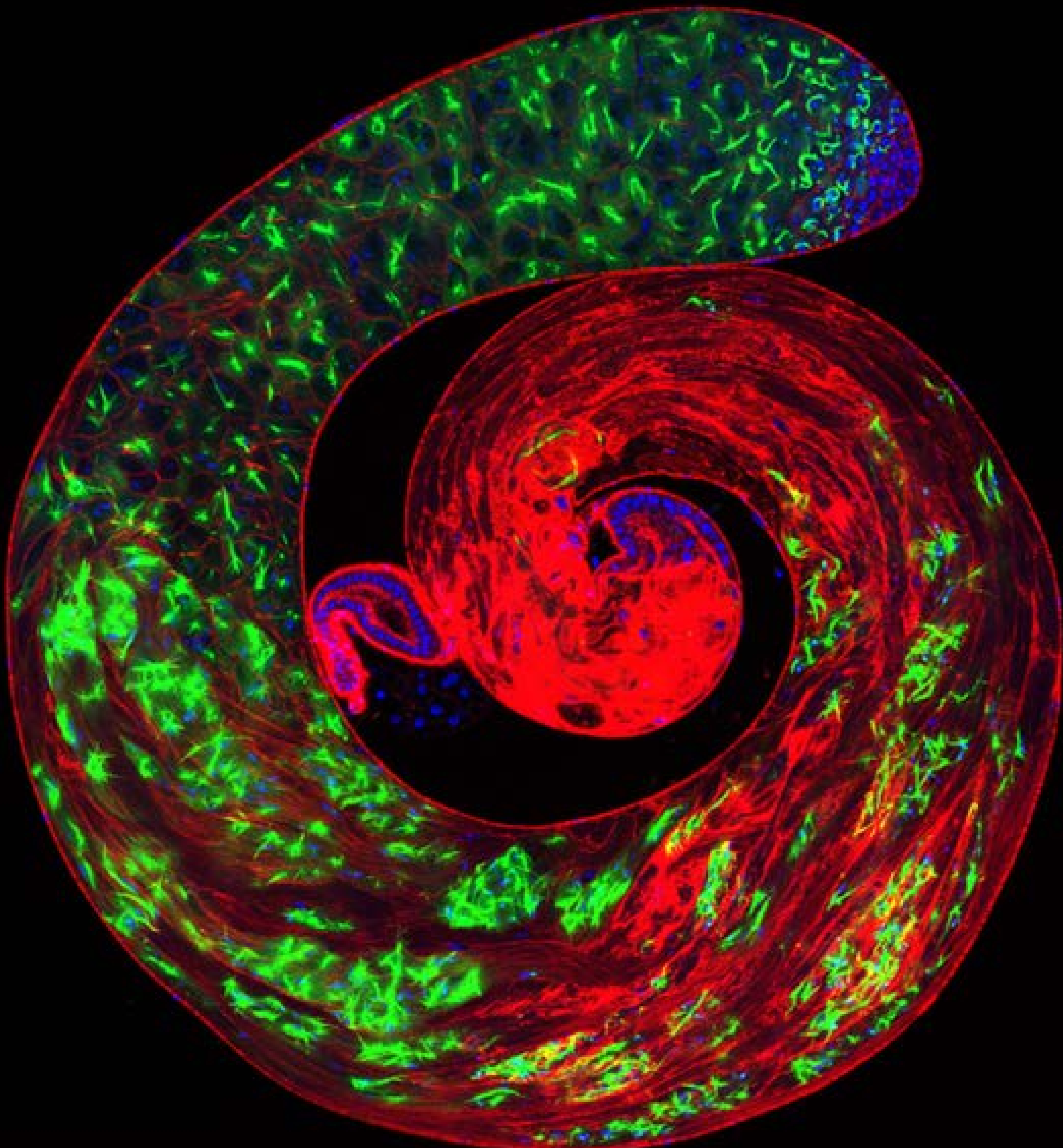
We are willing to take risks, make mistakes, and learn from them. We believe in breaking boundaries. We approach every challenge with boldness, rigor, and integrity. We don't give up, learning from our mistakes and retooling when necessary.

Learning

We are eternal learners and compassionate teachers, training the next generation of innovators. We value a training environment that fosters curiosity, innovation, and open-mindedness. We believe that a collaborative training environment emboldens our community to make a meaningful impact on science and society.

Our Science

Whitehead Institute forges new frontiers in science, uncovering insights today that unlock the potential of tomorrow. Our scientists make paradigm-shifting insights into the fundamental principles of life — seeking to tackle the complexities of life and to address challenges of global scope from disease to climate change. Explore the following updates on our principal investigators' accomplishments; then enjoy a selection of news stories and features on Whitehead Institute science in 2022.

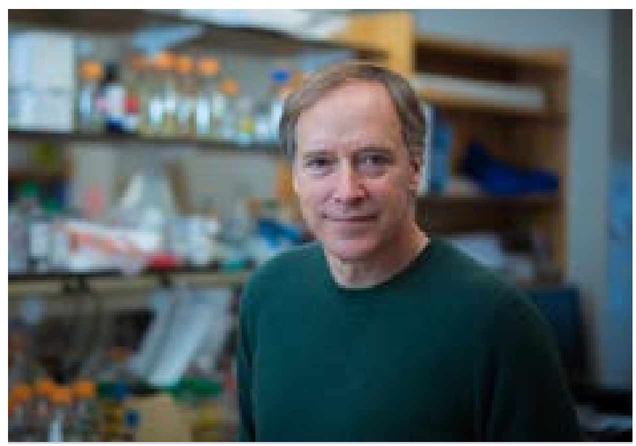


2022 Research highlights

This year we welcomed new people, new discoveries, new methods, and more. In this feature, Whitehead Institute Members and Fellows discuss facets of their labs' work, and other activities they have been pursuing over the past year about which they are particularly excited. In order to learn more, visit the collection of audio clips in the digital version of this report in which the researchers describe the highlights of their year.

Lindsey Backman, Valhalla Fellow

My research focuses on the biochemical strategies that bacteria exploit to compete with other microbes within the human microbiome. We're using a combination of structural, biochemical, and genetic techniques to probe these questions. Understanding the strategies that pathogens exploit to outcompete beneficial bacteria could lead to novel therapeutic targets.



David Bartel, Member

We've found that targeted destruction of microRNAs is important in animal development. Normally microRNAs direct the destruction of messenger RNAs, but we observed six fruit fly microRNAs that direct destruction of other microRNAs. If one of those is mutated and cannot direct microRNA destruction, embryonic flies develop defects. We're eager to study other effects related to microRNA destruction.

Iain Cheeseman, Member

Our lab has always been interested in the process of cell division and chromosome segregation. You may assume core cellular processes happen the same way over and over again. But those processes are not as constant or identical as anticipated—this has become a dominant theme across all projects in the lab.

Olivia Corradin, Member

We focus on genetic differences in neurons and glia across brain regions. We found that enhancers specific to the nucleus accumbens, a brain region controlling the reward circuitry pathway, can contribute to substance use disorders. We see a clear connection between these enhancers and the heritability of things like opioid use disorder.

Gerald Fink, Member

I'm quite excited to be writing the history of the Whitehead Institute. I'm an experimentalist, and Whitehead Institute was, at its time, a radical experiment. Whitehead Institute has many novelties, including the Whitehead Fellows program and building design. The Institute's pre-eminence is due, to a large part, being both part of, and independent of, MIT.

Mary Gehring, Member

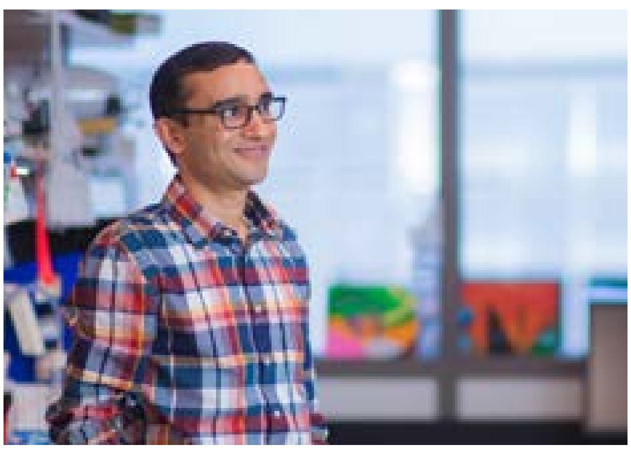
In Arabidopsis, four genes encode DNA demethylases. If we tried studying the fourth gene by mutating it, the plant couldn't live due to a reproduction defect. This year we got around that lethality, creating a plant with all four DNA demethylases disrupted. We can now understand more broadly what the genes' targets are.

Siniša Hrvatin, Member

We study torpor and hibernation at two different levels, working both with cells and animals. We have observed, very preliminarily, a remarkable result: it appears that certain markers of aging, specifically epigenetic clocks, seem to be slowing down dramatically in animals that are in torpor.

Rudolf Jaenisch, Member

Bats can handle many pathogenic viruses and are thought to be the source of SARS-CoV-2. We started working with bat iPS cells and got some very exciting results: while bat cells can get infected with SARS-CoV-2, they can control viral gene expression and replication. They don't produce any progeny virus, whereas infected human cells produce whopping amounts of virus.

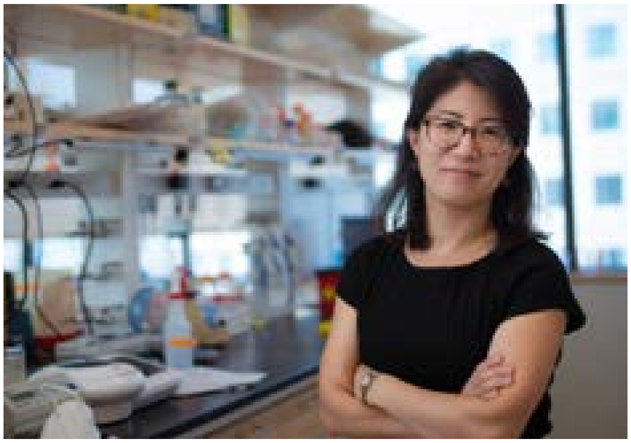


Ankur Jain, Member

Part of my lab focuses on non-membrane bound compartments called condensates. Condensates recruit specialized proteins and participate in many diverse biological functions. We have been investigating how these bodies assemble, which has implications towards understanding the ways that certain genetic mutations, linked with degenerative diseases, manifest themselves.

Ruth Lehmann
Member, President, and Director

In Drosophila, polarity is established within the egg cell. At both poles, RNAs are enriched in high concentrations. We hadn't been able to observe how these RNAs become active after fertilization. So, we developed imaging techniques to follow RNAs in real life synthesizing protein products as the embryo developed.



Pulin Li, Member

We are investigating how cells self-organize into structures or make collective decisions. A key question has been how a cell population controls its overall level of response to stimulation. We found that cell-to-cell communication affects what fraction of the population responds and we're exploring this principle in different tissue contexts.

Harvey Lodish, Member

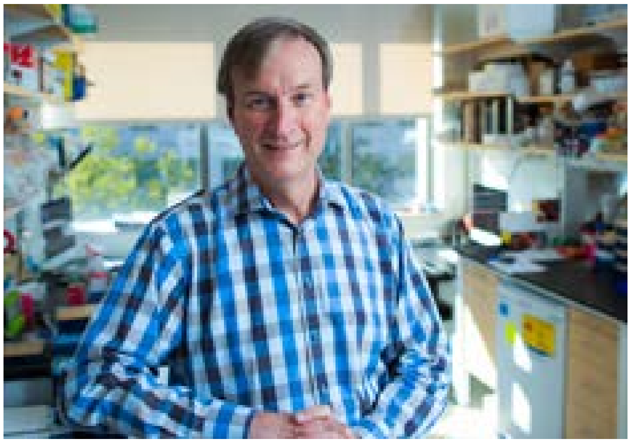
I work with a combination of university and political leaders to help them think through how one can take discoveries out of the university, and build biotech companies. Particularly, how to grow biotech companies from a startup, into a flourishing company that is manufacturing a product and beginning clinical tests.

Sebastian Lourido, Member

Two exciting studies came to fruition recently. One used a CRISPR-based approach to precisely edit genes in the parasite *Toxoplasma gondii*, allowing us to determine individual genes' function with unprecedented precision. The second assessed how individual proteins respond to small molecules; it enabled us to identify proteins at work during key transitions in the parasite's life cycle.

Tobiloba Oni, Valhalla Fellow

Cancer cells make up only a portion of a pancreatic tumor; the remaining cells actually support the cancer cells. We investigate how tumor cells shape their microenvironment. And we've identified new strategies to alter the microenvironment, enabling immune cells to destroy cancer cells.



David Page, Member

We've been learning that while the first X chromosome in biological males (XY) and females (XX) is essentially the same, the second X in females — called "Xi" and long considered inactive — is tremendously relevant. Our lab is focusing extensively on Xi's function and impact, and will probably do so for many years to come.

Peter Reddien, Member

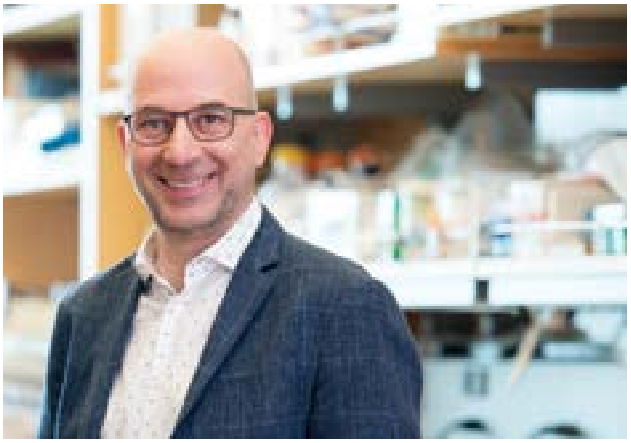
In studying how planarians initiate replacement of injured or lost tissues, we discovered a central role for the *equinox* gene. *Equinox* is expressed in the skin that covers a wound and is necessary for stem cells to know what kinds of cells are needed for replacement tissues. It's exciting to have found a gene that may be one of the keys to regeneration.

Robert Weinberg, Member

A common fate of disseminated cancer cells is that they enter a tissue and become dormant for months or years. Then suddenly, they start proliferating and create a clinical relapse. We've gathered convincing evidence that what provokes that awakening is cancer cells receiving signals from surrounding inflamed tissue.

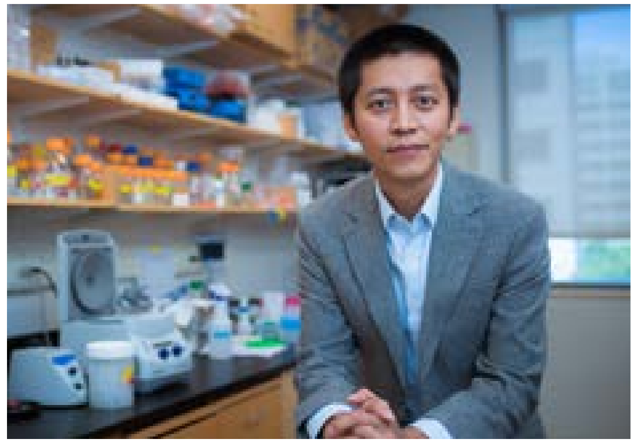
Kipp Weiskopf, Valhalla Fellow

In the lab we've found that certain lung cancers respond to new combination therapies that stimulate the immune system to attack cancer cells, and we're now applying them to other cancers. In parallel, we're learning a lot about genes and regulatory pathways controlling how immune cells called macrophages function within tumors.



Jonathan Weissman, Member

This year we introduced two significant tools that enable scientists to pursue systematic approaches to biological discovery. One tracks tumor evolution in vivo, using "molecular recorders" that inscribe a cell's history in its DNA. The second — called genome-wide perturb-seq — maps the function of every gene expressed in a specific cell.



Jing-Ke Weng, Member

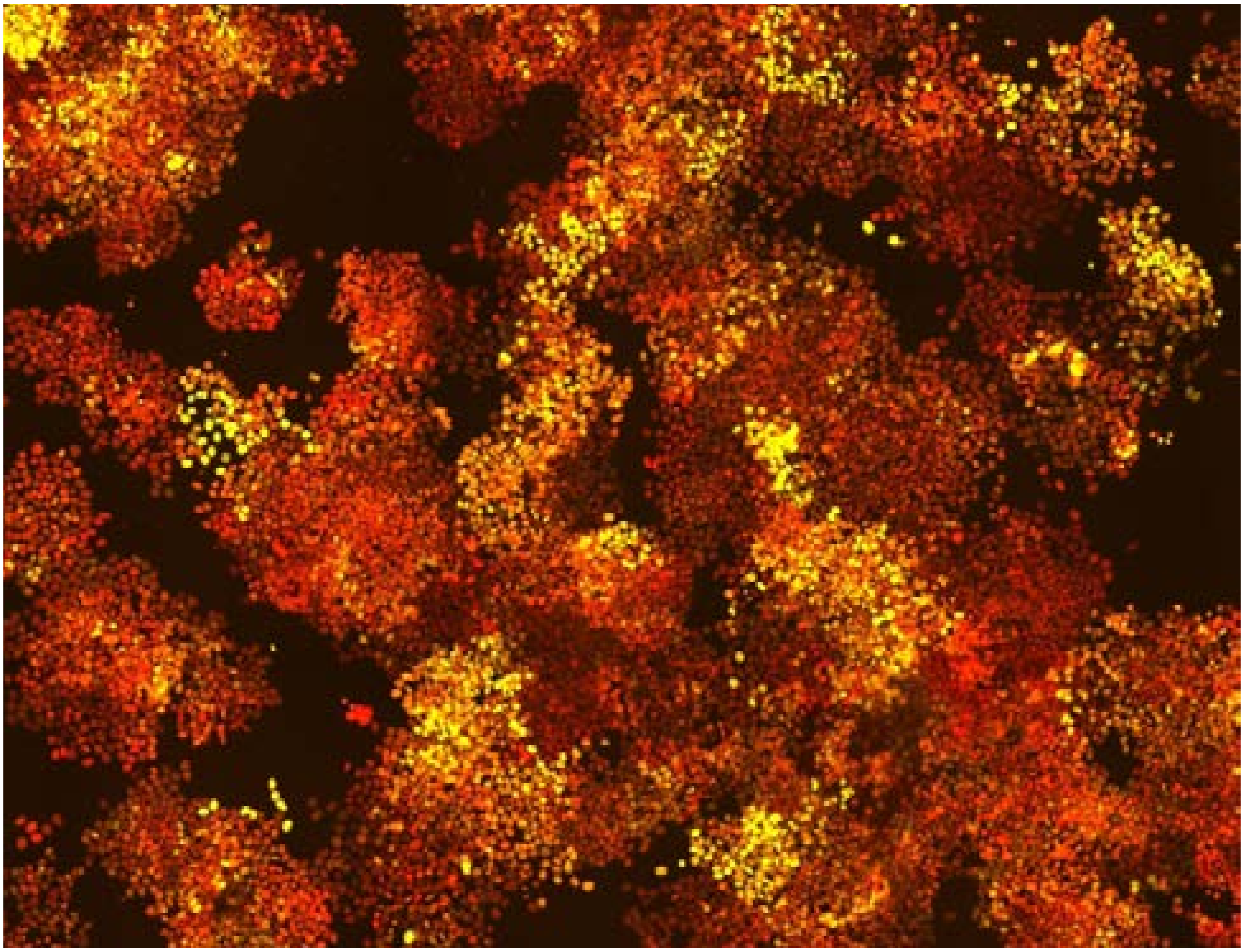
We study plant peptides, applying a process developed by our lab to use them to create potentially therapeutic molecules. One we're working on now comes from stinging tree venoms: It has an action mechanism similar to the chemotherapy drug Taxol, and holds promise to be developed into a new cancer treatment.

Yukiko Yamashita, Member

Ribosomes are the key protein synthesis enzymes, and ribosomal DNA (rDNA) — which codes for ribosome components — exist as repeated sequences. These repeats are susceptible to loss, which results in cellular aging. We began uncovering how germ cells, which transmit the genome through generations, maintain rDNA repeats such that the lineages of life continue through an evolutionary time scale.

Richard Young, Member

Researchers have learned that cellular proteins and other biopolymers can condense into membraneless structures called condensates to perform cell functions. We're investigating whether the behaviors of these condensates might explain long-standing mysteries in biology. And we're identifying how genetic variation and the environment alter condensate behavior to cause metabolic and neurological disease, thus leading to novel therapeutic strategies.



Recreating cell social networks in a dish

As a multicellular organism develops, proper tissue patterning depends on the organism's cells being able to send information to each other. Whitehead Institute Member Pulin Li studies how cells within growing tissues in embryos communicate.

"I'm interested in really understanding the rules of cell-cell communication and what controls, for example, how far cells can send the information to each other and how they interpret that information," says Li. "But in the developing embryo, you don't have access to all these cell types and the dynamics of the process."

To date, most scientists have taken a "top-down" approach to studying complex biological questions like embryo development: take an animal embryo and perturb it or mutate a gene and see what happens. "But now," Li explains, "there's a lot more interest about how we can build these complex processes from the bottom up — create biological systems from scratch to learn how they work."

“I’m interested in really understanding the rules of cell-cell communication [and] how far cells can send the information to each other and how they interpret that information.”

Li has developed a way to create synthetic signaling systems, starting on the level of individual cells. First, she engineered cells to be either signaling or receiving cells for various molecular signals. “We build fluorescent signal reporters into the cells, so that the cells glow when they receive the signal,” she said. “Then, we take movies over a two- or three-day period of time, and watch signals traveling from one side of the dish to the other.” Finally, Li analyzes these videos with image-analysis algorithms to make sense of the signals.

Going forward, Li intends to use her cell communication methods to create organoids — masses of lab-grown cells that work much like organs in the human body. “If we can accomplish that, it would open up new avenues for understanding the basic science of tissue development and for more effectively creating novel therapeutics,” she said.

New methods spur research advances

For decades, Whitehead Institute Members and Fellows have been globally renowned for creating new research tools and methods that drive major scientific advances. This past year, Whitehead Institute Member Jonathan Weissman introduced two major technical advances that have opened new pathways for exploring previously intractable biological questions.

In one advance, he and his colleagues combined CRISPR-based genetic screening with genome-wide use of the single-cell sequencing method called Perturb-seq to create the first comprehensive functional map of genes expressed in human cells—tying each gene to its job in the cell. The data creates myriad research opportunities for scientists worldwide. "Rather than defining ahead of time what biology you're going to look at in experiments, this map enables you to simply screen the database to see the genotype-phenotype relationships," said Weissman.

For example, his team used the data to explore cellular effects of genes with unknown functions, and to identify genes that cause chromosomes to be lost or gained.

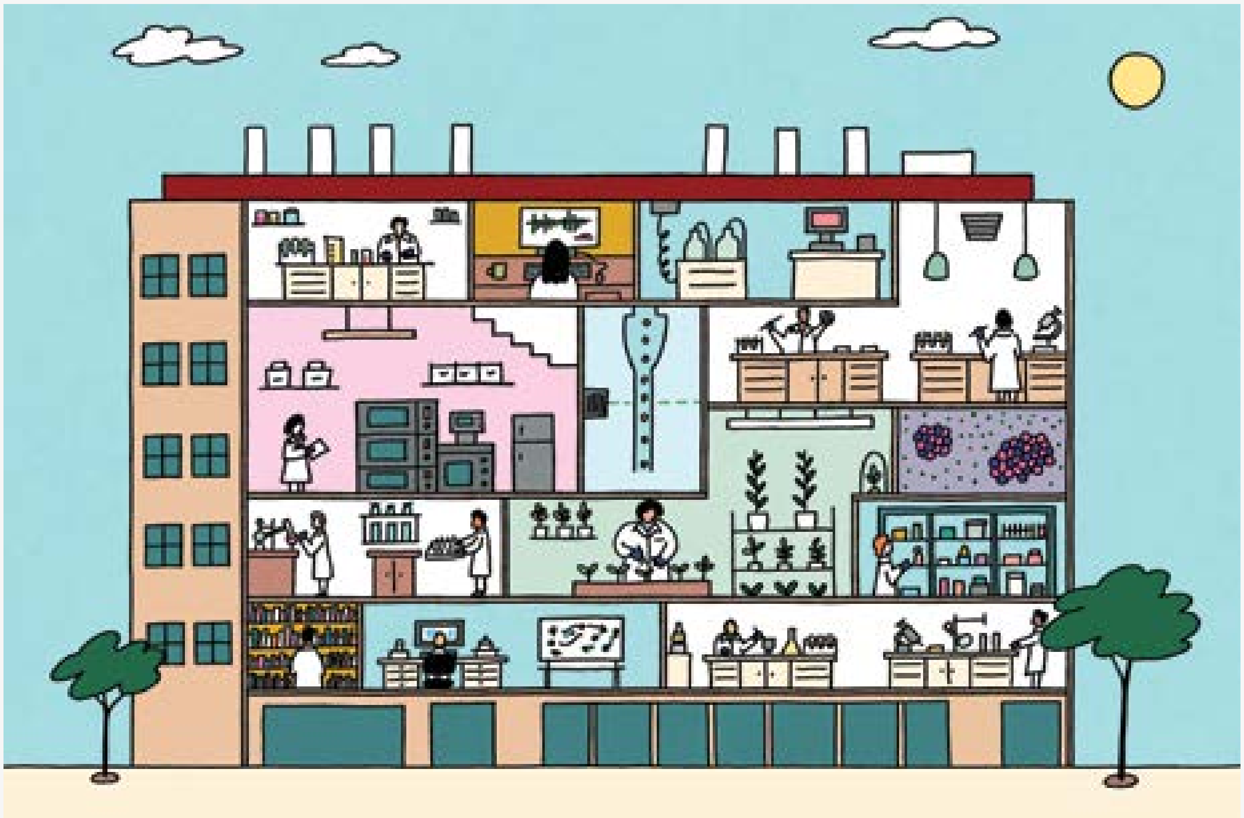
“Previously, the critical events that cause a tumor to become deadly have been opaque because they are lost in the cells’ distant past. But this gives us a new lens on that history...”

“This dataset is going to enable all sorts of analyses we haven’t yet envisioned, and allow innovative studies by people investigating a huge array of biological questions.”

In the second advance, Weissman and his collaborators developed a method for cancer lineage tracing: tracking individual cancer cell lines through their generations of development and observing the steps by which they evolve their most deadly traits. Their approach uses CRISPR technology to embed within each cell an inheritable and evolvable DNA barcode. Each time a cell divides, its barcode gets slightly modified. When the researchers eventually harvest the descendants of the original cells, they can compare the cells’ barcodes to reconstruct a family tree of every individual cell, just like an evolutionary tree of related species. Then researchers can use the cells’ relationships to reconstruct how and when the cells evolved important traits.

The team’s recently published study used the lineage tracing method to track lung cancer cells from the first activation of cancer-causing mutations. That research revealed new insights into how lung cancer progresses and metastasizes — and demonstrated the wealth of new knowledge that lineage tracing can provide. “Previously, the critical events that cause a tumor to become deadly have been opaque because they are lost in the cells’ distant past,” says Weissman. “But this gives us a new lens on that history, enabling us to view cancer evolution with much higher resolution than ever before.”

Partners in discovery



Helping to drive the Institute's path-breaking research are nine Technical Innovations Centers — core scientific facilities that provide both state-of-the-art equipment and highly trained, deeply experienced technical staff. The directors of these Centers are, themselves, leaders and pioneers in their fields. Leveraging their expertise, experience, and creative insight, they are partners in the research process, helping the Institute's investigators expand the boundaries of scientific inquiry and pursue previously inaccessible aspects of biology.

One of those research partners is Heather Keys, director of the Functional Genomics Platform. "We help Institute scientists use the CRISPR-Cas9 gene editing system and other large-scale approaches to study fundamental biological processes in a growing variety of systems," she says. (See previous article, New methods spur research advances). "CRISPR can also be used to uncover the answers to more specific questions — for example, by identifying gene targets that sensitize patient-derived cancer cells to a new treatment to help us fine-tune therapeutics."

One of the Platform's main strengths is its capacity to adapt and work closely with investigators to build new technologies. These fresh approaches enable Institute researchers to pursue answers to old, troublesome questions and to identify wholly new opportunities. "Looking down the road, one of the most exciting opportunities is the potential to use CRISPR to help create precision medicine pipelines for an array of medical conditions," says Keys.

The Institute's other Technical Innovations Centers provide technical capacities, expertise, and innovative approaches in bioinformatics, flow cytometry, genome technology, genetically engineered models, metabolite profiling, microscopy, quantitative proteomics, and stem cells.

Rejuvenation: studying the biology of aging, repair, and replenishment

Whitehead Institute researchers are breathing new life into the study of rejuvenation — the ability of cells to repair and replenish tissues — and are potentially learning how to slow or reverse the changes our cells experience over time. The following series of four articles highlights some of the most provocative and fundamentally important questions our scientists are seeking to answer.

From repaired organs to immortal cells

The root words of rejuvenation mean "young again." While we still can't turn back the hands of time, Whitehead Institute researchers are studying the biological markers of aging in order to better understand what cellular processes underlie the changes our bodies undergo over the years. Their work helps us understand what it means to "age" as a person, and may someday lead to therapies that can mitigate some of the effects of the aging process.

"Our bodies change dramatically in a lot of ways as we age," says Whitehead Institute Member Iain Cheeseman. "The connection between the ability of cells to divide and proliferate to repair and replenish tissues and what changes in our bodies as we age is something we're really curious to investigate. And I think we now have some molecular hooks that we can explore, ones that we didn't have just a couple years ago."

Cheeseman's work on cell division investigates not only how cells divide, but what's going on when cells are not dividing. Cells face an onslaught of challenges over time. "One of the biggest challenges that aging cells and their proteins face is oxidative damage," Cheeseman says. When a cell undergoes too much damage, it can lose its ability to divide. "It basically is entering this irreversible pause state, where it's going to start sending a bunch of signals that are sometimes problematic for tissue inflammation, or are interrelated to other kinds of diseases and cancer, and that can be a problem."

Cheeseman's work could eventually inform therapies for rejuvenating aging cells, prolonging life, or extending the fertility window for women.

Whitehead Institute Member Peter Reddien is also studying a form of rejuvenation: regeneration. His work on regenerative worms called planarians is revealing basic principles of how animals can rebuild their tissues when they are damaged. Planarians have never been documented to die of old age — in fact, they can reproduce by tearing themselves in half, meaning that every planarian at Whitehead Institute has the identical genetic makeup of one original animal. Reddien's work illuminates the cell types and genetic programs that confer this form of extreme longevity to the worms.

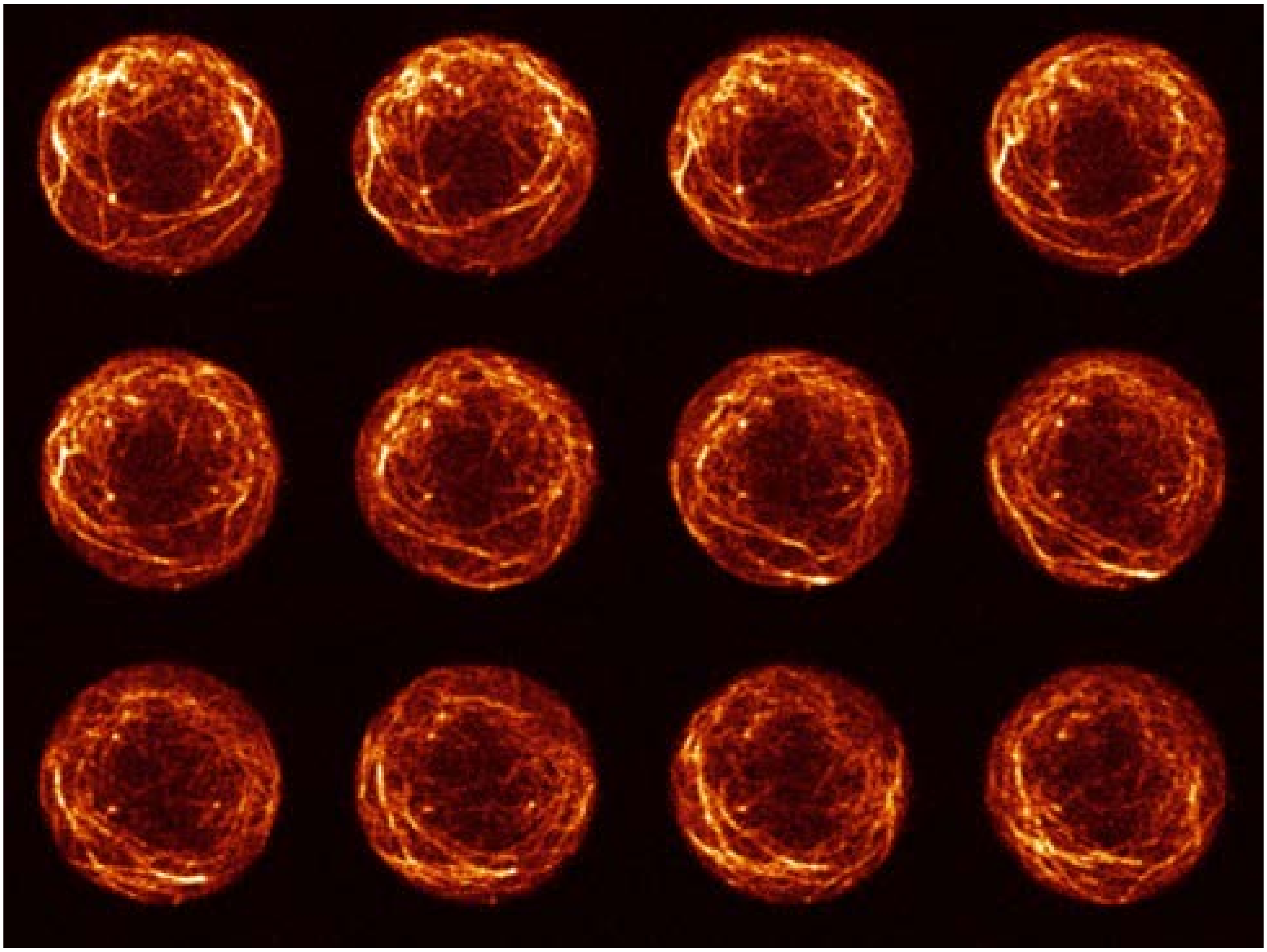
Some cellular markers of aging are programmed into the cells themselves. Researchers in the lab of Whitehead Institute Member Siniša Hrvatin study the effect of reduced metabolism on the body's epigenetic clocks — a series of changes over time to the structure of DNA that affects which genes are expressed. These epigenetic markers are often used to measure one's "biological age" — the progression of which, unlike chronological age, differs slightly from person to person. Hrvatin is using these markers to determine how different states — specifically torpor, a state similar to "suspended animation" used by many animals to survive extreme conditions — could affect the process of biological aging.

Whitehead Institute Member Yukiko Yamashita addresses another pre-programmed hallmark of aging: the loss of ribosomal DNA. The product of that DNA, ribosomal RNA, together with proteins, forms cells' protein-making factories. As time progresses, most cells in the human body lose some of their ribosomal DNA — but one cell type is able to retain the correct amount, and even make more. Yamashita's recent work explores how germ cells — sometimes called "immortal" cells due to their ability to escape the fate of somatic cells, which die with each organism and are made completely anew in the next generation — are able to bypass the gradual loss of ribosomal DNA over the years.

Whitehead Institute director Ruth Lehmann also studies these "immortal" cells, focusing on their life cycle and how they are able to persist throughout generations without aging to transmit the information needed to create an entirely new organism.

In the accompanying articles, we dive deeper into these research projects, and more.

The immortality of germ cells



Germ cells, the reproductive cells that eventually become eggs and sperm, are set aside early in embryonic development, when the embryo is just a hollow ball of cells called the gastrula. This means that the cells transferring genetic information to the next generation are already with us at birth.

There are many questions that researchers are still trying to understand about the immortality of the germline. “Not many people truly appreciate the crazy mystery of how germ cells have lasted 1.5 billion years,” Whitehead Institute Member Yukiko Yamashita says. Researchers at Whitehead Institute, including Yamashita and Whitehead Institute director Ruth Lehmann, study the many aspects of germ cells that set them apart from other cell types. They ask questions about how germ cells migrate across the embryo to meet developing gonads, and how germ cells ultimately give rise to eggs and sperm.

A central question in both Yamashita’s and Lehmann’s work is how germ cells use a unique regulatory system to maintain the potential to divide into any cell type, without actually doing so for decades on end. When germ cells produce progeny, the program of aging is reset, and the cells in the progeny begin afresh. This feature is in sharp contrast to most of the non-reproductive cells in the body, which differentiate into specialized cell types, age, and eventually die.

Lehmann has uncovered some of the ways in which germ cells are able to maintain themselves throughout the generations.

Learning how germ cells maintain their DNA in order to produce fit eggs and sperm, generation after generation, may lead to insights into how other cells throughout the body age. By better understanding how germ cells are maintained, it might one day be possible to slow or reverse aging processes in other cells.

Creating the germline

Early in embryonic development, the germline is set aside from the cells that make up the rest of the body, which are called somatic cells. The cells set aside are the predecessors of the mature germ cells that can make eggs or sperm, and these immature cells are called primordial germ cells.

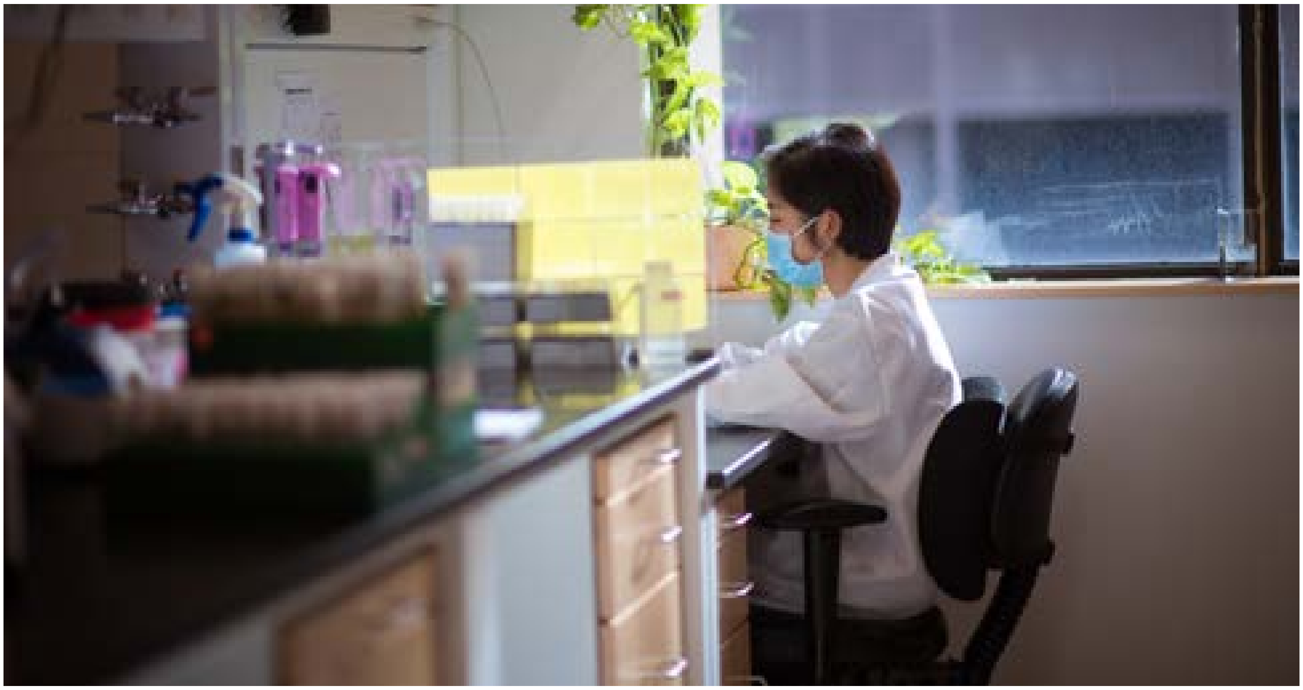
Lehmann has uncovered many aspects of how germ cell fate is assigned by studying female fruit flies. As a graduate student, Lehmann identified and characterized genes essential to the proper formation of the germline. Germ cell precursors form at one tip — the back end — of an early fly embryo. Lehmann found that a gene she named Oskar plays a key role in assembling the necessary ingredients for germ cells in this location. Oskar helps to seed germ granules, droplet-like structures unique to the germline that form as RNA and proteins assemble together. Germ granules regulate the translation of RNA into protein, thereby controlling gene expression, and helping germ cells to form and develop properly.

Primordial germ cells form before the embryo begins making a reproductive tract. As the gonads — ovaries or testes — develop, the primordial germ cells must migrate through the embryo to reach them. Whitehead Institute researchers have helped discover how the cells are guided on this journey and mature into cells capable of making eggs or sperm. Lehmann's lab has found factors involved in this migration. For example, they identified the signaling molecule that provides a trail of breadcrumbs for germ cell precursors to follow to their destination.

In recent work, Lehmann's lab figured out how the fly's body signals germ cell precursors to differentiate into mature germ cells in the right time and place — in the reproductive tract, once the ovaries are ready to host eggs — as well as what signals keep the precursors from maturing too early. Led by former Lehmann lab postdoc Torsten Banisch, the researchers identified swarm cells, whose function was previously unknown, as a critical relay that transmits cues to germ cell precursors that signal them to mature. If any of these processes goes awry — if the cells migrate to the wrong location, mature at the wrong time, or fail to receive the signal to mature — the fly is likely to lose its germline and become infertile.

Maintaining a healthy germline

We commonly think of cell division as one cell splitting into two identical copies. However, cells can divide asymmetrically, creating two daughter cells that are not identical to each other. Yamashita studies germ cells in male fruit flies and has found that dividing germ cells pack one of the resulting cells full of only the best components at the expense of the other cell. For example, Yamashita found that one of the resulting cells will receive the other's copies of certain genetic sequences that otherwise can be lost with age over the course of many cell divisions. The lab also found that chromosome pairs are non-randomly sorted into dividing germ cells, based on which has more copies of the genetic sequences that need to be maintained through generations. The finding shows that this is one way the germline prevents loss of important genetic sequences with aging. The cell that gets all of the best materials continues dividing, keeping the germline healthy and fit for generations. Stem cells outside of the germline also divide asymmetrically, in order to allow some of their descendants to



mature while others maintain the stem cell pool. Yamashita's work with germ cells sheds light on this broader biology, delving into various mechanisms that enable asymmetric cell division.

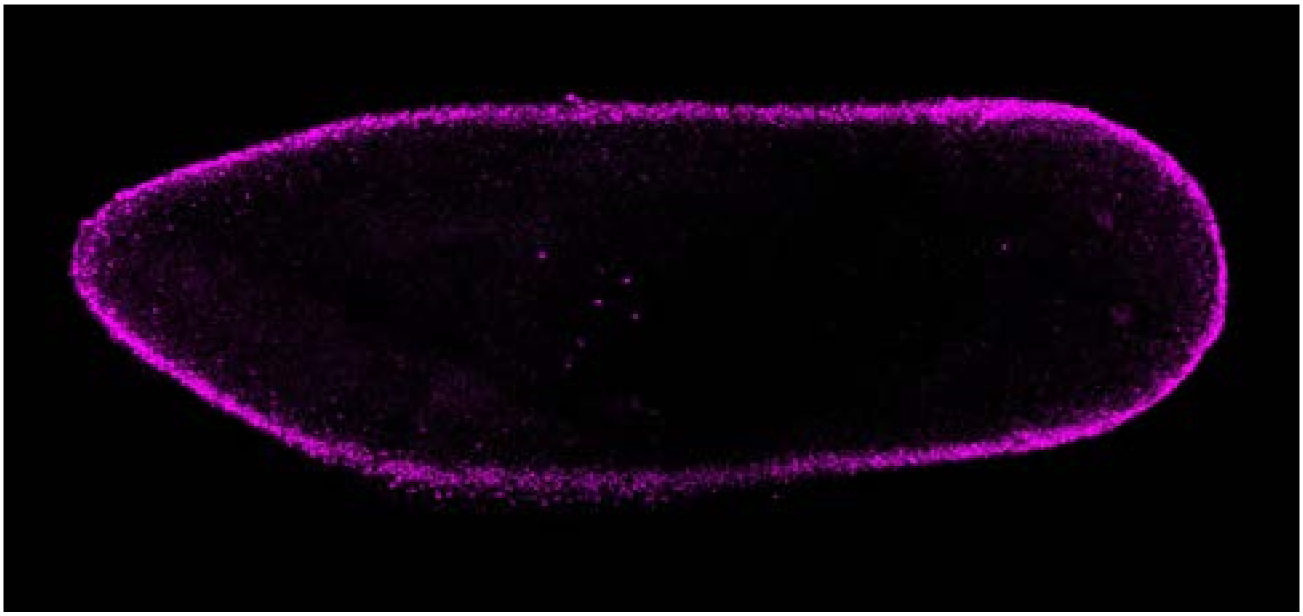
For other cell types, sacrificing half of their cells in the way that the germline does to maintain its health would be too resource intensive to afford — every cell is needed to keep the body going — and so over many divisions our body's cells degrade as we age. Germ cells are a small cell population that can afford to let only the cream of the crop survive — in fact, they need to be choosy in order for their descendants to keep dividing long after the rest of the body's cells die. Discovering the processes like this that germ cells use to maintain their immortality could also provide insights into other immortal cell types, like cancers.

Lehmann has uncovered some of the ways in which germ cells are able to maintain themselves throughout the generations. Her research illuminated how germ cells in flies protect their genomes from transposable elements or "jumping genes." These are DNA sequences that can move to new positions in the genome, which can lead to mutations or to changes in genome size. Germ cells must be protected from such changes to their genomes, as these will either be passed down to offspring or could degrade the germline to the point of infertility, putting an end to the cells' immortality. Lehmann has discovered how germ cells prevent such changes.

Lehmann also studies inheritance of non-DNA components in the maternal germline. All germ cells must carefully maintain their DNA so it can be passed down to the next generation. The maternal germ line's job does not end there, however; egg cells must pass on not only the mother's DNA, but nutrients, starter organelles, and cellular components — such as RNA — that the earliest stages of the embryo rely on to function before they can ramp up production of their own components. One organelle of particular interest to Lehmann is the mitochondria, a structure that provides energy for cells. Mitochondria have their own genome, unique to them, and mutations to mitochondrial DNA can cause serious diseases. Lehmann's lab studies how the maternal germline prevents passing on dangerous mutations in the mitochondrial genome.

As Yamashita and Lehmann continue studying the complex ways that germ cells preserve their immortality, they hope to discover insights into cellular aging and rejuvenation.

How one worm can rebuild its whole body



As we age and incur injuries, we often accumulate permanent scars. If we lose a body part to injury, that part is gone forever. However, some animals have no trouble recovering from even the most grievous injuries. Planarians, a type of aquatic flatworm, are one such super regenerator, able to restore their bodies by growing back anything from an eye or a tail to a head. If you cut a planarian in half, two new planarians will grow out of the pieces.

Whitehead Institute Member Peter Reddien seeks to understand how planarians (*Schmidtea mediterranea*) are able to regenerate so effectively. Researchers in his lab have uncovered many of the mechanisms and principles of planarian regeneration. This work may prove useful in the field of regenerative medicine, which aims to promote better healing or even regrowth in people.

“The more we understand about the mechanisms underlying regeneration in animals that naturally can accomplish it, the better we will understand the basis for the limitations of our own regenerative capacity and whether we might improve upon it,” Reddien says.

In pursuit of such understanding, Reddien and his lab members have discovered how planarians initiate regeneration, how they ensure that lost parts grow back in the right places, how their stem cells make choices about what cell type to become, and more.

Initiating regrowth

After an injury, animals have a wound healing response that triggers the body to seal off the open wound and repair the immediate area. In animals that cannot regenerate, the response ends there; but in planarians, healing transitions into regeneration, restoring any lost parts. The Reddien lab identified a gene, active in the skin that grows to cover the wound site, that plays a key role in triggering this transition in planarians. If the gene, which the researchers called *equinox*, is not active after large injuries, the wound site will still heal but the lost body parts will not regenerate. This finding expands researchers’ understanding of the cascade of events that has to happen for regeneration to take place.

"The more we understand about the mechanisms underlying regeneration in animals that naturally can accomplish it, the better we will understand the basis for the limitations of our own regenerative capacity and whether we might improve upon it."

Maintaining a body map

How do planarians know where to regrow missing body parts? In order to regenerate missing body parts in the right places, the planarian's cells follow a body plan blueprint that is maintained by what are called position control genes (PCGs). These genes function as a sort of GPS system, directing the cells in where to go and what to become. Reddien's lab discovered that in planarians, PCGs are active in muscle tissue. They later found that PCGs are also active in muscle tissue in three banded panther worms (*Hofstenia miamia*). The fact that muscle plays the same role in both species suggests that it also played the same role in their last common ancestor, which existed more than 550 million years ago. That common ancestor was also an ancestor to humans and many other animals, which indicates that muscle tissue was a source of positional information in our ancestry too.

Since discovering the role of muscle in maintaining the body's GPS grid, researchers in Reddien's lab have discovered more details of how this system works. One question that Reddien had is how cells adjust during the period right after an injury, when there is disagreement between the body's blueprint and its actual anatomy. If a worm gets cut in half, the GPS grid recalibrates quickly and anatomy adjusts to this new grid slowly. For example, a head fragment must start generating "tail" signals at the wound, and the "head" patterning information shifts away from the wound. While the "head" signal is in flux, how does the planarian know where to send stem cell progeny to maintain its eyes?

Researchers in Reddien's lab found that the cells involved in regrowing the body follow a set of rules to solve such dilemmas. For example, in the case of eyes in a head, eye progenitor cells that come close to an existing or already-growing eye will join that eye, rather than continuing farther forward. This prevents the planarian from repeatedly starting to regrow eyes in new locations as the GPS grid adjusts. The cells rely on a combination of anatomical self-organization and positional signals to control where they rebuild and maintain tissues. The researchers were able to manipulate these factors to create planarians with misaligned or extra eyes.

Building on what they learned about the principles that govern eye regrowth, the researchers discovered how the planarian rewires the connections between new eyes and the brain. Axons are the wires between the eye and brain, and they must route their way through the regrowing body to connect the two. Most animals have so-called "guidepost cells" that exist during their embryonic development to help guide axons in the right direction, but these cells are typically not present in adulthood, when they are no longer needed. Researchers in the Reddien lab found that planarians maintain guidepost cells as adults, so that axons can always find the right route. The researchers also found that guidepost cells are muscle cells in planarians, rather than neural cells as is more typical in development, once again revealing a key role for muscle as the source of adult positional information in planarians.

Staying primed for regeneration

Planarians have a pool of stem cells, called neoblasts, that can divide to become any cell type. Researchers anticipated that these cells might follow a typical funnel-like progression in their divisions, going through several intermediate stages on the way to their final cell type, with each division narrowing the options of what they can become. For example, in humans, a stem cell may become a blood cell progenitor, and then an immature white blood cell, on its way to becoming a white blood cell. However, Reddien and colleagues found that stem cells in planarians remain flexible in their fates. The cells make large, single jumps between a naive state and final fate choice — to make skin, gut, neuron, or something else — in the course of a single division. Neoblasts can divide asymmetrically, which allows them to switch paths rather than becoming stuck in a narrowing funnel of options. This flexibility helps planarians to regenerate by making it easy for the animal to generate any cell type rapidly from a pool of starting stem cells.

Building the resources to learn more

Reddien and his colleagues continue to study aspects of planarians' incredible regenerative abilities that are not fully understood. To help in that work, they have built a map, or cell atlas, of gene expression for every cell type in the planarian body. Their project required sequencing tens of thousands of cells, something that has only recently become feasible thanks to advances in technology. This complete planarian cell type gene expression atlas was the first of its kind for any adult organism. The researchers intend to use this atlas to dive even deeper into the principles governing regeneration.

"We're still in the early phases of realizing the potential of these tools," Reddien says. "Now we can apply them to many different problems in regeneration."

What hibernating animals — and cells — can teach us about aging

Much of biology is defined by activity: the rapid growth of an embryo, or the adventurous life cycle of a parasite, or the frenzied evolution of cancer cells. But for two Whitehead Institute researchers, there is much to learn by studying periods of rest.

Hibernating cells

Whitehead Institute Member Iain Cheeseman has been studying cell division for nearly 25 years. His work in the past has revealed key proteins in the kinetochore (the structure that enables chromosome segregation). But one very important question in Cheeseman's lab pertains to cells that aren't dividing at all.

"Of the 30 trillion cells in our body, on a given day about 50 billion of them are dividing, which is a lot," Cheeseman said. "You have a lot of things you need to replenish every day, like blood or other cells that are lost over time. But that means that 29.95 trillion cells in your body today are not dividing, and some of those cells will not divide ever again."

These cells that cannot divide make up tissues such as the brain, heart, and muscle fibers. That's one reason diseases of the heart and brain, as well as conditions such as muscular atrophy, are so hard to treat.

But there is another class of cells — such as egg cells, liver cells, and some blood cells — that aren't constantly dividing, but could if they needed to. Cells in this state are referred to as quiescent, and Cheeseman became fascinated with how they worked.

"A major change happened in our lab five or six years ago where it became really important to think about not only how cells divide, but how they persist," Cheeseman said. "Some have to persist, not just for a day or a week or a month, but for years. So how do you create a structure and a system such that a cell can exist there, but still be able to divide?"

To study quiescence, Cheeseman turned to one cell type in particular. "There's a lot of cells that need to hibernate and pause, but the cell in our body that I think is the champion of that is the oocyte," he said. Oocytes are immature egg cells. "They are made before a human is even born, and then those oocytes have to stay sitting there paused for decades before they are reactivated and used. That's a remarkable thing."

But while they can remain on pause for decades, there is an eventual end to oocytes' viability. "There are age-related decreases in human fertility, which can be a challenge in some cases," he said. "Ultimately, human fertility is related to how effective and faithful cell division in oocytes can be."

Cheeseman, alongside former postdoctoral scholar Zak Swartz, found that an essential cell division protein called CENP-A is being constantly turned over in egg cells, allowing them to have fresh, working cell division machinery at the ready if they need it.

The lab is now investigating methods to rejuvenate the centromeres of aging egg cells. Cheeseman, who was recently named a scholar of the Global Consortium for Reproductive Longevity and Equality, hopes the research will pave the way for treatments that could extend the window of female fertility.

Overwintering animals

While Cheeseman is investigating cellular states of rest, Whitehead Institute Member Siniša Hrvatin is studying a more organism-wide type of resting state called torpor. Animals such as birds, bats and some rodents employ torpor as a strategy to survive harsh conditions. To achieve this state, the animals must dramatically drop their metabolisms and body temperatures.

"Just before I came to Whitehead Institute, I started wondering whether, if we induce the state of torpor — a kind of hibernation-like state — in animals, does that affect their aging?" said Hrvatin. "And we observed very preliminary but really remarkable results where it looked like certain markers of aging — specifically, these epigenetic clocks — seem to be slowing down dramatically in the animals that are in torpor."

The "epigenetic clocks" include patterns of methylation — a type of genetic control that can activate or deactivate regions of DNA without changing their sequence — that change as an organism ages. "We can try to track those markers in animals that are out of torpor and in torpor, and we see that they are changing a lot more slowly when the animals are in torpor," Hrvatin said.

Hrvatin hopes to eventually understand the effect of torpor on other physiological markers of aging, including frailty and lifespan. "A lot of those studies are still ongoing and we don't have a clear result there yet," he said. In the long run, Hrvatin's research could have applications for inducing similar states of "suspended animation" in humans.

Cells and animals rest, but science keeps moving

Cheeseman and Hrvatin's labs, although they operate on very different scales, are complementary to each other, Cheeseman said. "Our labs have a lot of fun, constructive relationships and similarities," he said. "There are different axes to this: There's how an animal is responding to its environment, which is definitely on the Siniša side. Then there's what hibernation means on a cellular level, which I think is intimately tied with quiescence."

Cheeseman hopes the synergy between the labs will continue. "We overlap on a lot of cellular questions, and I know how excited Siniša and his lab are about them," he said. "I hope that there continues to be a lot of positive overlap."

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 environment.

“The Institute’s commitment to helping young researchers pursue their scientific visions – and to providing the tools, training, and collaborative support needed to push the boundaries of current thinking – is empowering.”

Institute welcomes new Whitehead Fellow

Lindsey Backman, who studies the structure and function of microbial organisms, has been named a Valhalla Fellow at Whitehead Institute and is the newest member of the Whitehead Fellows Program. Her lab will study the human microbiome, its constituents, and the ways that its resident bacteria protect the enzymes they rely on for survival.

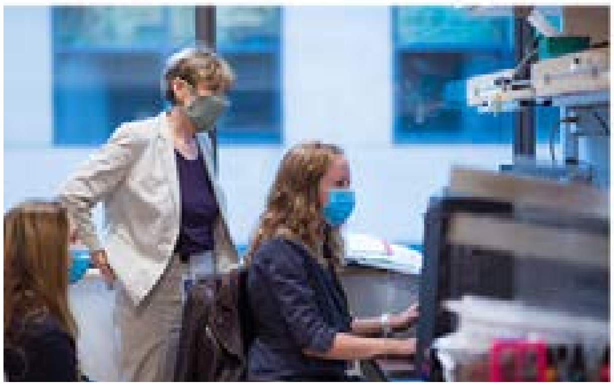
The Whitehead Fellows Program provides highly talented and accomplished recent PhDs the opportunity to launch their own research programs, instead of working as postdoctoral researchers in a senior scientist's lab. Founded in 1984, the Program has become the model for advancing the careers of biomedical research's most promising young scientists.

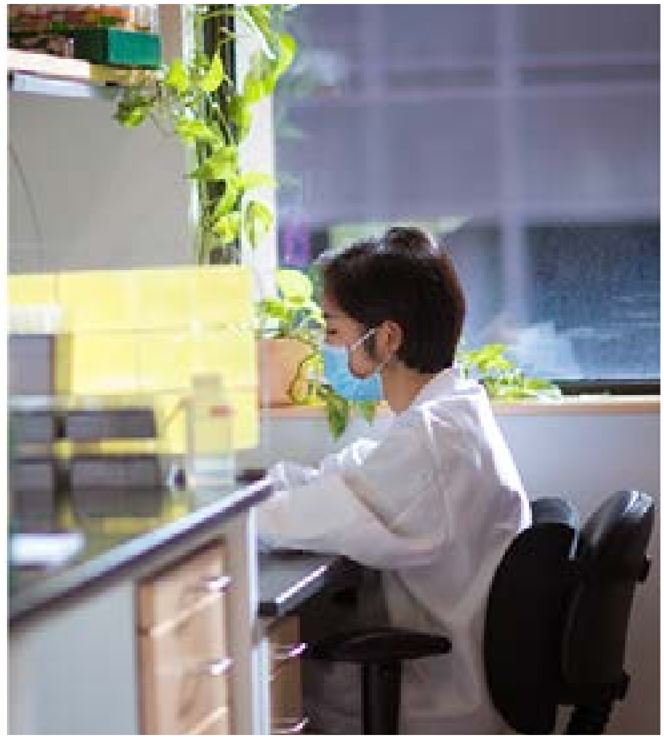
"Each Whitehead Fellow brings both a pioneering spirit and an exciting vision for researching important questions in biology," says Institute Member Yukiko Yamashita, who is co-director of the Whitehead Fellows Program. "Lindsey's work with microbiota will expand the range of our investigations and her perspectives will enrich the Institute community."

Backman received her PhD in chemistry from Massachusetts Institute of Technology (MIT) in 2022, having earned a bachelor of science in chemistry, summa cum laude, from the University of Florida in 2015. As an undergraduate, she received honors including the University of Florida Presidential Service and University Scholars awards. She also participated in Howard Hughes Medical Institute's (HHMI) Exceptional Research Opportunities Program and its Capstone Award program — which both enable students from underrepresented backgrounds to work with a university professor to pursue summer research projects. Through those programs, she worked for two summers as a research assistant in the lab of Catherine Drennan, MIT professor of chemistry and biology and HHMI Investigator, who subsequently became Backman's PhD advisor. In graduate school, Backman benefited from multiple programs that provided funding and a supportive community, including the HHMI Gilliam Fellows Program.

In her Whitehead Institute lab, Backman will continue to investigate the structure and biochemistry of the collection of gut microbes that comprise the human microbiome and that are a key to human health. One aspect she will focus on is how specific bacteria produce unique proteins to metabolize nutrients and repair broken enzymes. To advance those studies, at the outset of her Valhalla Fellowship at Whitehead Institute, Backman will work with the Hung lab at Broad Institute of MIT and Harvard, developing tools and methods to expand her investigations of bacterial function and the relationship between bacteria and human health.

"I'm grateful to be able to pursue the next steps in my investigations with the Valhalla Foundation's support and in the very special environment that Whitehead Institute offers," Backman says. "The Institute's commitment to helping young researchers pursue their scientific visions — and to providing the tools, training, and collaborative support needed to push the boundaries of current thinking — is empowering."





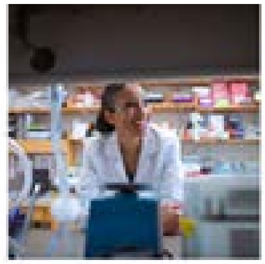
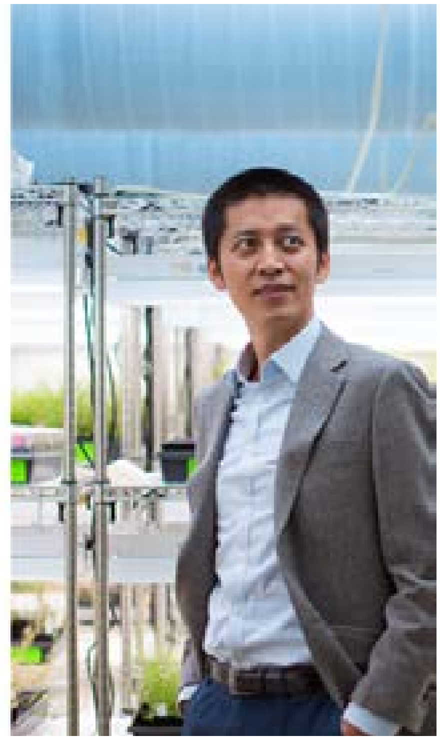
Pursuing the Institute's plan for diversity, equity, and inclusion

Whitehead Institute's ability to continue as a leader in biological research and training depends on our being a diverse, equitable, and inclusive community — a place where each person can thrive both individually and as part of a cohesive, highly effective organization.

Therefore, in July 2021 the Institute announced a multifaceted Strategic Plan for Diversity, Equity, and Inclusion (DEI). The core commitments made in the Plan include:

1. Improving the hiring, retaining, and promoting of diverse talent.
2. Creating and maintaining an inclusive culture that promotes physical and mental well-being and respect for all Whitehead Institute community members.
3. Developing partnerships to increase engagement and outreach with local communities to improve accessibility particularly for individuals from groups underrepresented in biomedical sciences.
4. Encouraging open dialogue and facilitating learning opportunities to address DEI topics, and making them available to the entire Whitehead Institute community.



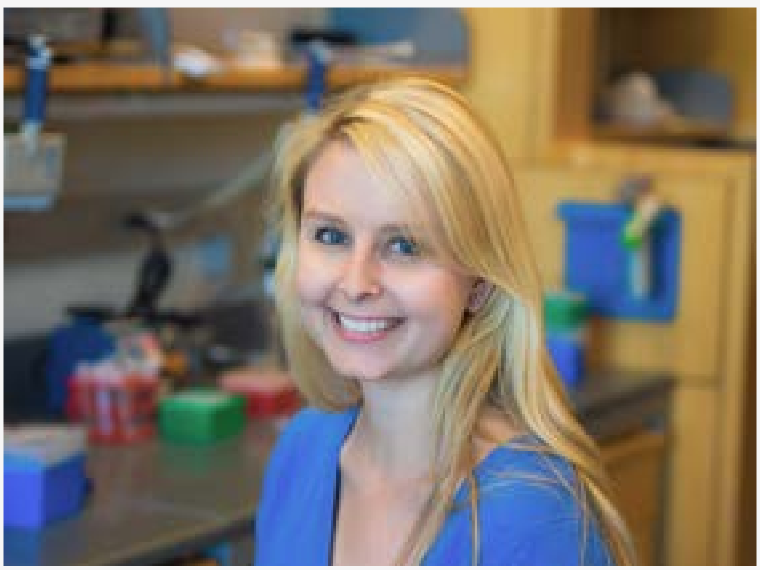

During the past year, the Institute has undertaken a range of new initiatives in line with those commitments, including:

- Formation of the Institute's DEI Council. Comprising representatives of faculty and administrative and research staff, Council members serve as ambassadors for diversity, equity, and inclusion throughout the Whitehead community, and are responsible for supporting the Institute's DEI commitments.
- Creation of a DEI Seminar Series, which enables the Institute community to learn from and engage with prominent speakers from across the sciences, social sciences, and humanities. Seminar topics have ranged from the origins of Juneteenth to Hispanic, Black, and Asian American/Pacific Hawaiian/Pacific Islander histories and heritages, to a celebration of Pride Month. In addition, we created the DEI Heritage Email series, which informs the entire Whitehead Institute community about those topics and others — including Native American Heritage Month, Women's History Month, and Mental Health Awareness Month.
- Launching the Whitehead Summer Internship Program, in which high school students in grades 10 to 12 who are from historically underrepresented groups work directly with our Members, post-docs, and staff scientists to explore biomedical science and gain experience with hands-on research.
- Broadening and diversifying the pool of applicants to the Whitehead Fellows Program by expanding awareness and permitting self-nominations; and creating an option that enables selected Fellows to supercharge their professional development through focused training in cutting edge tools and methods. We also launched an expansion of our post-doc mentoring program, offering these early-career researchers opportunities for formal mentoring relationships with primary investigators from other labs.
- Engaging the entire Institute community — including faculty, staff, trainees, and regular visitors — in a formal, small-group DEI and Gender Inclusion Training program that promotes interpersonal engagement; and planning for a second Training session in spring 2023.
- Appointing an Institute DEI Officer and DEI Specialist who bring focused energy and insight to advancing the initiatives described in the DEI Strategic Plan.

Sharing the joy of discovery

Many of Whitehead Institute's postdoctoral researchers say that they entered into research careers because of formative experiences with teachers and mentors. Without these experiences, they may not have realized that science was a good fit for them, or that they could succeed in it. Often, these postdocs are motivated to pass on those lessons to the next generation by teaching, mentoring, and participating in science outreach — including through Whitehead Institute's outreach programs. Here, some of the Institute's postdocs share what their experiences as mentors and mentees have meant to them.

Institute alumni continue to mentor the next generation of biomedical researchers



For many of Whitehead Institute's graduate students and postdoctoral researchers, the commitment to mentoring and to science outreach continues throughout their careers. Kara McKinley, who completed her doctoral research in Institute Member Iain Cheeseman's lab in 2016, is a good example. Now assistant professor of stem cell and regenerative biology at Harvard University, Kara studies the regenerative properties of the uterus. She also created Leading Edge, an initiative intended to improve the gender diversity of life sciences faculty in the United States. Here, she offers thoughts on how her Institute experience informs her own approach to mentoring members of her lab:

"I model a lot of my mentorship off of the mentorship I received from Iain. We're not the same, obviously, and I have also incorporated things I learned from my postdoc mentors. One of the most important things I learned from Iain was about being generous with your mentorship and sponsorship. He sat in the lab, not his office, and so we always saw how many people came to talk to Iain about job advice or things that were going on in their lab and things like that. I still talk to him a lot and he provides a lot of input and insight into challenges I might be facing as a new PI. He's a forever-mentor. It was important for me to see that model because it's something that I try to do as well, to be generous with the time I have for people."

"One other thing that I want to say about Whitehead Institute is how awesome the support staff were. They were really integral to everything that we did. As I have worked at other places, I have really come to appreciate the way that Whitehead Institute fostered a sense of community including both the people at the bench and the people who make it possible for them to be at the bench."

Deniz Atabay (Reddien lab)

"I have always been fascinated with biology in the extreme, such as in microgravity conditions. During my master's training, I was accepted to the Space Studies Program of International Space University, which allowed me to learn more about space biology and introduced me to the pioneers of this field. During my PhD, I got to be a mentor in the Genes in Space (GiS) program. A wonderful experience, and an amazing responsibility! This unique program asks high school students to propose experiments to be implemented on the International Space Station to expand the capacity for independent scientific research in orbit and beyond. Through the years, GiS pioneered many first molecular biology experiments in space. Through GiS, I met an extraordinary group of students with whom I still preserve deeply meaningful bonds. I learned that one's potential can only be realized with the guidance of key mentors in life, and I was lucky to have truly extraordinary mentors along the way. The relationship of a mentor and a mentee is one where both sides can experience the joy of discovery together. For both sides, the shared experiences are singular gifts, in which knowledge, perspectives, and unique ways of seeing this world are transferred."

Jordana Bloom (Page lab)

"Outreach is one of my favorite parts of science, tangential to the actual research. You can help nudge people who might be interested in the right direction. I think exposure is very important, to give people a chance to figure out if working in science is something they would like. I'd never met a scientist before going to college, and if I hadn't met scientists in college, like my biology professors, I still would be in the dark about what being a scientist even means. In the outreach work that I have done since, I have seen how big of an effect exposure can have. For example, I worked with a program that encourages middle school-aged girls to stay interested in STEM fields through a day of workshops and experiments, and I really enjoyed seeing how the students' engagement changed over the course of the day. They are sort of hesitant in the beginning, maybe thinking the workshops are going to be lame. But by the end of the day, they are really excited, asking what the next activity is! It's really cool to watch that transformation, and see the students realize that you can have fun exploring questions that you don't necessarily know the answer to or that don't necessarily have one answer."

Arash Latifkar (Bartel lab)

"I became interested in science primarily due to a middle school teacher who showed us really fun and exciting science experiments. He would ask us questions and then do experiments, and show us how we could use what we observed to figure out the answers. Seeing that as young students was really fascinating, that we could interrogate nature in an experimental way like that and figure out more about it. I knew that was something that I wanted to do, to go out and learn more. I have mentored others throughout my educational training since high school. Right now, I'm mentoring an undergrad student. I always look forward to these opportunities because you learn more during mentoring. It's really productive for both parties, I think. For example, the undergrad student working with me right now is a real expert in computational biology, which I don't have a lot of background in. We go back and forth between things that I know that she wants to learn and things she knows that I want to learn, so it's a really fun and exciting learning environment for both of us."

Ally Nguyen (Cheeseman lab)

"I do a lot of tutoring and volunteer work with young students. I also always try to have an undergraduate in the lab that I can help train. I like helping students discover what they are passionate about. I think watching a student finally work through a problem that they did not know they were capable of solving is what drives me. Seeing that 'aha' moment, and more importantly helping someone see that they can achieve anything if they put their mind to it, means a lot to me. When I was growing up, I didn't have many people invested in my education, until I went to college where I had a few amazing professors that were so personally invested in helping their students learn and getting us excited about science. I know that personally, getting that kind of support changed my life for the better. I want to give that same feeling back to the students, that feeling of discovering something I was passionate about and that I could actually be good at. I especially like seeing young women get excited about science and showing them all of the cool things that we don't yet know. Every day you can be discovering something new."

Amelie Raz (Yamashita lab)

"I was a Partner in Whitehead Institute's high school teachers program for several years, during which time I met with various teachers to share my expertise, answer scientific questions, and serve as a resource. That was a really wonderful experience for me, being able to learn about what current high schoolers and teenagers who are interested in science are talking about, and being able to share with them what I think are the really cool aspects of biology. What I would tell a high schooler about being a researcher is that you get to play with stuff all day. You get to cut up worms, or play with flies, and pour liquids inside of other liquids, play with pipettes and wander around and use your hands. For anyone who enjoyed playing in the dirt as a kid, this is just the best job. And then also, you get these amazing discoveries, these moments of seeing the cell do the thing and knowing that no one else in the world knows the cell does this thing, until you turn to the person next to you and show them."

Jarrett Smith (Bartel lab)

"In college I decided that I wanted to teach biology. I was the head teaching assistant and everything. I was told that if I wanted to teach at the college level, which I did, then I should get a PhD. I didn't feel that I could afford it because I thought of post-graduate degrees as expensive, but when I found out that you got paid to do science PhDs, that made a huge difference. During graduate school and now in my postdoc, I've had great mentors. They've been attentive, generous with their time, knowledgeable, and invested in promoting my development as a scientist. None of them have been black. And that creates this additional limitation to how much they can relate to my experience in science and how specifically they can advise me on navigating my career. It also contributes to the imposter syndrome I've felt for the majority of my career. As soon as I started grad school I was behind. This is a fact; I just didn't have the research experience that the majority of my classmates did and I was worried about how that reflected on me as the only black student in my cohort. Navigating the feeling of being an imposter under the spotlight that is often placed on trainees from underrepresented groups is challenging. In ten years, I plan to have my own lab to teach and mentor students. I'm glad that I'll have the chance to help people who might question whether they belong in the sciences."

Our Impact

Whitehead Institute's accomplishments reflect both the exceptional talent it attracts and its unique environment — one marked by ingenuity, belonging, courage, and learning. Within this supportive and collaborative community, our scientists are driving major discoveries, creating important research tools and methods, and spurring translation of their work into new therapeutics. Here are snapshots of our impact this past year.

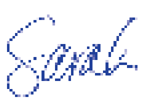
Shaping the future of biomedicine

One of the rewards of guiding an organization such as Whitehead Institute is knowing that you're helping advance its goal of improving the health of people. Indeed, I encourage you to read the newly refined statement of our compelling mission — and of the values guiding its pursuit — in this report. And I invite you to embrace and advocate for our mission: Whitehead Institute forges new frontiers in science, uncovering insights today that unlock the potential of tomorrow.

Each member of the board of directors knows that the scientific discoveries emerging from Institute labs today unlock biology's potential for future impact. We see that the Institute's labs and its technical innovation centers are creating next-generation technologies that open whole new vistas of scientific inquiry. And we see the way that Whitehead's eminent faculty trains some of the world's most talented students and early-career researchers — nurturing the next generation of leaders in biomedical research.

As proud as we are of all that Whitehead Institute has accomplished over this past year, we are even more enthusiastic about what its extraordinarily creative, skilled, and committed scientists can achieve in years to come. We envision even more discoveries that shed light on fundamental causes of disease — and that spur development of breakthrough therapies for conditions ranging from cancer to Alzheimer's to the next emerging viral disease.

We encourage you to continue learning about the courageous and impactful science being done at Whitehead Institute. And please consider how you can help us in our quest to answer some of the most pressing questions about health and disease.



Sarah Keohane Williamson
Chair, Board of Directors

Philanthropy advancing efforts to protect agriculture during climate change

For most of recorded history, climate changes occurred over centuries or millennia, allowing plants to adapt to variations in temperature, precipitation, and atmospheric composition. However, humans' actions are accelerating the pace of those changes, with far-ranging consequences: Food crop yields are diminishing in many regions, as is seed protein content in corn and rice crops.

These changes will jeopardize food security for large segments of the world's population, many of which already experience serious malnutrition. Mitigating these disastrous effects on agriculture and food security are key facets of Whitehead Institute's *Initiative on the Biology and Health of Climate Change*. And they are the focus of one of its cornerstone programs, the *Dr. Vincent J. Ryan Orphan Plant Project*. The Project exemplifies how philanthropy can power biological research and biotechnological development designed to improve quality-of-life for millions of people around the world.

The Project's goal is to bioengineer a series of food crops that are more nutritious and more resilient to climate change than many current crops. The resulting biotechnologies could ultimately help protect millions of people from starvation.

The research program is led by Institute Members Mary Gehring, Jonathan Weissman, and Jing-Ke Weng. "It's increasingly clear that current agricultural practices — and the most commonly grown crops — won't be sustainable with climate change," observes Weissman, who is a pioneer in applying gene-editing technologies. "If we hope to feed the world's growing population, scientists must develop transformative methods to bioengineer nutritious plants better adapted to variable environmental conditions."

The Project will focus initially on pigeon pea — a high protein plant farmed in India, Africa, and the Caribbean — and on other "orphan crop" species where the researchers can make rapid advances. "These plants are a largely untapped source of genetic diversity and possess valuable traits that make them highly nutritious and better-able to thrive in challenging conditions," says Gehring, who studies plant epigenetics, which is information outside of the DNA. "We intend to identify the molecular basis for these traits and develop genome-engineering technologies enabling us to increase their beneficial effects."

The Project's core objective is to improve orphan crop plants' food-producing potential and resilience to environmental stress, explains Weng, a plant biologist who has done path-breaking research on metabolic evolution in plants. "But we hope that what we learn about adaptive traits in those plants — coupled with the biotechnologies we develop—also enables us to improve widely grown crops such as corn, soybean, and rice."

Looking broadly, Institute director Ruth Lehmann explains that, "The philanthropic support that we've received for the *Dr. Vincent J. Ryan Orphan Plant Project* has been catalytic. Our long-term ability to leverage biological research to address the existential challenge of climate change depends on new philanthropic partners coming forward to work with us."

Talking with Brit d'Arbeloff

For more than five decades, Brit d'Arbeloff has seen and experienced the challenges facing women in science and engineering. She was the first woman to receive an engineering degree from Stanford and finished first in her class — but had difficulty getting a job after graduation. Then, earning her master's degree as the sole woman in Massachusetts Institute of Technology's mechanical engineering department, she grappled with the fact that no faculty advisor would grant her access to their research labs. Despite those and other hurdles, she had an accomplished engineering career.

In the years since, d'Arbeloff became a strong advocate for, and philanthropic supporter of, biomedical research. A longstanding member of the Institute's board of directors, d'Arbeloff is also one of its most abiding donors: Her contributions include a generous gift to establish the Brit Jepson d'Arbeloff Center on Women's Health.

Sharon J. Stanczak, Whitehead Institute's Vice President for External Affairs, recently had an opportunity to ask d'Arbeloff about the motivations for her continuing, significant engagement with the Institute. Here is a portion of their conversation.

SJS: What were the roots of your interest in biomedical science and Whitehead Institute?

BDA: I have a deep curiosity about how things work and it was natural for me to study engineering. Then, because I was excited by the idea of helping advance technologies with significant potential, my engineering career focused first on rocketry and high-speed aircraft and then on computer programming and systems analysis. But since I left engineering, I've focused a lot of time and energy on understanding how human biology works — and on helping advance biomedical research and health care. From the time that I first started paying close attention to Whitehead Institute in the late 1990s, I have marveled at the stream of scientific discoveries and technical advances by its researchers.

SJS: What have you enjoyed most about engaging with the Institute and its scientists?

BDA: As both a donor and board member, I've had many opportunities to attend Institute symposia, informal research talks, and — a special treat — the annual scientific retreat where Whitehead scientists discuss their in-progress work. Those sessions always give me a wonderful jolt of intellectual energy. I have to say, it's also been heartwarming to see the increasing number of women in (and leading!) Whitehead labs. Too often during my long career, I've seen hurdles thrown in the way of women audacious enough to think they would make good biomedical researchers; and I'm very pleased that the Institute is committed to creating opportunities for women to excel as both researchers and leaders in the science community.

SJS: While your philanthropy has supported an array of Institute scientists, your most substantial gifts are helping fund our Initiative on Sex Differences in Health and Disease. Why that program in particular?

BDA: Over the years, I came to understand that a biomedical gender gap existed not only in the research workforce, but in the research itself: Despite the fact that women and men often experienced disease differently, there has been a long history of disregard for research that would drive better preventive, diagnostic, and therapeutic care for women. That's why I've become passionate about research on the basic biology underlying medical conditions that disproportionately affect women. And I'm very excited about the work being done by Institute researchers to understand that biology, from the bottom up. David Page and his team are true pioneers in this effort. They're building a fundamental understanding of the effects that the X and Y chromosomes play in the function of the rest of the genome — as well as in the function of the human proteome, metabolome, and microbiome.

SJS: You sound confident that their work will have a concrete impact on medical care for women.

BDA: I certainly am! In the long run, determining the practical implications of those differences should lead to better, more effective treatments for both women and men. Although this work is still in the early stages, I firmly believe that the effort to understand sex differences in health and disease is as challenging and important as was the Human Genome Project three decades ago. No institution is better positioned to lead that quest than Whitehead Institute. As an advocate for basic science research, I can't think of a better long-term investment in the health of my grandchildren and their children than the support I provide Whitehead Institute.

SJS: And, from your long-term perspective, how is Whitehead Institute doing in the broader context of the role of women in biomedical research?

BDA: I am thrilled by Ruth Lehmann's commitment to the Institute's evolution as a broadly diverse and equitable research community — a place where every scientist is empowered to fulfill their potential. Under her leadership, Whitehead Institute is becoming a model of inclusive and courageous science even as it maintains its pioneering position in foundational biomedical research.

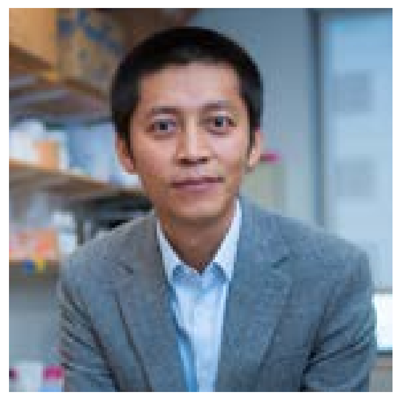
Marks of Excellence

Here is a sampling of the honors and major grants received by Whitehead Institute researchers this past year.

Founding director David Baltimore received the Lasker-Koshland Award For Special Achievement In Medical Science.

The Award, given for research accomplishments and scientific statesmanship that engender the deepest feelings of awe and respect, recognized Baltimore as, "One of the premier biomedical scientists of the last five decades, who is renowned for the breadth and beauty of his discoveries in virology, immunology, and cancer. [And who] has provided visionary academic leadership at multiple institutions and has mentored trainees who have later become prominent scientists in their fields." In 1982, Baltimore collaborated with philanthropist Edwin C. "Jack" Whitehead to launch the Whitehead Institute, which quickly gained a global reputation for pioneering biological research.

Proposals by Institute Members Mary Gehring and Jing-Ke Weng selected for the MIT Climate Grand Challenges program.



The multidisciplinary Massachusetts Institute of Technology effort aims to catalyze discoveries and innovations that lead to game-changing advances in addressing climate change. Gehring's and Weng's projects are key facets of Revolutionizing Agriculture with Low-emissions, Resilient Crops, an initiative pursuing two linked goals: ensuring that yields of agricultural crops do not continue to decrease due to climate change's effects on plant growth; and reducing the greenhouse gas emissions produced by agricultural fertilizer.

Institute Member Siniša Hrvatin received a National Institutes of Health (NIH) Director's New Innovator Award.

Hrvatin investigates how organisms enter the hibernation-like state called "torpor" and how their cells adapt and survive in these states. He has established an experimental paradigm for studying torpor behavior in mice; and has used it to discover the specific neurons that control entry into the state. The NIH Award — which supports unusually innovative research from early career investigators — will provide five years of funding for research projects building on that discovery, enabling his team to explore the mechanisms involved in torpor and to track their potential relationship to growth of cancer cells.

Institute Member Ankur Jain selected as a Pew Scholar in the Biomedical Sciences.

The Pew Charitable Trusts' program supports outstanding young investigators pursuing scientifically risky work that could benefit human health. The award provides Jain with four years' funding for studies of evolutionarily ancient metabolites called polyamines, which are essential for cell growth and survival. Ultimately, this work could underpin novel strategies for treating cancer or promoting healthy aging. Jain, who was previously named a Packard Fellow for Science and Engineering, is the third Institute Member to be named a Pew Scholar, following Mary Gehring and Jing-Ke Weng.

Institute Director Ruth Lehmann received the 2022 Gruber Genetics Prize.

The Prize — one of the most prestigious in genetics — was awarded to Lehmann and fellow developmental biologists James Priess (Fred Hutchinson Cancer Research Center) and Geraldine Seydoux (Johns Hopkins University). It recognized their discoveries on the molecular mechanisms underlying the earliest stages of embryonic development — findings that have transformed germ cell biology and helped answer the fundamental question of how germ cells faithfully transmit genetic information across generations. The trio's findings, the Gruber Foundation noted, have helped to revolutionize modern developmental biology. Lehmann also received the Vanderbilt Prize in Biomedical Science, awarded by the Vanderbilt University Medical Center. That award recognizes women scientists with a stellar record of research accomplishments who also have made significant contributions to mentoring other women in science. Lehmann was honored for both her determination to solve the deepest mysteries of life and her career-long efforts to mentor students and research fellows — for example, by developing a mentorship program that encourages and empowers junior faculty in science.

Institute Member Pulin Li selected as an Allen Distinguished Investigator (ADI).

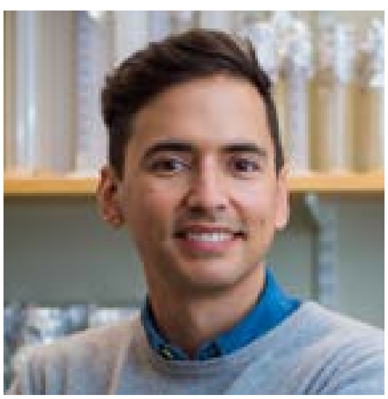
The Paul G. Allen Frontiers Group's ADI program provides three years of funding for notably creative, early-stage biological research projects that would not otherwise be supported by traditional research funding programs. Li combines approaches from synthetic biology, developmental biology, biophysics, and systems biology to study how circuits of genes within individual cells communicate to enable multicellular functions and create the patterns of varied cell types comprising a tissue. Li also received an NIH Director's New Innovator Award, which supports unusually innovative research from early career investigators. The Award will fund her investigations of how the different cell types in the body interact to form organs. The project is part of Li's broader study of how circuits of interacting genes enable cell-to-cell communication — work that could lead to ways to program stem cells to form tissues for regenerative medicine.

Institute Member Yukiko Yamashita received a major grant from the John Templeton Foundation to study germ cell immortality.

One of biology's biggest mysteries is how germ cells — the precursors of egg cells and sperm — avoid aging from generation to generation. The Templeton-supported project focuses on the numerous repeated DNA sequences that occur within the sections of the genome supporting ribosomal function in germ cells. Ribosomes are large enzymes that translate messenger RNA into proteins; and by exploring the importance of maintaining ribosomal DNA repeats, Yamashita's study could identify new approaches for mitigating the cell's aging process — and, potentially, new treatments for cancer.

Postdoctoral researcher Ngoc-Han Tran selected by the Howard Hughes Medical Institute (HHMI) as a Hanna H. Gray Fellow.

Working in the lab of Institute director Ruth Lehmann, Tran studies the endoplasmic reticulum as it operates in the ovary — seeking to understand how it is inherited across generations and how its malfunctions can lead to disease. One of 25 scientists selected for the prestigious appointment this year, the HHMI funding she receives will support her postdoctoral training and may continue into her early career year as independent faculty.



Institute Member Sebastian Lourido received a Smith Family Foundation Odyssey Award.

The Award — which advances high impact ideas with potential to drive new directions in biomedical research — supports Lourido's studies of developmental transitions in single-cell pathogens, such as those that cause malaria and toxoplasmosis. Like caterpillars and butterflies, some single-cell pathogens metamorphose between different forms; and in the process their shape, behavior, feeding abilities, and capacity for transmission change. Lourido seeks to understand the patterns of gene expression underlying such transitions and to find the genetic "master switches" orchestrating these metamorphoses — knowledge fundamental to learning how parasites infect humans.

Community outreach at the 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.

Our programs include:

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 November and lectures are held the first Monday of every month through June. *Visit wi.mit.edu/program/seminar-series-high-school-teachers*.

Spring lecture series for high school students

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 organizations, and opportunities to meet with young Whitehead scientists.
Visit wi.mit.edu/program/spring-lecture-series-high-school-students.

Expedition: Bio

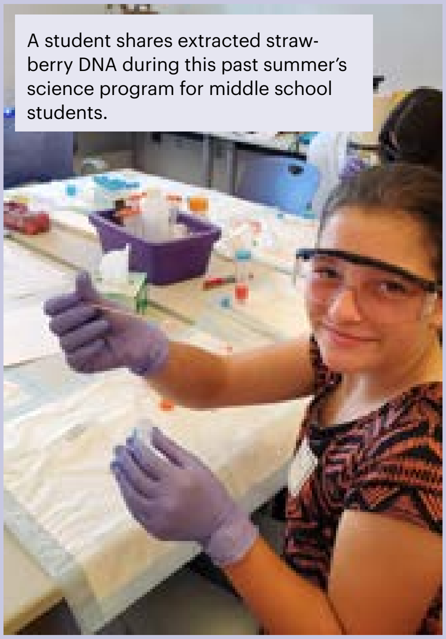
Designed as a two week exploration into the amazing biology that thrives in the world around us, this summer science program for rising 7th and 8th grade students provides immersion in hands-on activities taking students both inside and outside the classroom, laboratory experiments, and discussions with scientists, allowing 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!
Visit wi.mit.edu/program/expedition-bio.

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 opportunities through BioNook's After School Science Club, and ideas for nature-based activities. *Visit wi.mit.edu/bionook*.

Expedition: Bio


Students work together on a team building exercise during the kick-off session of Expedition: Bio.


A student shares extracted straw-berry DNA during this past summer's science program for middle school students.


This July and August, students got their hands on microscopes, micropipettes, and PCR during Expedition: Bio.

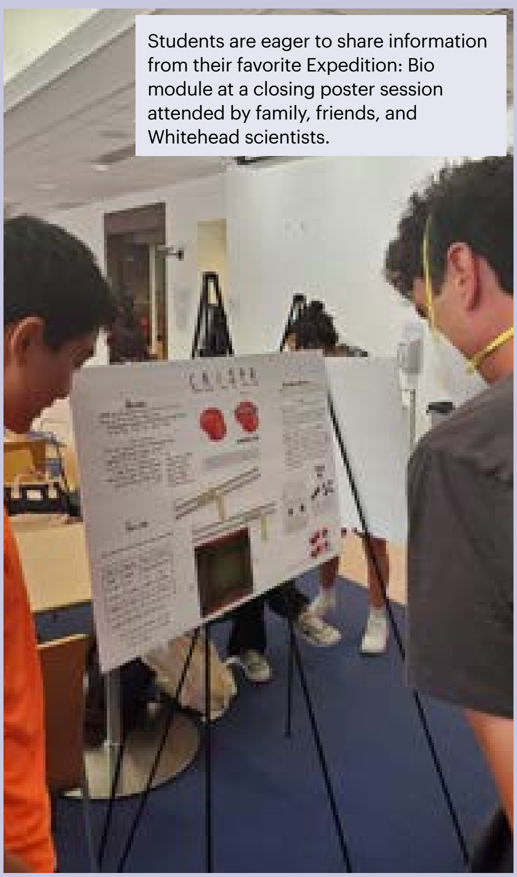

Mel Gadd, Lead Beekeeper at Mass Audubon's Drumlin Farm Wildlife Sanctuary, shares with students the importance of honeybees & how climate change is affecting the synchrony between flowering plants and their pollinators.


Onsite naturalists help Expedition: Bio students identify macroinvertebrates collected from ice pond at Drumlin Farm in Lincoln, MA.

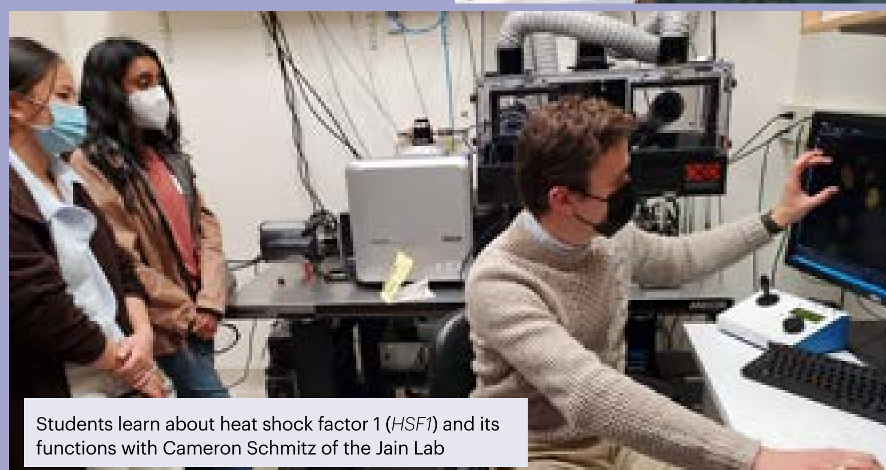
Spring lecture series for high school students

Middle school students line up for a chance to dissect Planaria during a hands-on module about regeneration with Postdoctoral Fellow Thomas Cooke of the Reddien lab.

Members of the Cheeseman Lab help high school students build their own portable microscopes during a module focused on imaging techniques and how microscopy is used in scientific discovery.



Students are eager to share information from their favorite Expedition: Bio module at a closing poster session attended by family, friends, and Whitehead scientists.



Students learn about heat shock factor 1 (*HSF1*) and its functions with Cameron Schmitz of the Jain Lab

Students work together to hone their micropipetting skills

Rebecca Povilus, Postdoctoral Fellow in the Gehring Lab, takes high school students on a tour of the greenhouse at Whitehead Institute to discuss the importance of studying rare and endangered species.

Online conversations on cutting-edge science

This year, thousands of participants tuned in to two of Whitehead Institute's online series that offer insights on leaders in biomedical science, biotechnology, and public health.

In the Director's Dialogue series, Whitehead Institute director Ruth Lehmann spoke with a wide range of experts and pioneers. Nobel Laureate Jennifer Doudna discussed her role in developing CRISPR-Cas9 genome editing. Kevin Churchwell talked about the challenges and opportunities of leading the premier pediatric hospital, Boston Children's. Shah Family Foundation president Jill Shah described her organization's partnerships with local governments to improve public health and nutrition. Massachusetts Institute of Technology researcher and entrepreneur Robert Langer shared his experiences in leading one of the world's most productive and successful academic biotechnology labs. And Boston Globe CEO Linda Henry, along with STAT executive editor Rick Berke, discussed the importance of accurate science-based communications.

This year's Scientific Webinar series spotlighted the work of several Whitehead Institute Members. Olivia Corradin shared her findings on the genetics of opioid addiction. Siniša Hrvatin discussed his studies on the mechanisms of animal hibernation and torpor. Rudolf Jaenisch described the results of his research into the genomic implications of SARS-COV-2 infection. Ruth Lehmann reviewed her investigations on the non-genomic mechanisms through which maternal information is passed on to progeny. And Robert Weinberg described his studies on the mechanisms through which cancer is able to proliferate in new tissues.

Recordings of Director's Dialogues and Scientific Webinars are available at *youtube.com/whiteheadpulse*.

Find information about upcoming Dialogues and Webinars at *wi.mit.edu/events*.

Jennifer Doudna

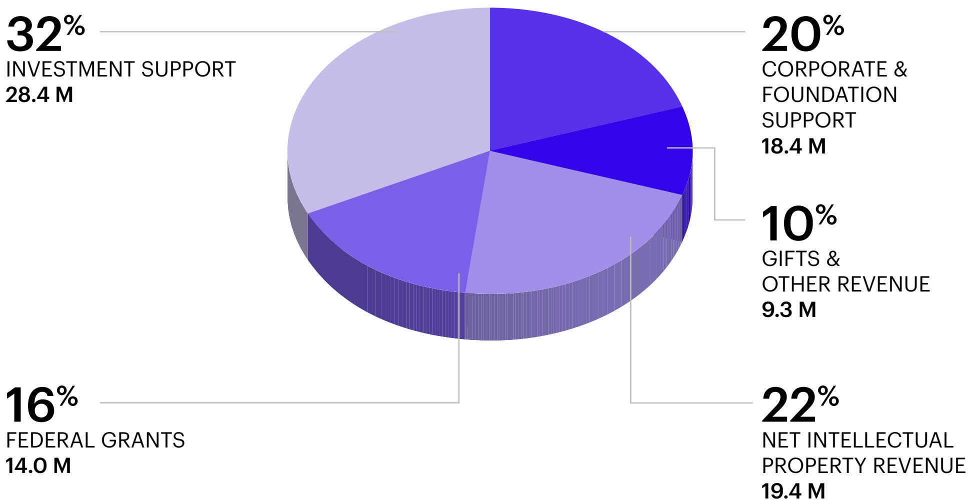
Kevin Churchwell

Robert Langer

Financial Summary

Revenues & Support

2022 TOTAL **$89.5 M**



2021

Investment Support
27.6 M [32%]

Corporate & Foundation Support
17.6 M [21%]

Gifts & Other Revenue
8.6 M [10%]

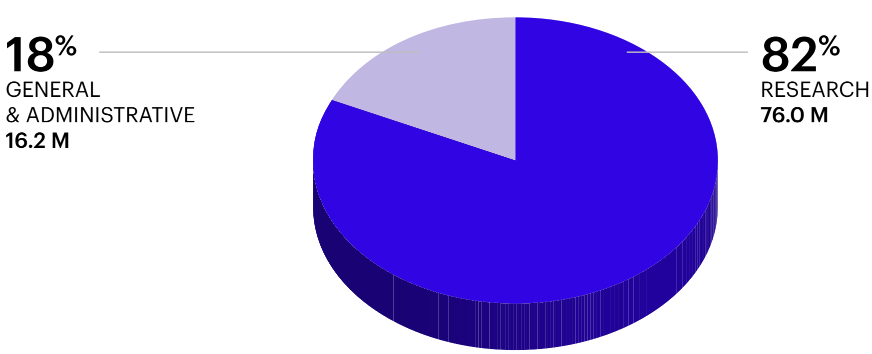
Net Intellectual Property Revenue
16.3 M [19%]

Federal Grants
14.9 M [18%]

TOTAL
$85.0 M [100%]

Operating Expenses

2022 TOTAL **$92.2 M**



2021

Research
67.7 M [80%]

General & Administrative
16.7 M [20%]

TOTAL
$84.4 M [100%]

Whitehead leadership

Director and President
Ruth Lehmann

Founding Members
Gerald R. Fink
Rudolf Jaenisch
Harvey F. Lodish
Robert A. Weinberg

Members
David Bartel
Iain Cheeseman
Olivia Corradin
Mary Gehring
Siniša Hrvatin
Ankur Jain
Pulin Li
Sebastian Lourido
David Page
Peter Reddien
Jonathan Weissman
Jing-Ke Weng
Yukiko Yamashita
Richard A. Young

Whitehead Fellows
Lindsey Backman
Tobiloba Oni
Kipp Weiskopf

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Stephen Elledge
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Harmit Malik
Geraldine Seydoux
Joanna Wysocka

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Monique Taylor, *Assistant Secretary*

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.