HARVARD STEM CELL INSTITUTE®

ANNUAL REPORT 2019

TRANSFORMATION

15 YEARS OF STEM CELL RESEARCH

REPORT DESIGNED BY
Opus Design

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ON THE COVER
Liver cells under the microscope.
Image courtesy of the Wagers lab.

PLACE

Boston is the global hub of biomedical innovation, and Harvard is at the center of it all. Our teaching hospitals, research infrastructure, and network of excellence provide rich ground for discovery, pushing the frontiers of science ever more swiftly towards cures for patients.

Harvard University and the Charles River.
Photo by Rose Lincoln.

FIFTEEN YEARS

of the Harvard Stem Cell Institute

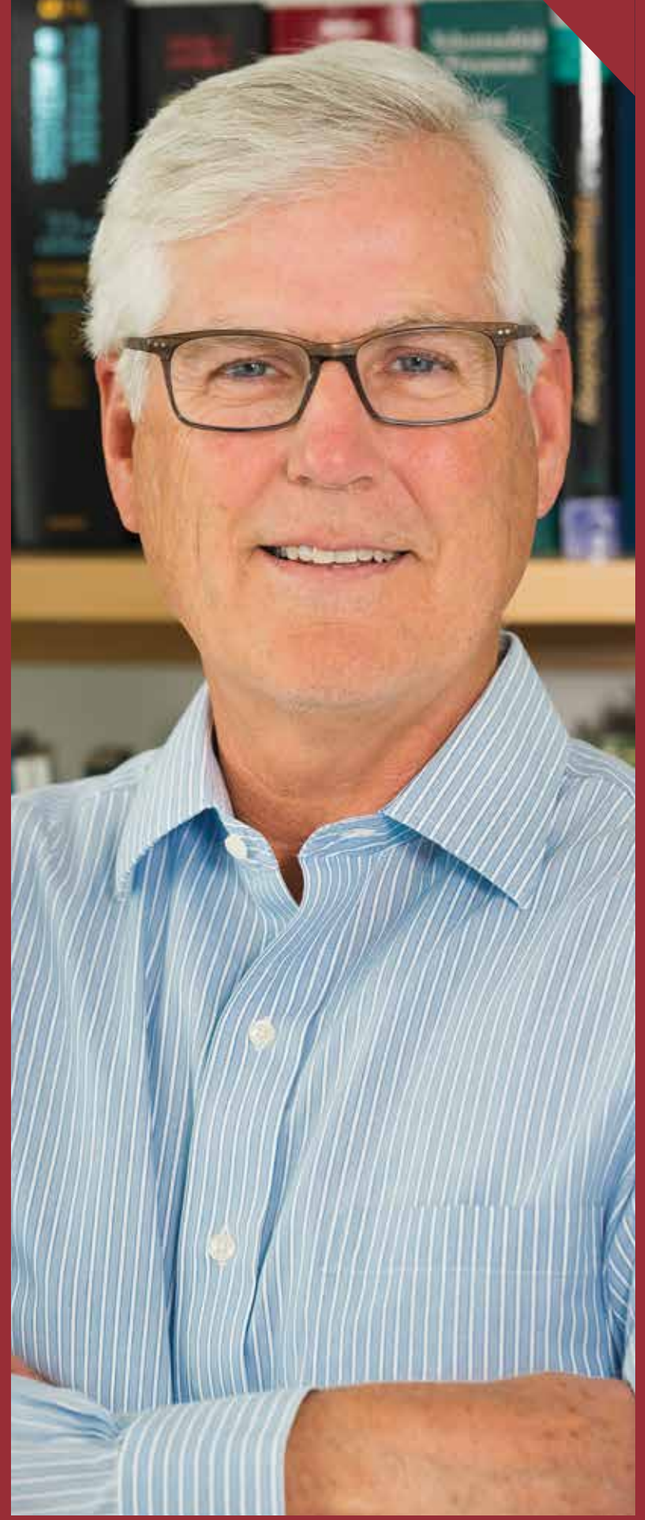
DOUGLAS MELTON, PH.D.

FOUNDING CO-DIRECTOR OF HSCI

HSCI has been breaking down barriers to collaboration in stem cell science for the past 15 years. We have been instrumental in changing the traditional model of research, which kept a wall between exploratory research and commercial development. Now, we bring communities together across sectors to work on shared problems and advance the frontiers of medicine. As an example, when you consider how far we have come towards cell replacement therapies for diabetes patients, you can appreciate how wildly successful that approach has been.

I am proud of the effect this change has had on younger faculty, who come to us from all over the world to share their ideas and make meaningful contributions to science and medicine. They join HSCI to be part of something much more meaningful than generating papers and advancing careers: together, we have been creating and applying new knowledge in ways that will change the lives of patients and their families for the better.

The rapid advances in stem cell medicine since 2004 have been thanks not only to breakthrough technologies, but to a culture that combines cross-disciplinary collaboration and visionary philanthropy. With Harvard as a wellspring of discovery and a strong network that embraces new ways of working, we are better equipped than ever to change human health in ways that will benefit all of society.



DAVID SCADDEN, M.D.

FOUNDING CO-DIRECTOR OF HSCI

When HSCI launched in 2004 it was not easy to engage with other scientists across institutions at Harvard. Basic research was so far removed from hospital- and industry-based research that we didn't have a clear path to translating discoveries into products that benefit patients.

HSCI has turned that around. We now have the flexibility to organize people across institutions and sectors to tackle specific biological problems, and that has changed the way Harvard thinks about scientific collaboration. HSCI discoveries made in academic labs can now move much more easily into nimble companies that can bring new knowledge and potential therapies to doctors and patients. And that is what matters.

Over the next 15 years, if we are successful we will discover how stem cells can be used not only to repair injury, but to prevent age-related disease effectively. As a physician, I could not be prouder of what we have achieved, or more excited about what's to come.

BY THE NUMBERS

39	HSCI FACULTY IN 2004
360	HSCI FACULTY IN 2019 *102 Principal + 258 Affiliate*
123	SEED GRANTS SINCE 2004
36	START-UPS BASED ON HSCI RESEARCH
557	UNDERGRADUATE INTERNS SINCE 2004

POTENTIAL

What holds more potential than a stem cell? By its very nature it can become anything: a new treatment, a target for a drug, or tool for studying disease. HSCI scientists are changing the face of biomedicine by exploring and exploiting this potential to the fullest.

Hair cells of the inner ear. Image courtesy of the Karp lab.

Advances in stem cell treatments

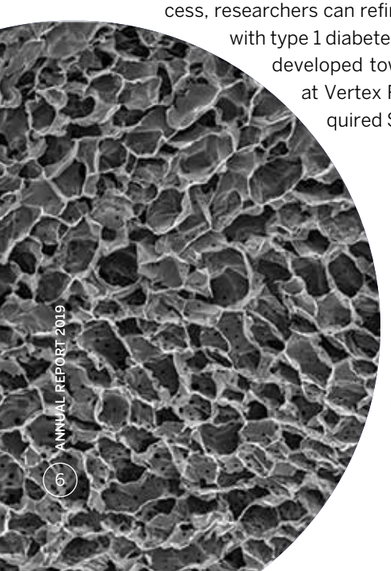
Stem cells have the potential to transform medicine by serving as a replacement source for diseased cells. In 2019, HSCI researchers made strides toward bringing cell therapies to patients by focusing on specific conditions such as diabetes and vision loss, and toward preventing the immune rejection of transplanted cells.

REFINING CELL THERAPY FOR DIABETES

In 2014, Douglas Melton, Ph.D. showed for the first time that stem cells could be converted to mature, functional beta cells in the lab, a major step toward giving diabetes patients their own source of insulin. In 2019, Melton developed a way to improve the conversion process, significantly boosting the yield of insulin-producing beta cells.

HSCI researchers analyzed beta cells using single-cell sequencing, and identified a protein expressed uniquely by those cells. By targeting the protein and adding a physical enrichment method developed by collaborators at Semma Therapeutics, the researchers improved the purity of beta cells from 30% to 80%.

With improved control over the beta cell production process, researchers can refine cell therapy for patients with type 1 diabetes. The work is being further developed towards clinical applications at Vertex Pharmaceuticals, which acquired Semma in 2019.



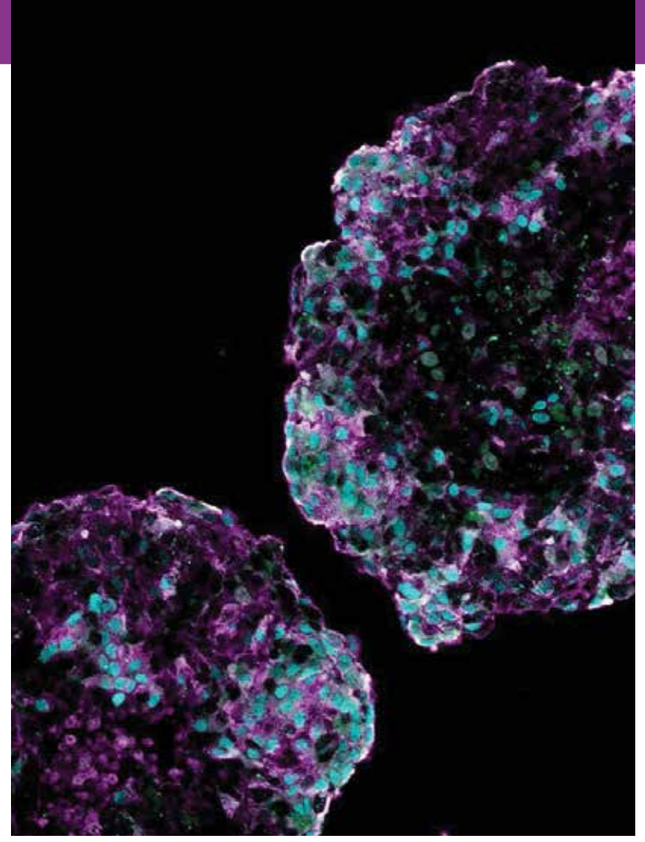
A bioengineered, injectable sponge improves immune response after a bone marrow transplant.

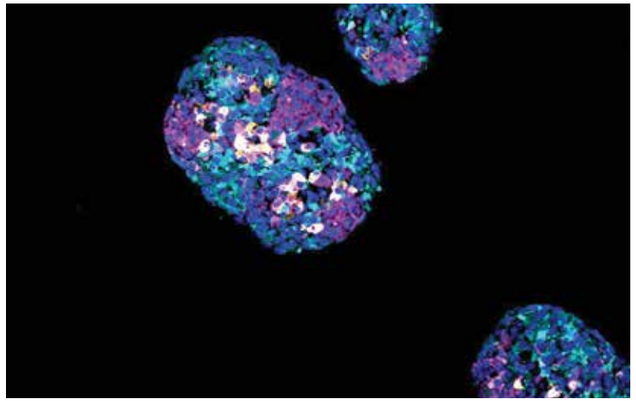
BIOENGINEERING IMPROVEMENTS FOR BONE MARROW TRANSPLANTS

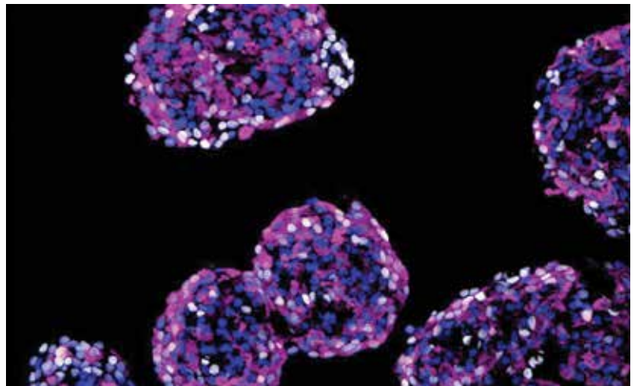
Bone marrow transplants are a life-saving treatment for a range of blood cancers and diseases, but many transplants fail due to rejection by the patient's immune system. One way to mitigate rejection is to augment bone marrow transplants with mesenchymal stromal cells (MSCs), which have the capability to help reduce the immune system's negative effects.

HSCI researchers David Mooney, Ph.D. and David Scadden, M.D. developed an improved method to deliver MSCs and enhance their effectiveness. They took a bioengineering approach to the problem, coating individual MSCs with a thin layer of hydrogel. The coating protected the cells from being cleared by the body, and improved the success of bone marrow transplants in mice.

In a separate study, the same team addressed a different problem: profound, long-term, immune deficiency experienced by patients after bone marrow transplantation. To protect transplanted cells, patients undergo chemotherapy and radiation to suppress their immune cell production. This compromises the patient's ability to generate immune cells long after treatment. Mooney and Scadden developed an injectable, sponge-like gel that enhances the production of T-cells after a bone marrow transplant. This bioengineered device, which can be injected under the skin, helps revive the immune system after bone marrow transplantation by increasing the quantity and diversity of immune cells.







Clusters of cells derived from stem cells, enriched for insulin-producing beta cells.

A CLINICAL TRIAL FOR RESTORING VISION

As the eye's outer layer of protection, the cornea needs to constantly regenerate to maintain a clear surface. Vision loss can occur when cornea-regenerating stem cells are damaged due to injury or genetic disease. Natasha Frank, M.D. and Markus Frank, M.D. developed a therapy to replace cornea-generating stem cells and restore vision — and in 2019, they tested it in a patient for the first time.

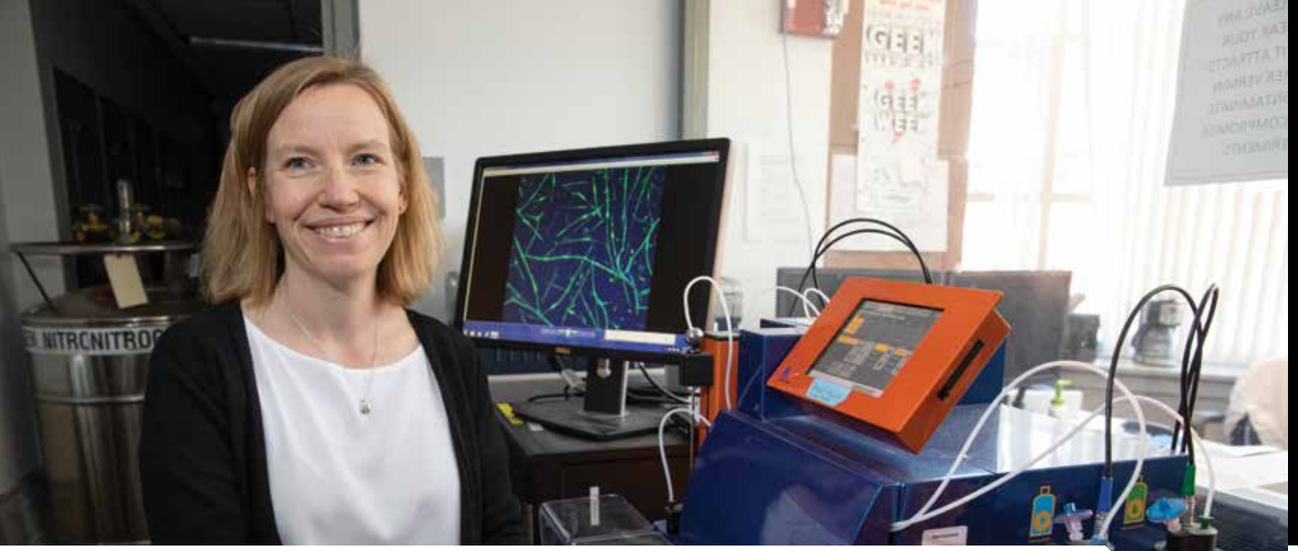
The researchers identified a molecule on the surface of cornea-regenerating stem cells that can be used to purify the cells. HSCI supported this work during its early, high-risk stage, before the clinical significance of the cell-surface molecule was understood. In the ongoing clinical trial, the treatment process involves taking donor eye tissue, purifying the stem cells, and transplanting the cells to patients with stem cell deficiency.

CELL THERAPIES FOR ANY PATIENT, ANY DISEASE

Organ transplants are sometimes rejected by the patient's immune system, a situation that can also happen with transplanted cells derived from stem cells. Innovations by HSCI researchers are now enabling a biotechnology company to develop a solution that may work in cell therapies for any patient with any disease.

With funding from HSCI, Chad Cowan, Ph.D. developed methods for making stem cells that are genetically engineered to hide from the immune system. The cells' genomes are modified to reduce the activity of genes that produce the proteins that can provoke the transplant recipient's immune system, and to increase the activity of genes that produce molecules that signal "friend," not "foe." The modified cells can then be converted into any cell type and transplanted into a patient.

In 2019, Cowan co-founded the start-up Sana Biotechnology. The company is commercializing the HSCI innovations, with the potential to improve cell therapies for many conditions.



Targeting stem cells at the source

Breakthrough research shows stem cell genes can be edited in living systems

In 2019, HSCI scientist Amy Wagers, Ph.D. demonstrated that gene-editing machinery can be delivered straight to stem cells where they live, rather than in a lab dish. The findings have major implications for the development of therapeutics for genetic diseases, such as Duchenne muscular dystrophy (DMD).

"If you want to change a genome to correct a disease-causing gene mutation, you have to change it in the relevant stem cells," said Wagers, an HSCI Executive Committee member. "If you don't change the stem cells, whatever cells you do fix may eventually be replaced with diseased cells fairly quickly. If you do fix the stem cells, they will create healthy cells that can eventually replace the diseased cells."

But fixing stem cells is harder than it sounds. Current cell therapies are limited because stem cells have to be extracted, kept alive and healthy, and genetically altered before being returned to the patient's body. This process is disruptive for the cells, which may ultimately be rejected or fail to engraft back into the patient.

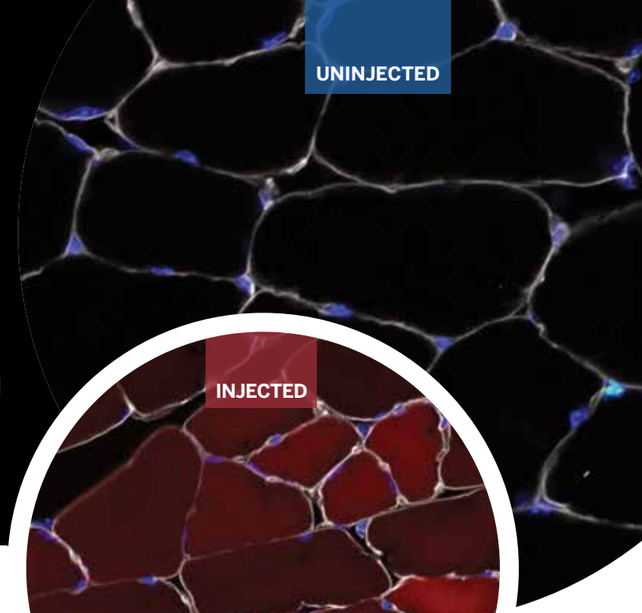
Each type of stem cell is well protected in its own "niche," often in hard-to-reach places like bone marrow. "When you take stem cells out of the body, you take them out of the very complex environment that nourishes and sustains them, and they kind of go into shock," Wagers said. "Isolating cells changes them. Transplanting cells changes them. Making genetic changes without having to do that would preserve the regulatory interactions of the cells — that's what we wanted to do."

Amy Wagers in her lab. Photo by Jon Chase.

60%
muscle stem cells successfully edited

38%
blood stem cells successfully edited

27%
skin stem cells successfully edited



Cells before and after being injected with gene-editing cargo, turning red when the cargo was successfully delivered.

TRANSPORT BY VIRUS

Wagers' group used an adeno-associated virus (AAV) that infects human (and mouse) cells — but does not cause disease — as a transport vehicle. Building on their earlier work in mice with DMD, Wagers and her colleagues created various AAV packages to deliver gene-editing cargo into several different types of skin, blood, and muscle stem and progenitor cells.

To test whether their AAV complexes managed to deliver, the researchers used mice that act as so-called reporter systems via a "reporter" gene that is normally silenced but can be turned on by gene editing. When the reporter gene is activated, the cell turns bright, fluorescent red.

UP TO 60 PERCENT EFFECTIVE

The researchers observed that in skeletal muscle, up to 60 percent of the stem cells turned fluorescent red. But the utility of the approach extends beyond muscle to other tissues. In cells that give rise to different types of skin cells, up to 27 percent of the cells turned red. Up to 38 percent of the stem cells that make blood in bone marrow were changed. That might seem low, but blood turns over so quickly that in some cases even a single healthy stem cell may be sufficient to rescue a defect.

"We looked at the skin of these AAV-transduced mice from the Wagers lab, and were pleased to see that many dermal cells were successfully edited as well," said Ya-Chieh Hsu, Ph.D., an HSCI Principal Faculty member. "Those included cells that give rise to dermal adipocytes, and cells that help regulate other stem cells in the skin. We've always needed a tool that lets us manipulate dermal cells *in vivo* rapidly — so for us, this is like a dream come true."

'THINGS MIGHT START TO MOVE VERY QUICKLY'

Delivering a gene therapy directly into a living system has been a barrier for biotech companies trying to develop therapies for diseases like spinal muscular atrophy.

"This is a really important resource for the community," Wagers said. "It changes the way we can study stem cells in the body — the AAV approach lets researchers investigate different genes for stem cells in their native environment, much more quickly than ever before. The delivery system is robust enough that it can also be used to target genes that affect many different tissues.

"It's also an important step toward developing effective gene therapies. The approach we developed gets around all the problems you introduce by taking stem cells out of a body and allows you to correct a genome permanently. AAVs are already being used in the clinic for gene therapy, so things might start to move very quickly in this area."

Tools to accelerate discovery

FIG. 1

FIG. 2

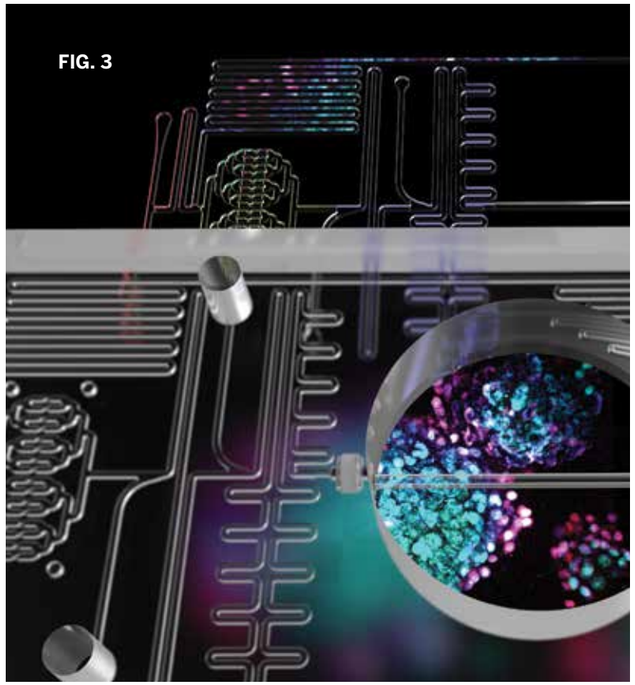


FIG. 3

Fig. 1 A brain organoid with multiple types of neurons, representing the complexity of the human brain.
Fig. 2 Kidney organoids connected by a network of blood vessels.
Fig. 3 Pancreas-on-a-chip device combines microfluidics technology and insulin-producing beta cells.

HSCI scientists develop innovative stem cell technologies that are changing the way we study disease. In 2019, HSCI researchers found new ways to reprogram stem cells to become specific tissues, for example taking skin cells from a patient and reprogramming them to become nerve cells in a dish. This makes it possible to model a patient's specific disease in the lab, study it to identify a potential therapy, and test that intervention safely in a dish before administering it to the patient.

ADVANCES IN ENGINEERED MINIATURE KIDNEYS

Stem cells can be grown in the lab and bioengineered to become miniature, three-dimensional organs, called organoids. Human organoids have opened up a new way to model and study human diseases directly. In 2019, an interdisciplinary study led by bioengineer Jennifer Lewis, Sc.D. and stem cell biologist Ryuji Morizane, M.D., Ph.D. led to the creation of kidney organoids that are vastly improved over initial models.

Lewis and Morizane grew their kidney organoids while exposing them to the frictional force of flowing biological fluids, mimicking the natural conditions of the body, As a result, the organoids developed networks of blood vessels that could circulate oxygen and nutrients, remove waste, and send messages between different cell types.

Whether they are used in drug screening or for understanding organ development and disease mechanisms, these new models will yield far more relevant and accurate results than past models.

REPRODUCIBLE HUMAN BRAIN ORGANOIDS

Animal studies of human neurological disorders rarely lead to results that translate to therapies for people, because differences in the brain are too great. In a major step forward for neuropsychiatric disease research, Paola Arlotta, Ph.D. and her colleagues created human brain organoids that consistently follow the growth patterns observed in the developing human brain. The optimized process allows organoids to grow for long enough that key cell types can form, opening the door to studies of a broad range of brain disorders.

The HSCI scientists used multiple stem-cell lines to form organoids of the cerebral cortex, the part of the brain responsible for cognition, language, and sensation. They found that across the different organoids, the same cell types were made in the same way, in the correct order.

Researchers can now use this reproducible experimental system to test drugs for neurological diseases like Alzheimer's disease, autism spectrum disorder and schizophrenia directly in human tissues.

PANCREAS ON A CHIP

Kevin Kit Parker, Ph.D. and Douglas Melton, Ph.D. collaborated on the design of a new device that will expand diabetes research, and that could improve beta-cell transplantation in diabetes patients.

The new "islet on a chip," inspired by the human pancreas, combines microfluidics and human, insulin-producing beta cells. It automates the process of monitoring whether or not islets are releasing insulin, and whether they are functioning as expected.

The device can make it easier for scientists to screen beta cells before transplanting them into a patient. It can also be used to test insulin-stimulating compounds, and to study the fundamental biology of diabetes.

FINDING A GENE THERAPY FOR HEART ARRHYTHMIA

William Pu, M.D. and Kevin Kit Parker, Ph.D. combined stem cell science and bioengineering to develop a potential gene therapy for a type of heart arrhythmia, a condition marked by racing and irregular heartbeats.

The researchers made heart muscle cells using the stem cells of patients, and put the new cells on an engineered surface, creating a tissue that modeled the disease. Using the disease model, they identified a gene as a potential therapeutic target. They targeted the gene in an animal model and succeeded in suppressing the arrhythmia.

Beyond heart arrhythmia, the gene therapy could be applied to other types of heart disease where the targeted biological pathway is involved. In addition, the combined approach shows the power of stem cell technology to discover therapeutic targets — a process that often takes many years.

IT'S HAPPENING NOW

15 YEARS OF HSCI

START UPS LAUNCHED

2004

HSCI LAUNCHES: HSCI is co-founded by Douglas Melton, Ph.D. and David Scadden, M.D., and launches with 7 Harvard schools, 7 teaching hospitals, 25 principal investigators, and ~100 scientists.

2005

MAKING STEM CELLS: Cowan, Melton, and Eggan labs fuse adult skin cells with embryonic stem cells to reset adult cells to an embryonic form.

2006

UNDERSTANDING STEM CELLS: Orkin lab identifies a protein network in embryonic stem cells, improving understanding of how to reprogram cells.

NEURON DEVELOPMENT: Macklis lab finds that the prion protein plays an important role in neuron development and differentiation.

2007

ALS RESEARCH ACCELERATES: Eggan lab develops the first mouse stem cell lines carrying human genes for Amyotrophic Lateral Sclerosis (ALS), making it possible to study potential treatments in a lab dish.

BOOSTING BLOOD STEM CELLS: Zon lab identifies a hormone in zebrafish that expands blood stem cell numbers; this will lead to a clinical trial about four years later.

Ipieirian and Fate Therapeutics launch

2008

Epizyme and Sentien Biotechnologies launch

A NEW WAY TO STUDY DISEASE: Daley, Cowan, and Hochedlinger labs create 20 disease-specific stem cell lines.

STEM CELL LINE FROM A PATIENT: Eggan lab creates the first patient-specific induced pluripotent stem (iPS) cells, marking the first time scientists ever produced a human stem cell line from adult patients with a genetic disease (ALS).

STEM CELLS TO TREAT MUSCULAR DYSTROPHY: Wagers lab treats muscular dystrophy in mice with muscle stem cell transplants.

2009

NEW FACILITY: HSCI establishes the iPS Core at Massachusetts General Hospital, which can provide cells for the entire Harvard stem cell community. The facility later moves to the Harvard campus.

2010

Moderna launches

NEW WAY TO DELIVER THERAPEUTICS: Rossi lab identifies a safer way to reprogram cells using modified messenger RNA, which also has applications for delivering therapeutics.

YOUTH FACTORS IN BLOOD: Wagers lab finds factors in the blood of young mice that make blood stem cells in old mice act like those in young mice.

2011

REPAIRING BRAIN INJURY: Macklis lab shows that neuronal transplants can repair brain circuitry and normalize function in mice with brain disorders.

HEART REPAIR: Lee lab identifies a specific cell population that can stimulate heart cells to repair damaged tissue.

MELANOMA TARGET: Zon lab finds a drug target for melanoma tumors.

GenSight Biologics launches

2012

ProteoThera and Scholar Rock launch

TOWARD CYSTIC FIBROSIS TREATMENT: Rajagopal lab grows lung-surface tissue from stem cells.

2013

CLINICAL TRIAL FOR TRANSPLANTS: Zon lab publishes initial results of a clinical trial for a treatment that enhances the engraftment of umbilical-cord-blood stem cells for adult transplantation.

Therapeutic licensed to Fate Therapeutics

AGING AND HEART FAILURE: Wagers and Lee labs identify a protein in mouse and human blood that may be the first effective treatment for age-related heart failure.

CRISPR Therapeutics, IVIVA Medical, and Tissium launch

2014

Audion Therapeutics, Intellia Therapeutics, Q-State Biosciences, Riparian Pharmaceuticals, and Yumanity Therapeutics launch

DIABETES GAME CHANGER: Melton lab uses human stem cells to create functional, insulin-producing beta cells in the lab.

ALS BREAKTHROUGH: Eggan and Woolf labs discover that stem cell-derived motor neurons from ALS patients point to a common problem among different forms of the disease. An FDA-approved epilepsy drug addresses the problem in a dish, leading directly to a successful clinical trial (2015–2018).

PAIN IN A DISH: Woolf lab creates pain-sensing neurons in the lab, opening doors to studying the biology of pain and developing new treatments.

2015

PARKINSON'S DISEASE ADVANCE: Isacson lab finds that dopamine-producing neurons, derived from the skin cells of primates, reduce symptoms of the disease.

SLOWING VISION LOSS: Cepko lab develops a gene therapy that slows vision loss in mouse models of retinal degeneration.

LAB-GROWN KIDNEYS: Morizane and Bonventre labs create 3D human mini-kidneys in a lab dish, using them to model human kidney development and genetic kidney disease, and to test for drug toxicity.

AMASA Technologies, Decibel Therapeutics, Frequency Therapeutics, and Semma Therapeutics launch

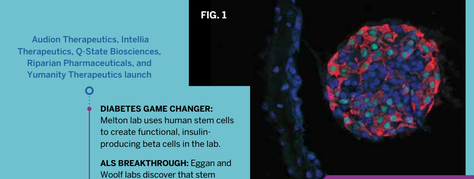


FIG. 1

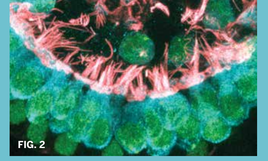


FIG. 2

Fig. 1 Beta cell image courtesy of the Melton lab.
Fig. 2 Ear hair cell image courtesy of the Edge lab.

2016

OPTIC NERVE REGENERATION: The He lab demonstrates that vision can be restored using an optic nerve regeneration approach that does not interfere with tumor suppressor genes.

ALZHEIMER PLAQUE PRODUCER: Young-Pearse lab identifies neurons that secrete the substance responsible for plaques that build up in the brains of Alzheimer's disease patients.

WORKING HEART MUSCLE GROWN IN THE LAB: Ott lab grows first-of-its-kind functional heart muscle by seeding biological scaffolds with stem cells.

Alivio Therapeutics, Fulcrum Therapeutics, Goldfinch Bio, Magenta Therapeutics, QurAlis, and Twenty-eight Seven launch

2017

ANEMIA TREATMENT: Daley and Zon labs use patient stem cells to identify a potential drug to treat Diamond-Blackfan anemia.

BETTER STEM CELL TRANSPLANTS: Scadden and Hoggatt labs uncover a novel drug combination that mobilizes stem cells within 15 minutes in a single injection in mice, offering hope for improved bone marrow transplants.

Clinical development by Magenta Therapeutics

HEARING LOSS: Karp and Edge labs develop a method to replace hair cells in both mouse and human ear tissue, an important step towards treating hearing loss.

Clinical development by Frequency Therapeutics

Akouos, Clear Creek Bio, and LifeVault Bio launch

2018

EXERCISE MAKES THE HEART YOUNGER: Lee and Rosenzweig labs find that exercising mice make over four times as many new heart muscle cells as their sedentary counterparts.

CYSTIC FIBROSIS BREAKTHROUGH: Rajagopal lab identifies the specific cells responsible for making CFTR, a key protein in cystic fibrosis.

TURNING CANCER AGAINST ITSELF: Shah lab engineers self-targeting cells that deliver therapeutic molecules straight to tumors.

VISION REPAIR: Two separate clinical trials start recruiting patients to test stem cell therapies that regenerate damaged corneas. The Jurkunas lab uses the patient's own cells, while the Frank labs use donor cells to stimulate repair.

Frank labs initiate clinical trial with Rheacell

CAMP4 Therapeutics, Elevian, Enclear Therapies, and Odylia Therapeutics launch

2019

EDITING STEM CELLS WHERE THEY LIVE: Wagers lab creates technology that delivers gene-editing cargo directly into several different types of skin, blood, and muscle stem and progenitor cells in mice.

GENE THERAPY FOR HEART ARRHYTHMIA: Pu and Parker labs bioengineer a heart tissue model of arrhythmia, use it to identify a potential gene target, then design a gene therapy and show that it suppresses the disease in an animal model.

UNIVERSAL DONOR CELL: Cowan lab develops method to make stem cells genetically engineered to hide from the immune system; the stem cells can be converted into any cell type and transplanted into a patient.

Further developed by Sana Biotechnology

Immunitas Therapeutics, Nocion Therapeutics, Sana Biotechnology launch


FIG. 3

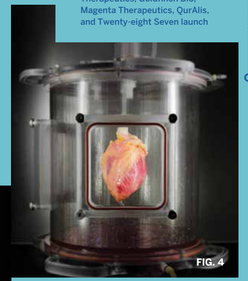


FIG. 4

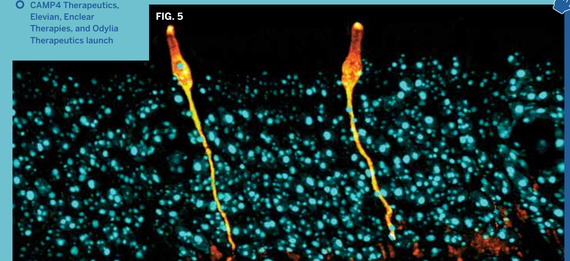


FIG. 5

Fig. 3 Kidney cells in a dish. Image courtesy of the Bonventre and Morizane labs.
Fig. 4 Heart muscle tissue image courtesy of the Ott lab.
Fig. 5 Ionocyte (CFTR-making cell) image courtesy of the Rajagopal lab.

BOSTON AREA BECOMES HOME TO A NEW CENTER FOR CELL AND GENE THERAPIES

A new center for advanced biological innovation and manufacturing in Massachusetts, launched in 2019 by Harvard, MIT, industry partners, hospitals, and state officials, is set to remove major bottlenecks in the development of cell and gene therapies.

An ongoing shortage of advanced biological materials has slowed down the process of turning new discoveries into therapies for patients. Because of high demand, researchers can wait up to 18 months for commercial manufacturers to produce the engineered cells and viral vectors needed for their work.

The 30,000-square-foot facility will ease that bottleneck for the project partners, including HSCI scientists. It will also provide the critical mass needed to develop and refine methods for DNA, RNA, peptide, and cellular therapies. Dedicated manufacturing spaces will provide the process control needed to manufacture materials for use in human trials, while innovation space will be dedicated to late-stage research from academic labs or start-ups.

Harvard and MIT are joined by industry partners Fujifilm, Alexandria Real Estate Equities, and GE Healthcare Life Sciences; Harvard-affiliated teaching hospitals Massachusetts General Hospital, Brigham and Women's Hospital, Beth Israel Deaconess Medical Center, Boston Children's Hospital, and the Dana-Farber Cancer Institute; and the Commonwealth of Massachusetts.

FIND OUT MORE: bit.ly/cabim2019

COMMUNITY

At its heart, HSCI is a close community of stem cell scientists who have a **shared purpose:** finding new treatments and cures for diseases. We bring people together to share knowledge, combine expertise in **creative collaborations,** and embark on new careers in science.

The HSCI Network

HSCI brings together scientists who have a shared interest in stem cell and regenerative medicine, making the most of Boston's compact science community and leveraging the infrastructure of Harvard University and its affiliated hospitals. In addition to organizing major annual events, we convene members at smaller, more focused gatherings throughout the year to foster a sense of community and shared purpose.

15TH ANNUAL HSCI RETREAT

The 2019 HSCI retreat, held at Harvard Medical School's Joseph B. Martin Conference Center, welcomed 300 scientists. The event was opened by Peter Marks, director of the FDA's Center for Biologics Evaluation and Research, who talked about the agency's efforts to harmonize gene and cell therapy regulation internationally, reflected on the rapid acceleration of the field, and addressed the serious issues caused by the spread of misinformation.

HSCI scientists Kevin Eggan, Brian Wainger, and Kasper Roet shared a story that has been over 10 years in the making. Together, they developed human stem cell models of ALS in the lab, used them to identify a biological mechanism of ALS and a potential drug to treat it, and brought the drug to a successful clinical trial in patients.

Following a day packed with scientific presentations, panel discussions, and poster browsing, retreat co-organizers Jonathan Hoggatt of Massachusetts General Hospital and Vikram Khurana of Brigham and Women's Hospital presented awards for the best oral presentation to Alicia McConnell, best poster presentation to Sekyu Choi and Nick van Gastel, and best video presentation to Yulia Shwartz.

FIG. 1

FACTS AND FIGURES

101 TALKS + SYMPOSIA
35 WORKSHOPS + MEETINGS

HSCI RETREAT

1 DAY
350 ATTENDEES
16 SPEAKERS

BRM CONFERENCE

3 DAYS
174 ATTENDEES
44 SPEAKERS

FIG. 2

FIG. 3

BUSINESS OF REGENERATIVE MEDICINE 2019

HSCI hosted the 12th annual Business of Regenerative Medicine conference in 2019, exploring how to define and create "value" in a field that is set to transform human health. Over three days, 150 scientists, CEOs, biotech pioneers, venture capitalists, and patient advocates gathered to share their perspectives on social, economic, and operational challenges in this emerging field.

Panelists at BRM 2019 discussed the issue that while scientific progress is rapid, health care markets remain unprepared to manage the one-time cost of cures. Featured speakers fired the imagination with presentations about the potential to print cells 'at the bedside' using 3D bioprinting that combines existing technologies; accelerating drug discovery with an 'intestine on a chip' that exposes human gut cells to complex biological forces; and using multi-layered biomaterials to deliver antibiotics, nucleic acids, and drugs within the same complex.

HSCI research featured prominently, including work from the David Scadden lab that is being taken forward by Magenta Therapeutics. Their revolutionary approach to bone marrow transplants would remove stem cells from a patient in a targeted manner with a single dose, with no side effects. If successful, the clinical trial slated for 2020 will be a major step towards making stem cell transplants an outpatient procedure.

The conference was opened by George Q. Daley, dean of Harvard Medical School and HSCI Principal Faculty member, who said: "We are at an inflection point in regenerative medicine, when CAR-T cells, dopaminergic neurons for Parkinson's disease, beta cells for type 1 diabetes, and treatments for the retinal epithelium are making history. But transformative therapies typically take between 30 to 40 years to mature, and we are one decade into our investments in regenerative medicine products."

Fig. 1 Beth Stevens, Boston Children's Hospital
Fig. 2 Amir Nashat from Polaris Partners (left) and Jason Hafler from Sanofi Ventures (right)
Fig. 3 Arnold Caplan, Case Western Reserve University (right)

Beginnings

SEED GRANT HIGHLIGHT

April Craft, Ph.D., an HSCI Principal Faculty member, is using stem cells to investigate exactly how joint tissues form. Armed with precise knowledge about healthy tissue development, her lab at Boston Children's Hospital has set out to radically improve joint repair.

"Cartilage is unable to repair itself after injury, and most of us, especially athletes, appreciate how serious this can be for overall joint health. To alleviate pain associated with cartilage damage and promote repair, many patients undergo a treatment called microfracture, but the fibrocartilage-like tissue that forms in the joint is not ideal. I think it's within reach to create a stem cell-based solution that will finally provide patients with pain-free, long-term joint movement," Craft said.

An initial seed grant from HSCI enabled Craft to optimize her tissue-engineering approach to ensure it is reproducible and easy to control. Thanks to funding for a full pilot study in 2019, she is now testing whether her stem cell-based cartilage tissue can repair joints in a pig model.

"Support from the HSCI has been instrumental for our translational work. This preclinical study in large animals will allow us to demonstrate that a stem cell-based cartilage implant will heal joints better than the existing treatment options available for patients. We are optimistic that we can move this discovery towards clinical care through collaborations with industry and venture partners," she said.

Craft expects progress towards clinical application to be rapid because many of the pieces are already in place: cell collection, tissue manufacturing, and surgical implementation pipelines are already well established. With some adjustments, that pipeline could well accommodate a stem cell-derived product.

"We are infinitely motivated to translate stem cell discoveries because they have great potential to help patients in need, perhaps much sooner than anyone realized. The grant from HSCI allowed us to transition from repairing cartilage in rat to pig, and to attract one of the best orthopedic and sports medicine surgeons to join our efforts.

FIG. 1

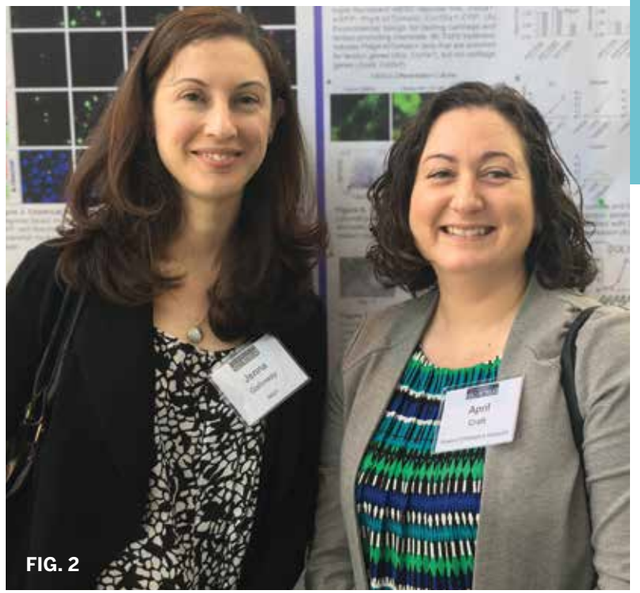


FIG. 2

Having support from the greater stem cell community builds confidence within our group that what we are doing will benefit patients in the near future," she said.

In 2019, Craft joined HSCI Executive Committee members Jenna Galloway, Ph.D. of Boston Children's Hospital and Vicki Rosen, M.D., Ph.D. of the Harvard School of Dental Medicine in launching the new HSCI Musculoskeletal Disease Program.

Fig. 1 HSCI Internship Program participants in 2019, pictured with program director Maureen Herrmann.
Fig. 2 HSCI faculty members April Craft and Jenna Galloway at the 2019 HSCI annual retreat.

INTERNSHIP STATS

650 APPLICANTS

35 SELECTED UNDERGRADUATES

21 COLLEGES + UNIVERSITIES REPRESENTED

12 COUNTRIES REPRESENTED*

**Bangladesh, Canada, China, Egypt, Germany, India, Jamaica, Sri Lanka, Thailand, Turkey, Vietnam, United States*

2019 SEED GRANT RECIPIENTS

Aging, blood, and fibrosis research: Suneet Agarwal, M.D., Ph.D. of Boston Children's Hospital, "Enhancing stem cell self-renewal via novel telomerase modulators" and Zhixun Dou, Ph.D. of Massachusetts General Hospital, "Empowering immunotherapy to treat age-associated diseases"

Nervous system disease research: Rakesh Karmacharya, M.D., Ph.D. of Massachusetts General Hospital, "Modeling synpatic pruning in schizophrenia with iPSC-derived microglia and neurons" and Mustafa Sahin, M.D., Ph.D. of Boston Children's Hospital, "Examining non-cell autonomous effects in Tuberous Sclerosis Complex using neuronal spheroids from human iPSCs"

Cancer research: Ruben Carrasco, M.D., Ph.D. of Dana-Farber Cancer Institute, "Mining the Wnt/β-catenin/BCL9 transcriptional complex for gastric cancer pathogenesis and therapy"

Cardiovascular disease research: Elliot Chaikof, M.D., Ph.D. of Beth Israel Deaconess Medical Center, "Immuno-evasive engineered living blood vessels"

Musculoskeletal disease research: April Craft, Ph.D. of Boston Children's Hospital, "Testing efficacy of hESC-derived cartilage in large animal model"

Lung disease research: Hongmei Mou, Ph.D. of Massachusetts General Hospital, "Regenerative capacity of human iPSC-derived airway basal cells"

HSCI INTERNSHIP PROGRAM

Jorge Diego Martin-Rufino was in his fourth year of medical school in Spain when he decided to apply to the HSCI Internship Program (HIP). Drawn to the prospect of working in a cutting-edge stem cell research laboratory, he gained much more from the experience: inspiring mentorship, new perspectives on science and medicine, and a new direction for his career.

"Coming from medicine, I was really interested in the potential stem cells have for regenerative medicine, to restore damaged tissues and structures. My experience as a HIP intern allowed me to explore that, and was the most important factor in my decision to pursue a Ph.D. at Harvard Medical School. My goal now is to be a physician-scientist, combining my interests in hematology and genomics," he said.

Martin-Rufino worked with Laurence Daheron in the HSCI iPS Core Facility and with HSCI faculty member Jerome Ritz at the Dana-Farber Cancer Institute, who provided mentorship and invited him to be part of a project to generate beta cells for replacement therapy in diabetes.

"The mentorship I received was amazing. Add to that all the biomedical infrastructure, and the connections between industry and the university and hospitals in the Boston area — it really sets it apart from other places. There is a strong focus on disease-oriented research at Harvard and HSCI, so for me it is a wonderful place to explore," he said.

For Martin-Rufino, one of the greatest assets of the internship program is the sense of community, and the way it brings together people from many backgrounds.

"The combination of seminar series, lectures from top researchers, hands-on research, and shared experiences with fellow HIP interns was priceless," he said. "The program shaped my approach to my career, and inspired me to become a physician-scientist. It is something I will never forget."

HSCI Leadership

HSCI is led by faculty directors Douglas Melton and David Scadden, and executive director Brock Reeve, all of whom are appointed by the provost of Harvard University. They are guided by an Executive Committee composed of leaders in the field from Harvard and its teaching hospitals.

Their combined expertise in both science and business provides HSCI with the essential intellectual venture capital to guide our strategy, shape our programs, and ensure stem cell research across Harvard can be harnessed for patient benefit.

FACULTY DIRECTORS

Douglas A. Melton, Ph.D.
Xander University Professor
Howard Hughes Medical Institute Investigator
Harvard Department of Stem Cell and Regenerative Biology

David T. Scadden, M.D.
Gerald and Darlene Jordan Professor of Medicine
Professor of Stem Cell and Regenerative Biology, Harvard University
Director, Center for Regenerative Medicine, Massachusetts General Hospital

EXECUTIVE DIRECTOR

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

EXECUTIVE COMMITTEE

Leonard Zon, M.D., Chair
Professor of Stem Cell and Regenerative Biology, Harvard University
Grousbeck Professor of Pediatrics, Harvard Medical School
Director, Stem Cell Program, Boston Children's Hospital
Howard Hughes Medical Institute Investigator

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HSCI Musculoskeletal Disease Program Leader

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Professor of Neurology, Harvard Medical School
Faculty Member, Harvard University Center for Brain Science

Jerome Ritz, M.D.
Executive Director, Connell and O'Reilly Families Cell Manipulation Core Facility, Dana-Farber Cancer Institute
Professor of Medicine, Harvard Medical School

Vicki Rosen, Ph.D.
Professor of Developmental Biology, Chair of the Department of Developmental Biology, and Interim Dean, Harvard School of Dental Medicine
HSCI Musculoskeletal Disease Program Leader

Lee Rubin, Ph.D.
Professor of Stem Cell and Regenerative Biology, Harvard University
HSCI Nervous System Disease Program Leader

Amy Wagers, Ph.D.
Forst Family Professor of Stem Cell and Regenerative Biology, Harvard University
Co-chair, Harvard Department of Stem Cell and Regenerative Biology
Senior Investigator, Joslin Diabetes Center

Awards

In 2019 HSCI faculty were recognized widely for their contributions to science and medicine. Here, we highlight just a few examples.

NATIONAL INSTITUTES OF HEALTH

Jason Buenrostro, Ph.D. and Ryuji Morizane, M.D., Ph.D. received the NIH Director's New Innovator Award in recognition of their genomics and kidney-organoid research, which has transformative potential.

Buenrostro investigates the many ways adult stem cells can harbor epigenetic errors, and how these tiny mistakes can lead to big changes in a cell's capacity to self-renew and differentiate. Buenrostro will use the award to gain insights into how changes in the epigenome may impact blood stem cells in normal and diseased states, and to identify therapeutic targets.

Morizane has pioneered research in stem cell differentiation and kidney organoids. He researches regenerative medicine for the kidney, genome editing in stem cells, and kidney disease modelling, with the ultimate goal of generating artificial kidneys as a novel form of renal replacement therapy.

NEW YORK STEM CELL FOUNDATION

Ya-Chieh Hsu, Ph.D. was named a NYSCF–Robertson Stem Cell Investigator by the New York Stem Cell Foundation in recognition of her skin regeneration research, which has the potential to accelerate the discovery of new treatments and cures. NYSCF–Robertson investigators have the freedom to pursue new and inventive ideas that may not get funded through traditional sources. Hsu uses skin as a model to understand how cells interact with larger biological systems. The creative, problem-solving research enabled by this award includes novel approaches to promote regenerative wound healing, and a deep investigation into how stress influences diverse changes in the skin.

AMERICAN CANCER SOCIETY

Two HSCI scientists were recognized by the American Cancer Society for their innovative, high-risk/high-reward research that has the potential to impact patients. Ya-Chieh Hsu, Ph.D. is studying the toxic side effects of chemotherapy — specifically, hair loss, slower wound healing, and loss of sensation — caused by a type of rapidly dividing skin cell. Carla Kim, Ph.D. is studying a gene that is often mutated in lung cancer, using patient-derived models to develop a targeted therapy.

AMERICAN SURGICAL ASSOCIATION

Elliot Chaikof, M.D., Ph.D. was recognized for his work in vascular disease, receiving the American Surgical Association's 2019 Flance-Karl Award for his seminal contributions in translational research that have applications to clinical surgery.

MASSACHUSETTS GENERAL HOSPITAL

Amar Sahay, Ph.D. was named an MGH Research Scholar for his work to improve memory in adulthood and aging.

VANDERBILT UNIVERSITY MEDICAL CENTER

Christine Seidman, M.D. received the 2019 Vanderbilt Prize in Biomedical Science in recognition of her groundbreaking work to identify the genetic causes of heart disease.

BRIGHAM RESEARCH INSTITUTE

Tracy Young-Pearse, Ph.D. received two awards from the Brigham Research Institute: the Pilot Funding Award, which she will use to study the links between Alzheimer's disease and Down syndrome; and the inaugural President's Scholar Award, recognizing contributions and exceptional potential in the field of neurology.

UNIVERSITY OF CALIFORNIA, IRVINE

Zhigang He, Ph.D. received the Reeve-Irvine Medal for his research into using viral vectors to modify genes to enable regeneration after spinal cord injury.

INTERNATIONAL SOCIETY FOR EXPERIMENTAL HEMATOLOGY

David Scadden, M.D. received the 2019 International Society for Experimental Hematology Honorific Award, which recognizes distinguished scientists who have made seminal contributions to science, mentorship, and leadership in the field of hematology.

AMERICAN SOCIETY OF HEMATOLOGY

Leonard Zon, M.D. received the American Society of Hematology mentor award for his sustained, outstanding commitment to the training and career development of early-career hematologists.

Joan's Story

Joan Finnegan Brooks lives with cystic fibrosis (CF), managing the disease by taking more than six different aerosols and 50 pills a day. She champions stem cell research through the Cystic Fibrosis Foundation, which supports efforts to develop sustainable, effective treatments and discover a cure.

JOAN FINNEGAN BROOKS: "When my brother and I were children, there were very few treatments available to us. We struggled to breathe and my parents pounded our backs to help us get the thick, sticky mucus out of our lungs. They always encouraged us to lead 'normal' lives, and not dwell on our health challenges. Sadly, we lost my brother when he was just 15 in 1969.

"Medicine has come so far since then. Improved treatments and my involvement in sports have helped me maintain my lung function, but at age 59, managing my disease has gotten more difficult. I experience recurring lung infections requiring treatment with multiple antibiotics more frequently and I worry about how long those drugs will keep working. There are many young people whose lives will be cut short by this disease, and I want to do everything I can to help them.

"I support the Cystic Fibrosis Foundation's commitment to fund innovative research in pursuit of new and effective CF therapies, including stem cell biology in laboratories across the world, including many in HSCI. It is my hope that these scientists will be able to translate discoveries and insights into vital new treatments and clinical care practices for people living with CF."

HSCI FACULTY MEMBER JAYARAJ RAJAGOPAL, M.D.: "We've known for a long time which specific gene causes cystic fibrosis when it gets mutated. But it wasn't until last year that my colleagues and I were able to identify where in the lungs this gene gets expressed. That was possible because of advances in sequencing technology and cell biology, and because we had the support of the Foundation.

"Joan stressed that we need to find both a cure for very young patients, and effective treatments for mature patients.

"We have seen so much progress toward understanding the disease and finding new treatments, but there is still a long way to go."

Joan Finnegan Brooks (left) and HSCI faculty member Jay Rajogopal (right) addressed the Business of Regenerative Medicine meeting in 2019, sharing Joan's story about living with cystic fibrosis and the challenges of finding a cure.

John W. Cammett

CO-FOUNDER, REALTERM

Up to my 30th reunion at Harvard, I was giving broadly to support the needs and objectives of the University. Since then, I have become more involved in supporting talented researchers and investigators working on solving a problem from different directions. As a result, my giving has become more focused.

When I met Doug Melton at a JDRF [Juvenille Diabetes Research Foundation] event in 2014, I learned his children were both Type I diabetics. Being a diabetic myself, I had been involved in the work of the foundation for several years, and began a conversation with Doug and his work at the HSCI to find a cure for diabetes. I had heard about his work on beta cell replacement before, but after speaking with him I was motivated to help advance his research. It was important to me that Doug should be able to progress the science without financial barriers or restrictions, thereby allowing him to make the right research decisions expeditiously.

I know it will take time to advance the science to see patient benefits. While some of the research solutions are progressing to the clinic, many of the promising developments in this field are still in the research stage. However, progress and protocols are advancing quickly thanks to the collaborative culture amongst researchers across the Greater Boston area. Doug promotes and supports an exceptional environment, keeping people working together to play key roles in moving the science forward — a real tribute to HSCI!

Collaboration is essential if we are going to crack this nut and find a cure for T1D, and I feel that team spirit whenever I visit the labs. Harvard is an incredible place, having the available resources, both financial and intellectual, to solve global health issues like diabetes. It's hard to find places with an outlook like Harvard, looking not just for immediate results but solutions that will make a real difference over time.

This is such an exciting time in beta cell replacement and immunotherapy. I am glad to be part of it, and honored to be able to support leading investigators and scientists moving the field forward towards new treatments and, eventually, a cure.

Mike Vranos

CEO, ELLINGTON MANAGEMENT GROUP

I started supporting the Harvard Stem Cell Institute when it was first founded — a time when the federal government had restricted funding for highly promising stem cell research. Doug Melton and David Scadden brought this incredible passion to the research, and Harvard University provided the space — they just needed help to move it forward.

I thought then that we would go through a revolution in the life sciences, and that has absolutely come to pass. Fifteen years ago, "stem cell research" meant to many people, "regenerating replacement parts" for patients, and over this span of time Doug has been able to create functioning pancreatic beta cells from stem cells. Today we've witnessed the use of stem cells for a broad range of research, such as the testing of drugs on stem cell-generated tissues that carry disorders. It is incredible that discovering how to redirect stem cells to grow into specialized cells would bring about all these applications no one had ever thought of before.

Research at HSCI has always surprised me, to the point where I'm no longer surprised that I'm being surprised. Given the progress made in just this short time, I believe that stem cell research will continue to flourish. Stem cells *are* potential — they will change how we think about aging, autoimmune disease, and many other areas. This is already having an impact on medicine, but it's hard to predict all the different ways stem cells will change health care.

The collaboration across HSCI is unique, and not something you often see in other areas of science. It has a strong culture of breaking down barriers; working across academic labs, hospitals, and companies; and sharing know-how to speed up progress. As the institute has grown, this collaboration has become increasingly important. Supporting HSCI and its ambitious projects has brought one revelation after another, and I am very proud to be a small part of it.

DIRECTOR'S MESSAGE

BROCK REEVE, M.PHIL., M.B.A.

EXECUTIVE DIRECTOR OF HSCI

Stem cell science has far exceeded expectations, with cell replacement therapies now in the clinic, *in vivo* gene editing a reality, and miniature organs transforming neuroscience research. Armed with new technologies, data, and knowledge that would have seemed like science fiction 15 years ago, HSCI scientists are poised to achieve breakthroughs in regenerative therapies that address age-related disease and injury.

As the largest collaborative network of stem cell scientists in the world, we have truly made the most of Harvard's outstanding research talent. The university's open, interdisciplinary culture fosters curiosity, while its teaching hospitals provide a perfect environment for early-stage clinical trials. Beyond Harvard, we have been working with companies like Boehringer Ingelheim, Bristol Myers Squibb, and GSK to lay essential groundwork for the future development of new therapies, and to understand pathologies that underlie human disease.

Over the past 15 years our members, funders, and partners have done much to be proud of. Together, we are helping to usher in a new era of research into both specific diseases and broad areas like immunology, aging, and fibrosis, which touch on all diseases. This support continues to empower our scientists and physicians to move research out of the lab and into the clinic, where it can make a difference in people's lives.

OUR AFFILIATES

Beth Israel Lahey Health
Beth Israel Deaconess Medical Center

Boston Children's Hospital
Until every child is well™

BWH BRIGHAM AND WOMEN'S HOSPITAL

Dana-Farber Cancer Institute

Joslin Diabetes Center

McLean HOSPITAL
HARVARD MEDICAL SCHOOL AFFILIATE

MASSACHUSETTS EYE AND EAR

MGH MASSACHUSETTS GENERAL HOSPITAL

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