HSCI HARVARD STEM CELL INSTITUTE

ANNUAL REPORT 2018

DISCOVERY

FROM LAB TO CLINIC

Top to bottom: – – – Laurence Daheron and Shahryar Khattak, Clifford Woolf and Lee Barrett, Rachel Oshiro and Jessica Whited, Chad Cowan with members of his lab, Max Friesen.

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Letter from the Directors

Medicine has the potential to transform the lives of individuals, families, and societies. It has shaped the world as we know it, and continues to do so in surprising ways. These advances are the result of curiosity—the very human impulse to find new discoveries by diving into the unknown.

Curiosity-driven research powers the Harvard Stem Cell Institute (HSCI). We enable our scientists to take a chance on big, risky ideas, and to put their heads together to push the frontiers of our knowledge. That first, exciting step is crucial to the scientific enterprise, but it is by no means the end of the story.

Our mission is to find cures and develop better therapies for diseases. That means propelling the most promising research from the laboratory into startups and onward to the clinic, where we can translate our new knowledge into possible treatments for real people.

In that regard, 2018 was nothing short of exceptional. Curiosity-driven research from HSCI has advanced to the clinic, bringing us closer than ever to new treatments for conditions such as ALS and vision loss. It has opened up a whole new approach to treating disease, and led to new technologies that are now under intense development in Boston-area startups.

These success stories are not the only advances made in our extraordinary network over the past year, but they are perfect examples of how HSCI is keeping the innovation pipeline moving. By fostering collaborations across Harvard and strategic partnerships throughout the world, we enable a healthy interchange of information and ideas, ensuring the best ones can be taken forward.

The stories you will read in this report highlight our contribution to the innovation pipeline, from discovery to startups to clinical trials. We show how interdisciplinary teams across Harvard have allowed us to study human diseases in human tissues, far more accurately than ever before. We also share new directions in research, for example how we are intensifying our focus on immunology, tricking cancer into turning against itself, and identifying the genetic culprits of cystic fibrosis.

We hope these snapshots in time give you a sense of the momentum we've built at HSCI. To the many people who continue to support this work, you are an essential part of this great endeavor. Thank you for investing in the people and ideas that will change medicine for the better, and improve the lives of people everywhere.

Sincerely,

Douglas Melton, Ph.D.
Founding Co-Director

David Scadden, M.D.
Founding Co-Director

Brock Reeve, M.Phil., M.B.A.
Executive Director

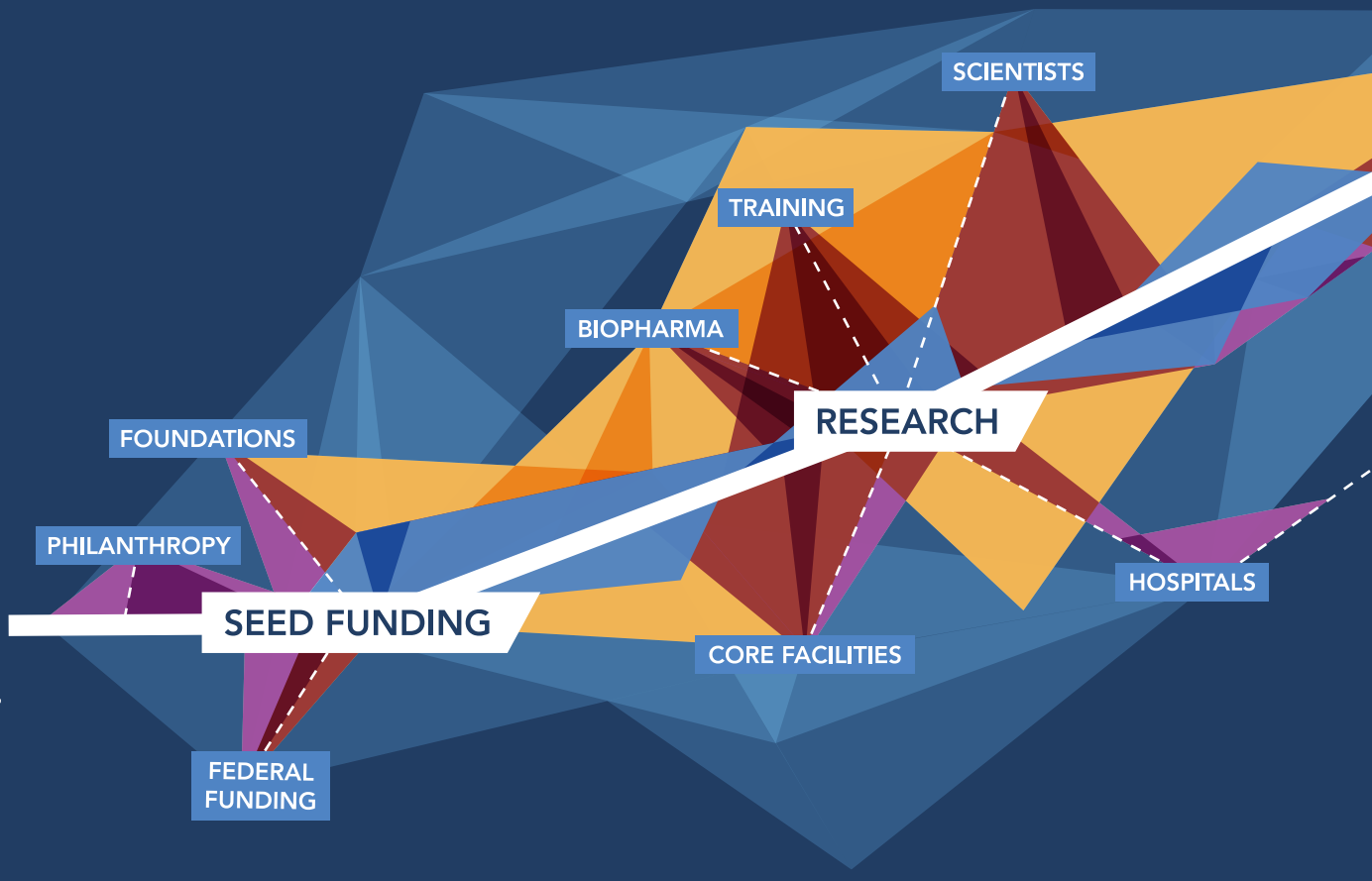
Our Ecosystem of Innovation

The Harvard Stem Cell Institute (HSCI) cultivates brilliant ideas across the university's schools and teaching hospitals in Boston and Cambridge. We leverage knowledge exchange, ingenuity, and entrepreneurship to transform discoveries into new therapies as quickly and efficiently as possible.

The high caliber of our scientists' research attracts funding from many different sources. This makes it possible for them to explore new concepts, gathering cross-disciplinary teams and sharing state-of-the-art equipment.

The discoveries from collaborative projects are often licensed, enabling venture capitalists and industry to invest in them. The resulting startup companies develop foundational discoveries into new therapeutic products and platforms.

From there, technologies can be taken forward to the clinic.



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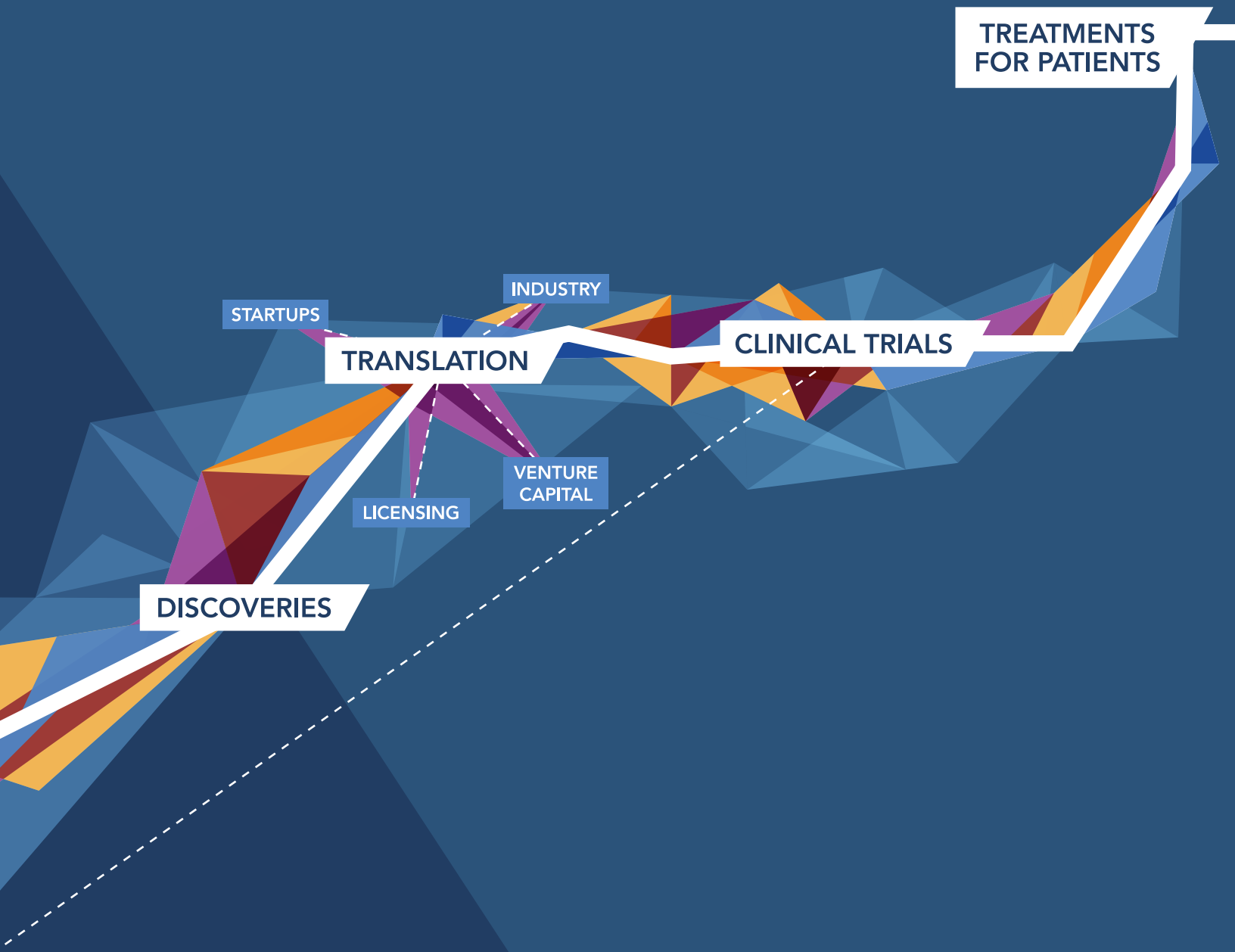
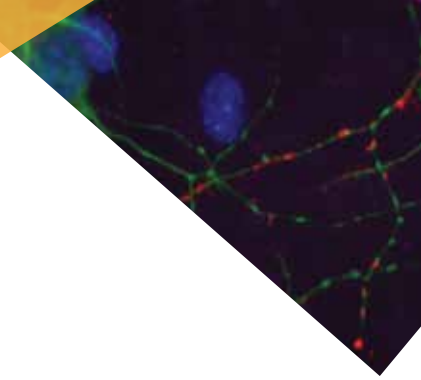


HSCI researchers share what they learn at each stage, disseminating new knowledge throughout the ecosystem. This helps generate more viable, creative ideas, perpetuating the virtuous cycle of innovation.



Accelerating a Treatment for ALS

Clinical trial success based on stem cell models in the lab

Amyotrophic lateral sclerosis (ALS) is a neurodegenerative disease with no known cure, where motor neurons are hyperexcitable—they are overactive and burn out. In 2018, HSCI scientists completed a clinical trial in patients with ALS, showing that the drug retigabine lowers motor neuron excitability.

"This is the first time in a neurological disease where we used patient stem cells in the lab to identify a potential drug, then brought the drug to clinical trial," said Brian Wainger, M.D., Ph.D., HSCI Principal Faculty member and leader of the trial.

"It's exciting that retigabine has a potentially positive effect in patients with ALS, although the benefit on the physiological outcomes in the study may or may not translate into a clinical benefit for patients."

Better models in the lab

The development of retigabine as a potential ALS treatment started a decade ago, when HSCI Principal Faculty member Kevin Eggan, Ph.D. came up with a better way to study ALS in the lab.

ALS is a complex disorder that can be caused by hundreds of different mutations in dozens of genes. This makes studying the disease difficult, both in mice and in humans. Drug responses observed in ALS patients with one mutation may not be observed in ALS patients with another.

"So far, every ALS therapy studied in animal models has not worked in every patient," said Eggan. "When you have all of these different mutations, cell models can help you search for commonalities, or categorize different patient subtypes."

In 2008, Eggan's lab was the first to create patient-specific stem cell lines to study ALS. The researchers collected skin cells from patients with ALS, reprogrammed them into induced pluripotent stem cells, then converted them into the type of motor neurons affected by ALS.

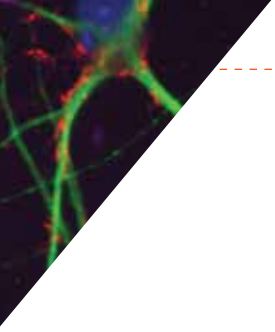
Since then, Eggan has been able to use a model of ALS in a lab dish to study how different mutations impact disease development.

2008

HSCI's Kevin Eggan was the first to make patient-specific stem cell lines to study ALS in the lab.

2014

HSCI scientists identified what the ALS patient cell lines had in common: the motor neurons were hyperexcitable.



Neurons made from induced pluripotent stem cells. *Credit:* Eggan Laboratory.

Targeting hyperexcitability

In 2014, Eggan—collaborating with HSCI Principal Faculty member Clifford Woolf, M.B., B.Ch., Ph.D.—discovered a commonality among the different ALS patient cell lines. They found that most of the genetic mutations caused the motor neurons to become hyperexcitable, or overactive.

The next step was to find and test a drug that reduces excitability in motor neurons. The researchers narrowed in on retigabine: a drug developed to treat epilepsy that prevents seizures using just such a mechanism.

This research was spearheaded by two of Eggan's and Woolf's then postdoctoral fellows, Wainger and Evangelos Kiskinis, Ph.D. Both of them now run their own labs that study ALS: Wainger at Massachusetts General Hospital (MGH), and Kiskinis at Northwestern University.

From lab dish to clinical trial

Because retigabine had previously been shown to be safe in people, and because the retigabine results in the ALS lab models were so robust, the researchers were able to go directly from testing in a dish to testing in a clinical trial—bypassing the time-intensive animal testing that typically goes into therapy development.

Working with GlaxoSmithKline, the pharmaceutical company producing retigabine at the time, Wainger and his MGH colleague Merit Cudkowicz, M.D. ran the trial to test the drug's effects on patients with ALS.

The trial results were positive: retigabine successfully lowered motor neuron excitability in patients with ALS.

Moreover, most of the trial participants have agreed to donate their cell lines for further research, adding to the research team's genetic catalog.

"With the cell lines that we collect from the trial, we'll be able to categorize ALS patients by physiology and genotype in a way that no one has ever done," said Eggan.

The team will further use the cell lines to match patient subtypes to clinical results, and start to tease out the links between which groups of mutations respond best to retigabine or future therapies.

Beyond retigabine

To continue investigating retigabine and other drugs that target motor neuron excitability, Eggan and Woolf founded the biotechnology company QurAlis. Kasper Roet, Ph.D., a former postdoctoral fellow of both Eggan and Woolf, is leading the company.

QurAlis is developing precision medicine for ALS, with one of its programs focusing on hyperexcitability. The company is exploring the opportunity to bring retigabine commercially to ALS patients, and researching alternatives to retigabine that might have the same efficacy with fewer side effects.

2015

An HSCI-supported clinical trial was initiated to test retgabine—a drug that lowers motor neuron excitability—in patients with ALS.

2016

HSCI scientists co-founded the start-up QurAlis to further pursue this therapeutic strategy.

2018

The clinical trial ended with positive results, showing that retigabine lowers motor neuron excitability in patients with ALS.

Below: Brian Wainger led the successful clinical trial.

Stemming Vision Loss

A new clinical trial is using stem cells from the eye to regenerate damaged corneas

The cornea, the clear outer part of the eye, is constantly regenerated by nearby stem cells. Infections, burns, and other conditions can cause the stem cells to die off—leading to a scarred, opaque cornea and vision loss.

Ula Jurkunas, M.D., affiliate faculty member of the Harvard Stem Cell Institute (HSCI), is developing a therapy to replace the cornea-generating stem cells in a damaged eye. After more than a decade of steady progress, a clinical trial to test the stem cell transplant in patients opened to enrollment in 2018.

From one eye to the other

Jurkunas focuses on cases where stem cells are lost in only one eye. Her strategy is to take stem cells from the healthy eye and transplant them into the damaged eye. This 'self-donation' approach ensures the patient's immune system does not reject the transplant.

"This idea of transplanting stem cells to regenerate the cornea is not new," said Jurkunas, who is an associate professor of ophthalmology at Harvard Medical School and Massachusetts Eye and Ear. "Multiple other countries have this treatment as a standard of care, but it is not available in the U.S. because the U.S. requirements for processing methods are very different."

Transplants in other countries are prepared using animal products, and do not meet the manufacturing standards established by the U.S. Food and Drug Administration (FDA).

"We set a goal to develop a transplant product that could be validated under U.S. regulations, and to come up with a clinical trial to test that product," said Jurkunas. "We believed that none of the transplant production was standardized in other studies."

Developing the transplant

In the new therapy, only a small number of stem cells are taken from a patient's healthy eye—so the cells must be multiplied and processed before they can be transplanted into the damaged eye.

"We developed a lot of innovative techniques, in both my lab and Myriam Armant's lab at Boston Children's Hospital, to grow those cells and get them ready for transplant," said Jurkunas.

Researchers typically grow stem cells in a lab dish alongside mouse cells, which provide a rich source of nutrients. To avoid the risk of contaminants, Jurkunas's team figured out how to grow the stem cells without mouse cells.

2006

Ula Jurkunas started working in the lab to develop a transplant to replace damaged corneas.

2010

The research team received grant funding to develop the transplant according to regulatory standards.

Microscope image of cornea-regenerating stem cells.
Credit: Jurkunas Laboratory.

Next, the team worked on growing the stem cells in a layer that could be easily transferred from the dish to the patient's eye during surgery.

"We decided to grow the cells on an amniotic membrane, which is already used as a bandage for eye injuries and is FDA-approved," said Jurkunas.

Because the membrane is taken from placentas, it contains helpful proteins that prevent inflammation, scarring, and blood vessel development—all of which would be detrimental to establishing a clear cornea.

"We also use rings made of medical-grade silicone to secure the membrane within the dish," said Jurkunas. "Then during surgery, we take the membrane out of the ring and transplant it along with all the stem cells."

From bench to bedside

To make sure that the transplant meets FDA regulations, Jurkunas works closely with Jerome Ritz, M.D., HSCI Executive Committee member and professor at Harvard Medical School. Ritz directs the Connell and O'Reilly Families Cell Manipulation Core Facility at Dana-Farber Cancer Institute, which specializes in manufacturing cell therapies according to federal standards.

Jurkunas's team has developed a two-step process for making the transplant: growing the stem cells to large numbers, then putting them on the amniotic membrane to form a layer.

"If you take the cells and put them on the membrane right away, you don't have enough cells to do all the regulatory tests that are required," she said.

Instead, the researchers first focus on growing the stem cells and testing them for cleanliness and the right biological properties. After passing the tests, the researchers put the cells on the membrane to grow into a transplantable layer.

"We did something unprecedented: we developed a treatment all the way from the lab bench to the bedside, in an academic setting, without involving the biopharmaceutical industry," said Jurkunas. "We were able to go through the process using the resources provided by HSCI and its affiliated institutions."

A rigorous trial

In 2018, a clinical trial to test the stem cell transplant in patients opened to enrollment, supported by grants from the National Eye Institute. The trial will continue through 2021, since each bespoke transplant is carefully made one at a time.

"We are doing this very controlled and rigorous trial ourselves, in order to show the feasibility and safety of the transplant," said Jurkunas. "Once we show that, we can scale up and bring this therapy to more patients."

2018

A clinical trial to test the transplant in patients opened to enrollment.

2017

The team received funding for a clinical trial from federal grants NEI UG1EY026508 and UG1EY027726.

Below: Members of the clinical trial team, from left to right: Stephan Ong Tone, M.D., Ph.D.; Jia Yin, M.D., Ph.D.; Ula Jurkunas, M.D.; Lynette Johns, O.D.

A New Class of Therapeutics

HSCI scientist Derrick Rossi was an academic co-founder of biotech company Moderna, which is working to bring a new class of medicines to patients

Unexpectedly, Derrick Rossi's HSCI-funded exploratory research led him to discoveries that informed a broad effort to use messenger RNA (mRNA) as a new kind of therapeutic. Now Moderna, founded by Flagship Pioneering in 2010, has 20 pipeline programs, with 11 in clinical studies. Their initial public offering in December 2018 was the largest ever for a biotechnology company.

Backing early-stage, high-risk research makes success stories like Moderna's possible. Without HSCI's support, Rossi's mRNA research might have foundered. Rossi was able to follow unexpected leads, develop new ideas fully, gain the attention of investors, collaborate with other academic co-founders, and contribute to the creation of a company that is on its way to bringing a new class of treatments to patients.

Bypassing DNA

Messenger RNA is an intermediary. It converts the instructions in DNA into proteins: everything from insulin to antibodies. A protein must have the right sequence and shape to function properly—but if a gene is damaged, the mRNA might not be able to carry out the instructions correctly.

Rossi's goal was to exploit this intermediary. Rather than trying to fix a patient's DNA by inserting genes into target cells, he wanted to insert mRNA equipped with the right instructions to create healthy proteins. The challenge was to introduce those instructions into the cell without setting off alarms.

"When you introduce RNA into a cell, the cell responds as if it is being infected by an RNA virus. The cell goes through a massive antiviral response, shutting down functions or even self-destructing to prevent the 'virus' from replicating. That is the last thing you want if the goal is to have the introduced mRNA encode therapeutic proteins," explained Rossi.

Rossi's approach was to modify the mRNA to appear like the patient's own. Making the right mRNA is a matter of reverse engineering: once the target protein is identified, researchers can figure out the corresponding modified mRNA that can be introduced into cells without eliciting the antiviral response.

According to Rossi, the new, improved mRNA can be 'read' by a patient's own ribosomes—cellular machines that manufacture proteins—and turned into healthy proteins efficiently, without causing any adverse reactions in the cells.

2009

HSCI funded Derrick Rossi's exploratory project, which aimed to deliver mRNA into cells to improve the process of making induced pluripotent stem cells.

2010

Rossi's landmark study was published, successfully demonstrating the new technique.

2010

Flagship Pioneering's VentureLabs innovation team conceived and launched early mRNA platform technology. Biotech company Moderna was founded to bring the new class of treatments to patients.

Cells cultured in the laboratory.

More than meets the eye

"When I first presented the project to HSCI, I mainly wanted to make a better tool for stem cell research," Rossi said. "The idea was to find a new methodology for making induced pluripotent stem cells (iPS cells), using mRNA. The technology we developed ended up being so much more than that."

Rossi's original concept was to make iPS cells without interfering with the genome, by using mRNA that the cell would recognize as its own.

"We found a way to render mRNA invisible to the immune alarm systems of the cell, and that was the key to turning mature cells into iPS cells efficiently," he said.

By working with experienced entrepreneurs as co-founders, Rossi learned that moving around a cell's fate with their new technology wasn't the most interesting part of their findings.

"What was really exciting was seeing how we could make any protein with this technology—because if that was possible, we would have a whole new therapeutic paradigm. Defective proteins underlie much of human disease, and here we had a technology that would allow us to fix those proteins," he said.

Moderna is using their mRNA platform as a treatment paradigm. They hope to achieve a whole new approach to vaccines and therapeutics.

Supporting the discovery pipeline

"When I met with Doug Melton about our project, he saw right away that it was going to be potentially transformative," recalled Rossi. "He also realized it was so exploratory that we wouldn't be able to get it funded through the regular channels. He suggested I apply to HSCI, which I did, and we got seed funding.

2018

Moderna completed the largest-ever initial public offering of a biotech company, attesting to the potentially transformative value of the technology.

"Our real breakthrough touched on a huge unmet clinical need; a lot of patients are in desperate need of specific types of proteins to treat their illness. But remember—that wasn't what we set out to do. This is often how science works: you think you're working on one thing, and it turns out you're working on something else," said Rossi.

Investors have been confident in the potential of Moderna's technology for creating transformative treatments: the company's IPO in December 2018 was the largest of any biotech to date, underscoring the potentially transformative nature of the science on which it is based.

HSCI Executive Director Brock Reeve said, "When HSCI gives outstanding, innovative, and imaginative scientists like Derrick Rossi seed grant support, it can change a field quickly and dramatically. Derrick's initial exploratory idea has transformed into so much more: a technology that could make a real difference to patients and their families."

Moderna at a Glance

Based on initial research supported by HSCI

Founded in 2010 by Flagship Pioneering working with academic co-founders **Derrick Rossi**, Kenneth R. Chien, and Robert Langer.

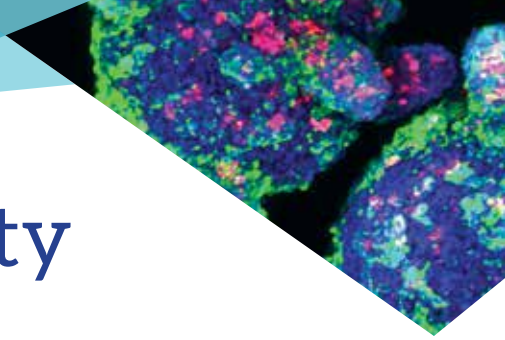
11 research programs have entered clinical studies

$1.7B in private funding received before IPO

$2.6B raised overall

Major stakeholders: Flagship Pioneering, AstraZeneca, Merck

Credit: Moderna.



Advances in Autoimmunity

HSCI researchers investigate how we can protect the body from immune attack, and prevent stem cell transplants from being rejected

The immune system normally defends the body against invaders: everything from microscopic viruses to meters-long parasitic worms. But when it sets its sights on the body's own cells, disaster ensues. Over the past 30 years, autoimmune diseases have reached epidemic proportions.

Harvard Stem Cell Institute (HSCI) researchers are tackling the issue from many different angles.

Type 1 diabetes: transplant vs. autoimmunity

Patients with type 1 diabetes cannot produce insulin because their immune cells attack their own beta cells. Located in the pancreas, beta cells produce insulin, the molecule necessary to convert food into energy. Without it, patients must monitor their blood and inject themselves with insulin multiple times a day.

HSCI Co-Director Douglas Melton, Ph.D. discovered how to make beta cells from stem cells in 2014. With this method, a patient's own stem cells can be converted to beta cells in the lab and transplanted back, enabling them to produce their own insulin.

The next step is to figure out how to protect those transplanted cells from immune attack.

Protecting the beta cell

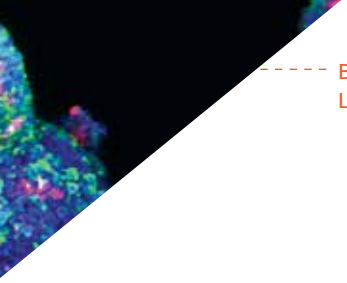
"We've decided to protect the beta cell, no matter how the immune system might attack it," said Melton, describing his lab's work. "We want to make it invisible to the immune system altogether, and to do that we are using genetic modification."

The biology of pregnancy gives some clues about how the body protects 'foreign' tissues. Half of the genes in a fetus are foreign to the mother, as they come from another person. To shield itself from attack, the fetus expresses protective molecules that make it 'invisible' to the immune system.

Could this approach work for beta cells? To find out, Melton's group is searching for protective molecules that would make immune cells see beta cells as the body's own.

"When we grow cells to transplant into a person, we grow around 500 million of them. So we have plenty of material to experiment with," Melton explained. "We remove one gene at a time from

Nayara Leite, postdoctoral researcher in the Melton lab, holding a flask of 500 million beta cells.



Beta cells made from stem cells. *Credit:* Melton Laboratory.

each beta cell. Most of those mutated cells would still be killed by the patient's immune system. But wouldn't it be fantastic if there was some mutation that made the beta cell invisible to immune cells?"

A shot in the dark

Stephan Kissler, Ph.D. and his colleague Peng Yi, Ph.D. of the Joslin Diabetes Center have completed an experiment similar to the one Melton is planning. They mutated a collection of mouse beta cells to produce a mixture of millions of cells, with different mutations in every possible gene.

"We took an approach that was a bit of a shot in the dark," Kissler said. "We put the cells in a diabetic mouse, and then we just waited. The immune system killed off beta cells like it normally does. But after two months, we went back and found a small number of cells that were still there."

The protected beta cells had mutations in just a dozen different genes, whittled down from thousands. In follow-up experiments, the collaborators compared regular and modified beta cells directly.

"Regular beta cells that aren't protected with the mutation are gone within days, and beta cells with the mutation kick around for weeks," Kissler said.

Now, Kissler and Yi are investigating how these particular genes are involved in autoimmunity. In collaboration with the Melton lab, they are testing the genetic modifications that worked in mice in a human cell experimental system.

"Our two top candidate genes are associated with diabetes in people, and we're very excited because that provides relevance to human disease," Kissler said. "That gives us a lot of hope that if we were to do this in human cells, we might get similar effects."

Early support from HSCI

Melton, Kissler, and Yi learned about their shared research plans by serendipity.

"Doug Melton just happened to ask our opinion about something he wanted to do," Kissler said. "He had the idea of doing a similar genetic screen in human cells, but he didn't know about what we were doing yet."

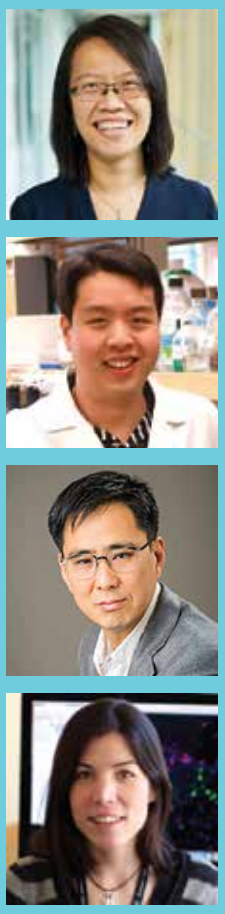
When Kissler and Yi shared the early results from their screen, Melton and HSCI supported their work.

"HSCI provided us with enough funding to get started," Kissler said. "The screen itself wasn't very resource-intensive, but everything that came after required a lot more support. Based on the results of that initial work, we applied for and received JDRF and NIH support. So now we can really keep going."

Autoimmunity across diseases

In 2018, collaborators in the HSCI Junior Faculty Program started to investigate how stem cells respond to autoimmune attack, so they can discover how to protect cells in a number of different diseases. They are studying the interactions between stem cells and immune cells in different parts of the body, including the skin and gut.

Crossing disciplines and institutions to work together, their complementary approaches hold promise for identifying treatment targets for autoimmune diseases.



Collaborators in the Junior Faculty Program, from top to bottom: stem cell biologist Ya-Chieh Hsu, Ph.D.; neuroimmunologist Isaac Chiu, Ph.D.; autoimmunity expert Jun Huh, Ph.D.; and immunologist Judith Agudo, Ph.D.

Research Highlights

With over 1,000 scientists at Harvard and its eight affiliated hospitals, research at the Harvard Stem Cell Institute (HSCI) spans diseases and disciplines to bring treatments to patients.

Our scientists innovate along all stages of discovery: investigating the biological mechanisms that drive disease, building disease models that improve the quality and speed of drug discovery, and engineering new therapies.

HSCI researchers published over 250 studies in 2018. Here, we highlight just a few examples.

Exercise may help make the heart younger

Exercise is good for the heart, but scientists still do not completely understand why. Research led by Richard Lee, M.D. and Anthony Rosenzweig, M.D. uncovered one potential reason: exercise stimulates heart regeneration.

The researchers gave mice voluntary access to a running wheel, and administered a labeled chemical to measure the production of new heart muscle cells. They found that healthy mice that exercised made over four times as many new heart muscle cells as their sedentary counterparts. After experiencing a heart attack, mice that exercised showed a larger area of heart tissue where new muscle cells were made.

Because heart attacks and aging lead to a loss of heart muscle cells, figuring out how to promote heart regeneration is key to maintaining a healthy heart.

Heart research gets a better 3D model

Heart models used in stem cell research are typically made up of flat layers of cells in a dish. One of their major shortcomings is that they do not capture the 3D nature of the heart. An HSCI collaboration between bioengineer Kevin Kit Parker, Ph.D. and cardiovascular researcher William Pu, M.D. set out to solve the problem.

First, the researchers built a scaffold by spinning nanofibers into the shape of a heart chamber. Then, they added heart muscle cells that were either from rats or derived from human stem cells. Their new 3D heart model contracted spontaneously, pumping fluid in and out of the chamber.

By combining bioengineering with stem cell technology, this 3D model can be used to study heart disease and test potential new therapies.

How to build a whole organism from a single cell

One of the leading scientific journals, *Science*, named research by HSCI scientists as the 2018 Breakthrough of the Year.

Alexander Schier, Ph.D. and Allon Klein, Ph.D. analyzed the genetics of individual cells in zebrafish and frog embryos during the earliest stages of development. As part of the studies, they created a genetic roadmap for building an entire organism from a single cell.

This technology for tracking cells in fine detail is an invaluable tool for studying what goes wrong in human cells during the progression to cancer, diabetes, and other diseases.

A deeper understanding of cystic fibrosis

Scientists have known for decades that cystic fibrosis is caused by a defective *CFTR* gene. But until a new study led by Jayaraj Rajagopal, M.D., published in 2018, the specific cells responsible for making CFTR were unknown.

The researchers used single-cell sequencing technology to measure gene expression in the mouse airway. With this data, they built a detailed catalog of many different cell types. This allowed them to identify a rare new cell type, called an 'ionocyte,' in which *CFTR* gene expression was concentrated.

Armed with this new understanding of normal lung biology and lung diseases, researchers can focus their efforts and accelerate progress in fighting cystic fibrosis.

Turning cancer against itself

Cancer cells have a self-homing ability, moving around the body to locate tumors. Khalid Shah, M.S., Ph.D. exploited this ability, engineering self-targeting cells that deliver therapeutic molecules to tumors.

Using CRISPR gene editing, the researchers equipped cancer cells with a therapeutic protein. They also engineered the cells to have a self-destruct mechanism. The engineered cells targeted and eliminated primary and metastatic tumors in mice, and were successfully removed after doing the job.

The study demonstrates that engineered cancer cells are a potential therapeutic strategy for different types of tumors.

High-fat diet could drive aggressive prostate cancer

Many men who are affected by prostate cancer do not die of it: the tumors are typically slow-growing and self-contained. But when prostate tumors metastasize, or spread beyond the prostate, the disease is invariably fatal.

A study by Pier Paolo Pandolfi, M.D. linked dietary fat, an environmental factor, with aggressive prostate cancer. In mice with a genetic background that predisposed them to prostate cancer, tumors metastasized only when the animals were fed a high-fat diet.

Motivated by these results, Pandolfi is planning a clinical trial to test whether an obesity drug that blocks fat production can be used treat prostate cancer.

Background image: Hair follicles and fat cells in the skin. *Credit:* Hsu laboratory.

Donor Stories

Philanthropy is crucial to the success of biomedical research, where the quest for solutions is full of unexpected twists and turns. Our donors are committed to scientific progress, and believe in the potential of stem cell science to change medicine for the better. They support HSCI not only because Harvard produces groundbreaking research, but because our scientists reach across traditional boundaries to work together and find cures for disease. Here, Scott Malkin and Doug Tinker talk about why they have supported HSCI over the years.

Scott Malkin
Harvard alumnus and HSCI donor

The power of interaction

Scott Malkin, HSCI donor

Harvard, and its community, will be measured by how we make a tangible, positive impact on the world. Supporting innovative science through unrestricted giving allows great talent to experiment, to flourish, and to make a lasting contribution to society. At Harvard today, this is what it means to support excellence.

HSCI reflects the qualities that define a great research university. Year after year, its network of scientists are doing extraordinary things and are the model for what should be normal at Harvard. The brightest young stars are competing to work here, adding their enthusiasm and originality to the Boston-area biotech ecosystem.

> The energy and passion of HSCI's many outstanding scientists exemplify Harvard at its best.

My wife Laura and I were first introduced to the work of HSCI, and its cross-University mission, some 15 years ago. Doug and David have since then created a multi-institutional enterprise built upon the collaboration of brilliant, committed scientists. HSCI has generated spontaneous interactions between such scientists across various disciplines; this approach opens the door to important discoveries.

Discovery can occur abruptly and decisively. Harvard needs to fuel endeavors like HCSI to maintain momentum in stem cell science and continue to attract the best scientists from around the world. In the end, it is this intersection of opportunity and talent that will make the real difference.

Laura and I remain inspired by Doug and David's vision for HSCI. The energy and passion of the many outstanding scientists who are contributing to this shared enterprise exemplify Harvard at its best.

Left to right: Alana Allen and Torsten Meissner, Ya-Chieh Hsu and Meryem Gonzalez Celeiro.

Supporting high-risk, high-reward research

Doug Tinker, Bowes Acceleration Fund at HSCI

The William K. Bowes, Jr. Foundation was founded nearly three decades ago through the vision of Bill Bowes. I worked closely with Bill for many years, and since his passing I have been guiding the foundation to carry his wishes forward. One key way we do this is by supporting high-risk, high-reward research at the Harvard Stem Cell Institute.

> This is a high-risk approach, and we choose it because of the high degree of success it can accomplish.

Bill was a very strong believer in the potential of stem cells and regenerative medicine to move our society forward. Supporting HSCI is a natural fit with his perspective, not only because of HSCI's mission to cure human diseases, but also because of how the mission is achieved: by forming a vibrant community of a thousand scientists, and seeding collaborations between academic and hospital environments.

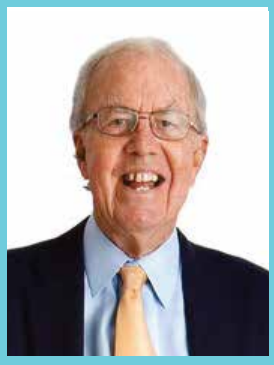
In particular, we established the Bowes Acceleration Fund at HSCI to support early-stage, exploratory projects. The fund reflects Bill's experience as a venture capitalist and businessman—we fully understand that this is a high-risk approach, and we choose it because of the high degree of success it can accomplish.

Just as one example, a decade ago we supported a pilot project to improve how stem cells are made in the lab. The technology from that project has since become the basis for an entirely new class of therapeutics. In 2018, the company developing these therapeutics had the largest ever initial public offering for a venture-backed biotech company. *[Ed. Read the full story on pages 8–9]*

We are also excited by the diversity of projects that the Bowes Acceleration Fund has supported. Researchers are like entrepreneurs: they're searching for discoveries that can be very elusive, and they need to be persistent.

This is why we support many well-thought-out, targeted projects across different disciplines—it keeps everyone working to move the ball forward, and that's what it will take to achieve success.

Doug Tinker
President of the William K. Bowes, Jr. Foundation



Bill Bowes
Founder of the William K. Bowes, Jr. Foundation

2018 in Review

Allon Klein and Alexander Schier published studies showing how to build a whole organism from a single cell. Their research was named the **Breakthrough of the Year** by leading journal Science.

2 companies co-founded by HSCI faculty went public:

Magenta Therapeutics
Moderna Therapeutics

3 **new industry collaborations**

HSCI's Harvard Fibrosis Network and **Bristol-Meyers Squibb** are collaborating to discover and develop potential new therapies for fibrotic diseases, including fibrosis of the liver and heart.

HSCI scientists are collaborating with **Frequency Therapeutics** and the **U.S. Army Institute of Surgical Research**, using small-molecule drugs to address different muscle conditions.

HSCI scientists and biotech company **Orig3n** are collaborating to develop cell therapies to treat cardiovascular disease.

HSCI launched a collaboration with the **Qatar Biomedical Research Institute** to train QBRI scientists and facilitate knowledge exchange, with joint research projects in diabetes and other areas.

4

faculty joined the Junior Faculty Program, crossing disciplines and institutions to study autoimmunity.

12

HSCI faculty received awards or recognitions.

14th year of the **HSCI Internship Program**

600 applicants in 2018
32 undergraduate interns
19 colleges/universities represented

7 countries represented in 2018: Bolivia, Canada, India, Italy, Sri Lanka, Turkey, United States

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