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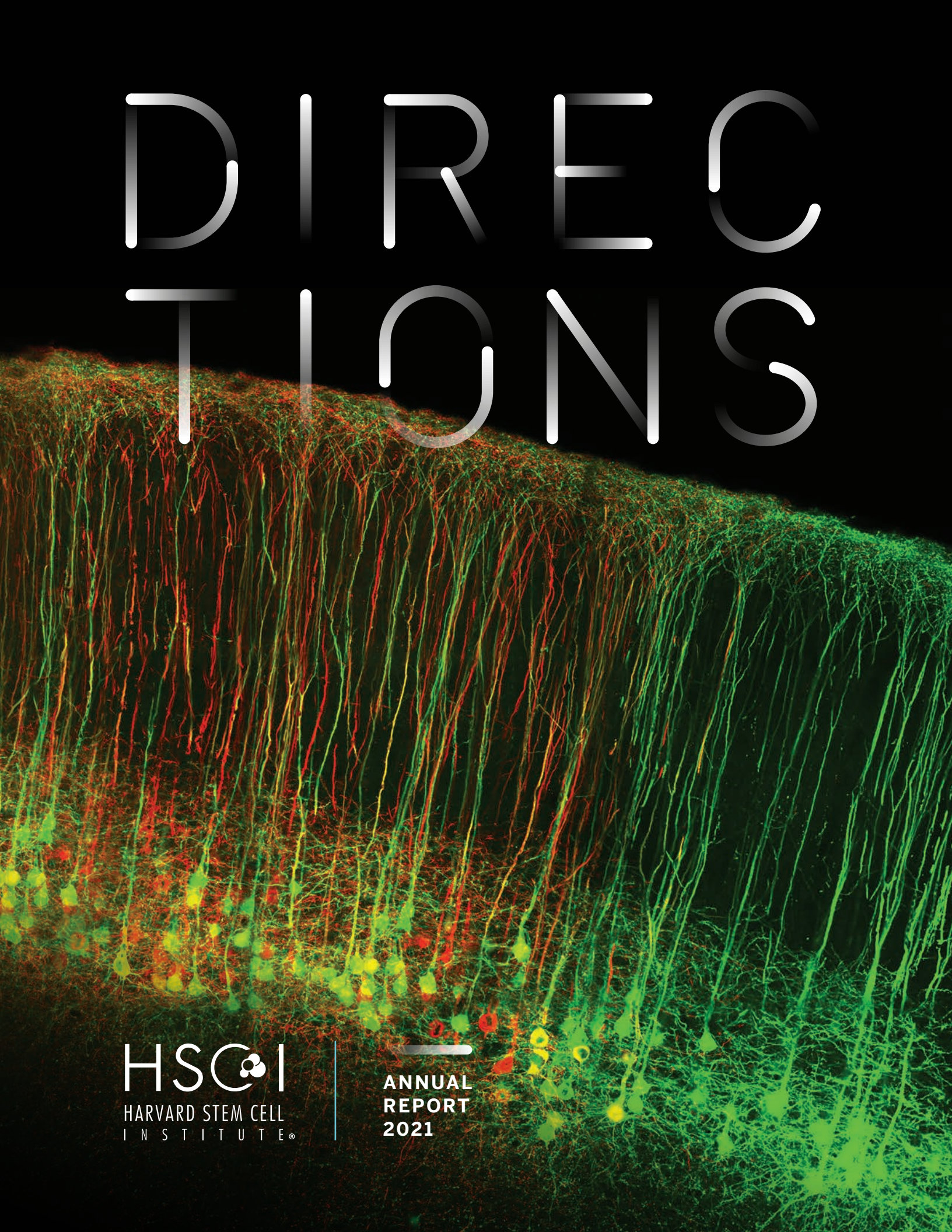


HSCI
HARVARD STEM CELL INSTITUTE®

ANNUAL REPORT 2021

MESSAGE FROM THE DIRECTORS

One day at the end of last November, we opened the New York Times and immediately saw the front-page headline: "A Cure for Severe Diabetes? For an Ohio Patient, It Worked."

The news article told the moving story of Brian Shelton, the first patient with Type 1 diabetes to be successfully treated with beta cell replacement therapy. As a participant in a clinical trial run by Vertex Pharmaceuticals, he received a transplant of pancreatic beta cells created using stem cells, which gave him his own source of insulin and drastically reduced the need for daily insulin injections.

This groundbreaking result is the culmination of nearly two decades of work at the Harvard Stem Cell Institute. After showing that the adult body cannot make new beta cells, Douglas Melton embarked on the process of figuring out how to direct embryonic stem cells to become functional beta cells. He further developed the technique into a therapy by launching Semma Therapeutics, which was later acquired by Vertex.

This achievement in cell therapy is exactly the type of transformative work that we set out to do when the institute was founded in 2004. At the time, our goal was to leverage the emerging science of stem cell biology to have a concrete impact on patients and disease. Now, the idea of using cells as medicine is coming into its own, driven by both a deep understanding of fundamental biology and a commitment to clinical application.

As we mark this milestone, we are also looking ahead to what we can achieve together in the next few years. The next step for beta cell replacement therapy is to better protect the transplanted cells from immune attack and rejection. HSCI researchers are investigating the interactions between immune and pancreatic cells, using the knowledge to genetically engineer and mask the beta cells. Beyond diabetes, we are directing our efforts toward stem cell-based therapies for devastating conditions including cancer, heart diseases, nervous system diseases, and many others.

Stem cells converted into insulin-producing beta cells, the type of cell affected in Type 1 diabetes. Credit: Melton Lab, Harvard University

HSCI researchers are conducting a wide range of basic and translational research across the labs of Harvard's schools and affiliated hospitals, and we are proud of the many advances highlighted in this annual report. Our scientists are dissecting the fundamental biological pathways that give rise to disease, paving the way for new approaches to intervene. In another approach, our researchers are directing stem cells to become specialized cells such as neurons, giving us better lab models to study conditions including Alzheimer's disease and ALS. HSCI scientists are also fine-tuning our control over cell behavior, for example turning on and off the activity of engineered immune cells, so that they target cancer while limiting side effects.

This report also showcases HSCI's approach to finding and incubating the next big ideas that will transform the field. Our community is home to imaginative, ambitious young scientists who have a wealth of innovative ideas. We identify high-risk projects that have the potential to change the course of medicine and support them with grants such as the Barry Family HSCI Innovation Award for Early Investigators.

Our projects mature within the unparalleled ecosystem of the Boston area, well known for being a central hub for academic labs, startup and biopharmaceutical companies, and investors. The ecosystem was further strengthened by last year's announcement of Landmark Bio, a joint Harvard and MIT venture to accelerate the transition of cell and gene therapies from academic labs into the clinic. It is within this unique environment that HSCI researchers have launched over 40 startup companies to date, including two in 2021, which move our discoveries to patients and garner support from investors independent of HSCI.

All of HSCI's work would not be possible without the sustained support of our donors. Thanks to your continued philanthropy over the years, we have shown that we can create a whole new class of cell-based medicines and make a direct impact on patients' lives. Your leadership has made all the difference, and we hope that you will join us as we look forward to the many breakthroughs to come.

Sincerely,

Douglas Melton, Ph.D.
Founding Co-Director

David Scadden, M.D.
Founding Co-Director

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

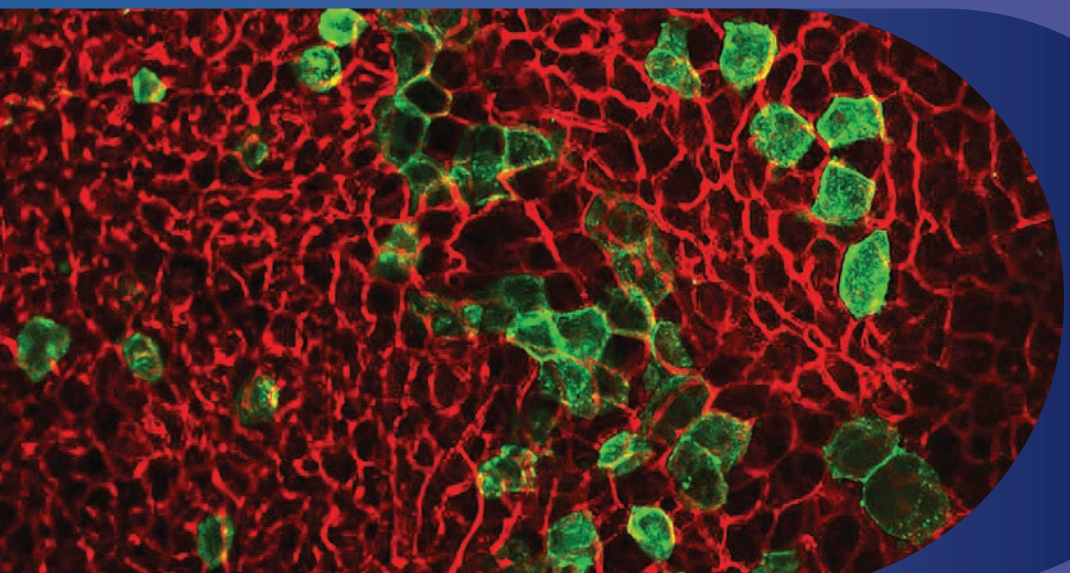
DOUGLAS MELTON, PH.D.

DAVID SCADDEN, M.D.

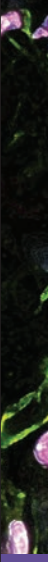
BROCK REEVE, M. PHIL., M.B.A.

UNCOVERING THE DIRECTION OF BIOLOGICAL PATHWAYS

Developing new therapies requires a foundational understanding of how the body works, including both healthy and disease processes. Harvard Stem Cell Institute (HSCI) researchers are investigating these biological pathways in fine detail, following the directions of molecules as they move within and in between cells, with the ultimate goal of therapeutic intervention.



Brown fat cells derived from cells expressing the Trpv1 receptor protein (in green), in mice exposed to cold temperature. Credit: Tseng Lab, Joslin Diabetes Center



Underneath the hair follicle, dermal papilla cells (green) produce the Gas6 molecule that activates hair follicle stem cells. Credit: Hsu Lab, Harvard University

A direct control system for blood production

Researchers led by HSCI Co-Director David Scadden, M.D., discovered a new way that the immune system responds to stress such as infection. They showed for the first time in animals that in the bone marrow, bone-forming cells released RNA that is packaged in vesicles, or small membrane-enclosed particles. The vesicles were taken up by blood stem cells, which in turn ramped up the production of immune cells. This process was more direct than the conventional system of activating a complex hormone-signaling pathway, and is a new way of thinking about how the body rapidly reacts to infection.

A new source of energy-burning fat cells

Brown fat cells direct the process of thermogenesis, becoming activated in cold temperatures to burn calories and generate heat. As a result, they are a potential target for treating obesity. Researchers led by HSCI Principal Faculty member Yu-Hua Tseng, Ph.D., identified a new source of these energy-burning brown fat cells.

The researchers used single-cell RNA sequencing to study brown fat from mice housed at different temperatures and lengths of time. They found that smooth muscle cells expressing Trpv1—a receptor protein that senses noxious stimuli, including pain and temperature—gave rise to brown fat cells. Trpv1 can be potentially targeted to increase the number of brown fat cells, a strategy to treat obesity and other metabolic disorders.

How chronic stress leads to hair loss

HSCI Principal Faculty member Ya-Chieh Hsu, Ph.D., identified the biological mechanism of how chronic stress leads to hair loss, confirming long-standing observations that the two are connected.

The researchers used a mouse model of chronic stress to study hair follicle stem cells, which regenerate the hair follicle and hair. They found that the stress hormone corticosterone directed hair follicle stem cells to stay in an extended resting phase without regenerating tissue. The stress signal was first received by dermal cells surrounding the hair follicle, preventing them from releasing Gas6, a molecule that activates stem cells. When researchers added back Gas6, stem cells could regenerate hair even under stress.

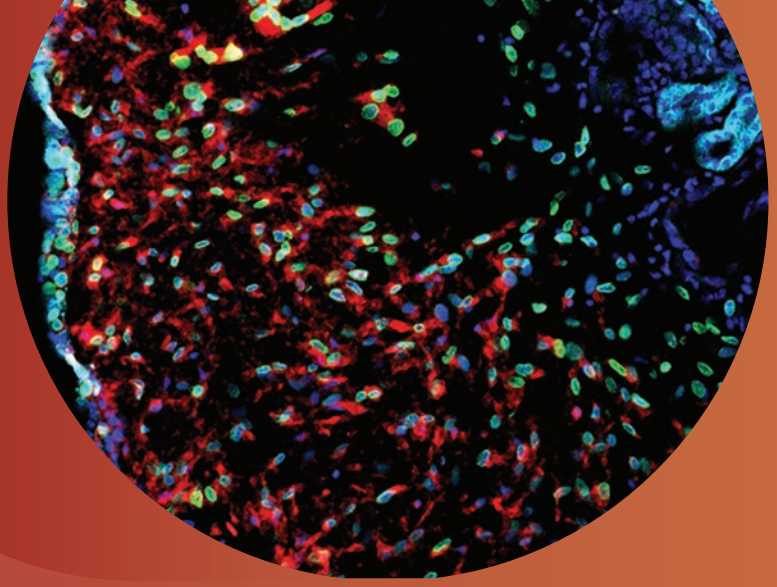
The Gas6 pathway is a potential target for promoting hair growth. More broadly, researchers now have a better understanding of how stress plays a role in stem cell biology and cross-organ signaling.

Metabolism's role during red blood cell development

Each tissue in the body has different requirements for metabolism, or how it uses energy to function. For example, a muscle needs different molecules to fuel a contraction compared to a pancreas that produces insulin. Even though metabolic pathways may be the same across tissues, it is not fully understood how each tissue directs which one to predominantly use for its own specific needs.

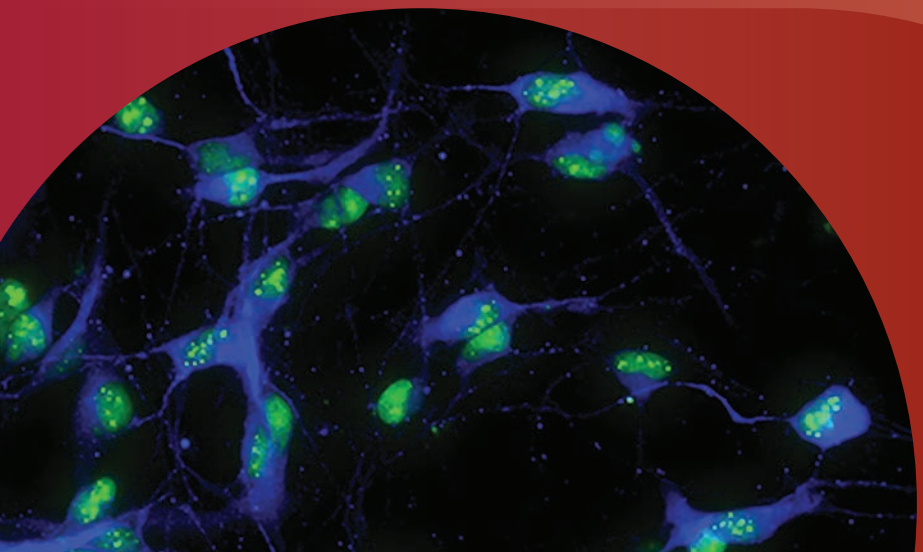
Researchers led by HSCI Executive Committee Chair Leonard Zon, M.D., found a new connection between metabolism and red blood cell development. The researchers studied a zebrafish model of anemia, which was defective in producing red blood cells because it lacked a specific DNA-binding protein. They identified the detailed mechanism for how red blood cell precursors use the DNA-binding protein to control metabolism in the mitochondria. This pathway can be potentially targeted in diseases such as anemia to restore red blood cell production, as well as certain types of cancer.

Zebrafish embryo that models anemia, containing a defective DNA-binding protein that leads to an inability to produce red blood cells. Credit: Zon Lab, Harvard University



DIRECTING CELLS INTO DISEASE MODELS

Patient stem cells are a powerful tool for understanding disease and testing therapies, since they can be converted into the specific cell types affected by disease — whether it be a neuron or kidney cell. At the Harvard Stem Cell Institute (HSCI), our researchers are pushing the boundaries of how we can take advantage of these disease models to understand mechanisms and find potential therapeutics.



"This is the first time we have a system in place to study living human brain cells from many people to understand better why some develop Alzheimer's disease in a very specific way and others are resistant to the disease."
— Tracy Young-Pearse, Ph.D.

Patient-specific models of Alzheimer's disease

Alzheimer's disease progresses differently across patients in terms of underlying cause, genetic makeup, age at onset, and disease course, among other factors. To model how an individual's unique genetic background influences disease development, a large set of stem-cell-derived neurons was created by HSCI researchers led by Tracy Young-Pearse, Ph.D., Co-Leader of the Nervous System Diseases Program and Principal Faculty member.

The researchers studied a group of 53 individuals — with and without Alzheimer's disease — that had multiple types of data available, including long-term clinical measures of cognitive decline and genomic sequencing. The researchers created stem cells from each individual and turned them into neurons. The specific types of amyloid beta protein and tau protein found in the neurons predicted whether the individual developed the disease, as well as the rate of cognitive decline. Additionally, the researchers found a specific molecular pathway that linked the two proteins' behavior.

This collection of neurons is a powerful way to model the complexity of Alzheimer's disease, opening the door to understanding an individual's risk of developing the disease and which specific drugs are most effective.

An organoid model of kidney tumors

In the genetic disease Tuberous Sclerosis Complex, most patients develop a tumor called renal angiomyolipoma (AML), which can lead to kidney failure and premature death. Researchers' understanding of AML has been limited by a lack of lab models, since animals with the necessary genetic mutations largely die before birth. HSCI Affiliate Faculty member Dario Lemos, Ph.D., took a new approach to solve this problem.

The researchers started with patient stem cells, genetically edited them, and directed them to become kidney cells. The cells showed characteristics of AML and formed organoids, or 3D miniature organs, in a lab dish. The researchers transplanted the organoids into rats, successfully using the resulting model to find a mechanism of tumor resistance and to treat tumors in a targeted way. This organoid transplantation model is an innovative way to study disease mechanisms and develop potential therapies.

A high-throughput platform to discover ALS drugs

HSCI Principal Faculty member Clifford Woolf, M.B., B.Ch., Ph.D., developed a high-throughput platform for discovering drug targets to treat amyotrophic lateral sclerosis (ALS). The researchers used stem cells derived from patients with ALS to create motor neurons, the cell type affected in ALS. Advanced imaging technology was used to measure whether drug candidates reduced the neurons' hyperexcitability, or tendency to fire excessively.

After screening a library of 2,900 compounds, the researchers confirmed two known ALS drug targets and identified a new one. A drug for one of the targets is currently under clinical development by QurAlis, a biotechnology company founded by Woolf and former HSCI Principal Faculty member Kevin Eggan. Additionally, their approach of using patient-derived cell models to screen for drugs can be applied to many other diseases.

Facing page, top left: Neurons made from human stem cells, used to study Alzheimer's disease development. Credit: Young-Pearse Lab, Brigham and Women's Hospital

Facing page, top right: A kidney organoid model of a tumor, made using patient stem cells. Credit: Lemos Lab, Brigham and Women's Hospital

Facing page, bottom: Neurons created from ALS patient stem cells. Credit: Woolf Lab, Boston Children's Hospital

LEARNING HOW TO DIRECT CELL BEHAVIOR

At the Harvard Stem Cell Institute (HSCI), our researchers are finding new ways to fine-tune cell behavior. For instance, scientists can engineer therapeutic cells and direct them to eliminate disease cells. On the flip side, researchers can also target and stop the activity of abnormal cells. Together, these approaches are an important avenue for developing better treatments.

A T cell that can be engineered to attack cancer cells.

Engineering stem cells to target metastatic breast cancer

HSCI Principal Faculty member Khalid Shah, M.S., Ph.D., created engineered stem cells, directing them to eliminate breast cancer that had metastasized to the brain. The researchers analyzed patient samples, identifying two types of receptors that were important for tumor growth. The researchers then engineered stem cells with a molecule that targeted both receptor types.

In three different mouse models of brain metastasis, the engineered stem cells successfully crossed the blood-brain barrier and improved survival rates. This stem cell therapy is a promising approach for treating cancer across the blood-brain barrier, which is challenging using most therapeutics.

Controlling CAR T cell behavior during immunotherapy

In CAR T cell therapy, immune cells are engineered to recognize and attack harmful cells. This approach has shown success in treating certain types of advanced cancers, but CAR T cells can also trigger inflammation as a toxic side effect. HSCI researchers led by HSCI Principal Faculty member Benjamin Ebert, M.D., Ph.D., developed a way to better control the activity of CAR T cells: they engineered switchable CAR T cells that could be turned on or off by giving a commonly used cancer drug, lenalidomide.

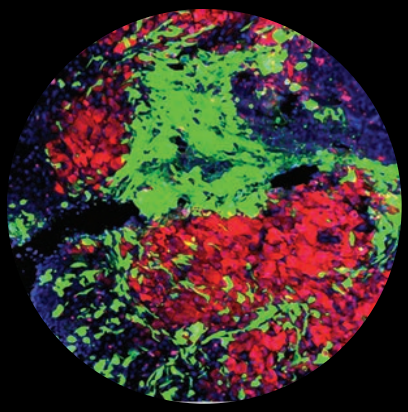
The CAR T cells designed with a molecular "off-switch" could be quickly and reversibly turned off by administering the drug. Alternatively, CAR T cells designed with an "on-switch" only killed tumor cells during drug treatment. These approaches of improving control over CAR T cells can lead to safer and more targeted cell therapies.

Why therapy resistance occurs in metastatic prostate cancer

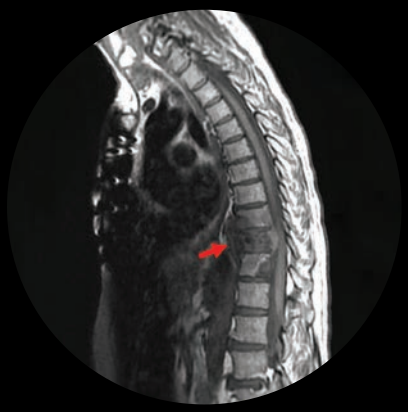
HSCI researchers investigated why metastatic prostate cancer responds poorly to immunotherapy, which usually boosts the body's own immune system to target cancer cells. The scientists were led by Affiliate Faculty member Peter Kharchenko, Ph.D., Principal Faculty member David Sykes, M.D., Ph.D., and Co-Director David Scadden, M.D.

The researchers used patient samples of prostate cancer that had metastasized to the bone marrow, asking why the cancer had evaded the immune system. They found that inside the bone marrow, the tumor caused the development of abnormal immune cells that suppressed the normal immune defenses. Blocking the suppressive signal could restore proper immune behavior and improve the animals' survival.

Controlling the suppressive signal is a promising approach to treat metastatic prostate cancer, especially since one option is to repurpose compounds that have already been tested in people for other diseases.



In the mouse brain, engineered stem cells (green) target metastasized tumor cells (red).
Credit: Shah Lab, Brigham and Women's Hospital



MRI scan of a patient's spine, showing prostate cancer that has metastasized to the bone marrow.
Credit: Philip Saylor, Massachusetts General Hospital

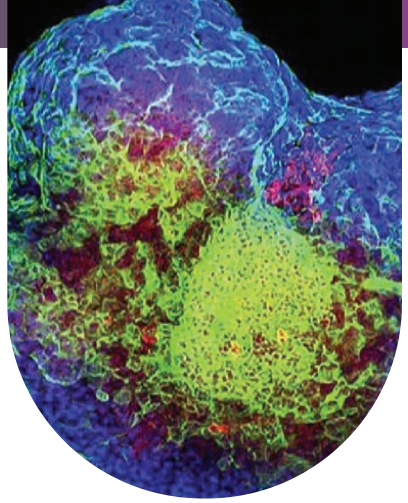
"We found that a group of cells sends a signal that turns off the immune attack of T cells. Interrupting that signal releases the brake and the immune system can go after tumor cells enough to extend the lifespan of animals. There are agents that have been tested in humans in other settings which target the 'off' signal. This work supports testing them in metastatic prostate cancer."

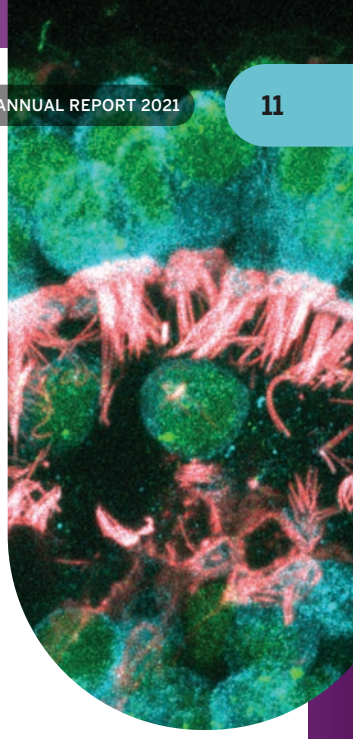
— David Scadden, M.D.

DIRECTING CELLS TO BECOME NEXT-GENERATION THERAPIES

Harvard Stem Cell Institute (HSCI) researchers push toward our ultimate goal of using stem cell biology and regenerative medicine to cure disease. Working across the spectrum of human disease, our researchers are creating next-generation therapies by developing cell transplants, coaxing existing cells to regenerate, and taking the first steps toward growing replacement organs.

Insulin-producing cells created from stem cells.
Credit: Melton Lab, Harvard University





Right: When grown together in a lab dish, heart muscle cells and pre-epicardial cells organize into a complex structure. Credit: Ott Lab, Massachusetts General Hospital

Far right: Hair cells of the inner ear, which are affected in patients with Norrie disease. Credit: Edge Lab, Massachusetts Eye and Ear

The first clinical trial results for Type 1 diabetes cell transplants

In Type 1 diabetes, the immune system attacks beta cells in the pancreas, so that they can no longer produce the insulin necessary to control blood sugar. Over the last 15 years, HSCI Co-Director Douglas Melton, Ph.D., pioneered the process of directing stem cells to become functional beta cells, which can be then transplanted into patients. To bring this therapy to the clinic, Melton previously launched the startup company Semma Therapeutics, which was later acquired by Vertex Pharmaceuticals.

In 2021, Vertex announced the initial results of their clinical trial: the first patient to receive a stem-cell-derived beta cell transplant could successfully produce insulin and control blood sugar, greatly reducing the need for the usual insulin injections. The next step of developing this therapy will be to control the immune system's reaction, so that patients can receive cell transplants without having to take immunosuppressants.

Pathways for preventing and rescuing hearing loss

HSCI Principal Faculty member Albert Edge, Ph.D., identified the biological pathway that can lead to deafness in Norrie disease, a rare condition caused by mutations in the *NDP* gene. The researchers studied a mouse model of Norrie disease that lacked the *NDP* gene. Without NDP, the hair cells of the inner ear died over time, leading to progressive deafness.

The researchers were able to restore hearing loss using two methods: 1) by stimulating a pathway previously found to be important for hair cell regeneration, and 2) by expressing NDP in cells located next to the hair cells. These approaches direct hair cells to recover their function, and are potential treatments to rescue hearing in both Norrie disease and other forms of hearing loss that are caused by hair cell death.

Generating cells that direct heart development in the embryo

During embryonic development, a type of cell called the "pre-epicardial cell" (PEC) helps to direct heart formation. Previously, researchers were able to create heart muscle cells in a lab dish, but not PECs. HSCI Principal Faculty member Harald Ott, M.D., identified a way to convert human stem cells into PECs.

When the PECs were grown together with heart muscle cells, both cell types matured and created a beating structure, both in 2D and — excitingly — in 3D cultures. This advance is an important step toward generating a tissue with the complex structure of the heart, which is a potential therapy for heart failure.

DOUGLAS MELTON, PH.D.

STEPHAN KISSLER, PH.D.

NEW MULTI-INSTITUTIONAL CENTER FOR TYPE 1 DIABETES RESEARCH

Douglas Melton is directing a new multi-institutional center to advance the next stage of Type 1 diabetes research. At the JDRF Center of Excellence in New England, researchers use stem cell and gene editing approaches to investigate why immune rejection happens and to create beta cells that can withstand it. The center is a collaboration with HSCI Principal Faculty member Stephan Kissler, Ph.D., at the Joslin Diabetes Center, as well as scientists at JDRF, UMass Chan Medical School, and the Jackson Laboratory.

DIRECTING THE HSCI PIPELINE

At the Harvard Stem Cell Institute (HSCI), we direct our mission toward making a difference in patients' lives. We start by funding promising, early-stage projects that have a high initial risk and may not be supported by more traditional funders, but have great potential for changing the paradigm of regenerative medicine.

A critical part of our approach is bringing together leading scientists from across the HSCI network of schools and hospitals to exchange ideas and advance research. To deliver on the promise of the next generation of therapies, our scientists launch startups and engage in industry collaborations. Here, we highlight HSCI's 2021 accomplishments throughout our pipeline of innovation.

1

HSCI FUNDS EARLY-STAGE PROJECTS THAT ARE HIGH-RISK, HIGH-REWARD

Collaborative seed grants

Interplay between immune and beta cells in diabetes
Stephan Kissler, Ph.D.
Nika Danial, Ph.D.

Gene expression analysis to improve platelet production
Alan Cantor, M.D., Ph.D.
Jeffrey Moffitt, Ph.D.

Lung regeneration after infection
Ruth Franklin, Ph.D.
Fei Chen, Ph.D.

Nerve regulation in tooth repair
Yingzi Yang, Ph.D.
Jennifer Gibbs, D.D.S., Ph.D.

Engineering inactive blood stem cells
Christian Brendel, Ph.D.
Daniel Bauer, M.D., Ph.D.

Disease Program Pilot Grants

Nervous System Diseases Program:
Blood-brain barrier

Musculoskeletal (MSK) Program:
Tendon and cartilage repair

« VIDEO:
MEET OUR SCIENTISTS

BIT.LY/HSCI-MSK

Barry Family HSCI Innovation Award for Early Investigators

Advancing transplantation biology with single-cell technologies
Jason Buenrostro, Ph.D.

Muscle fibers made using muscle stem cells. Credit: Wagers Lab, Harvard University

2

HSCI SCIENTISTS COLLABORATE ACROSS DISCIPLINES AND INSTITUTIONS TO SPARK NEW IDEAS

16th Annual HSCI Retreat

The annual retreat is our hub for sharing latest advances, where we feature speakers from our community, as well as leading research institutions and pharmaceutical companies.

The retreat also focuses on the professional development of early-career scientists. In 2021, the award for best trainee presentation went to Christa Haase from the Charles Lin lab at Massachusetts General Hospital, for her work on using spatial RNA-sequencing to analyze leukemia progression.

9 Disease Program seminars spanning diverse topics

Cancer

Musculoskeletal disease and injury

Heart disease

Alzheimer's and other nervous system diseases

Kidney disease

3

HSCI SCIENTISTS ADVANCE THEIR DISCOVERIES FROM THE LAB INTO THE CLINIC

2 new biotech startups joined the 40+ companies launched by HSCI scientists

Garuda Therapeutics

Founder Dhvanit Shah, Ph.D., and co-founder David Scadden, M.D.

Clade Therapeutics

Co-founder Chad Cowan, Ph.D.

HSCI scientists accelerate research by working with biopharmaceutical companies

Co-Leader of the HSCI Nervous System Diseases Program and Principal Faculty member Lee Rubin, Ph.D., formed an R&D alliance with Resilience, Inc. to develop novel muscle stem cell therapies.

As part of the Harvard Fibrosis Network, HSCI researchers are working with Boehringer Ingelheim and Bristol Myers Squibb to discover and develop potential new therapies for fibrotic diseases.

HSCI LEADERSHIP

The Harvard Stem Cell Institute (HSCI) is led by Faculty Co-Directors Douglas Melton and David Scadden, and Executive Director Brock Reeve. They work alongside the Executive Committee, which includes top scientists from our broad network of Harvard schools and affiliate hospitals. Together, the HSCI leadership has deep expertise in basic science, translational research, and commercialization—all critical to advancing HSCI's mission to deliver on the promise of stem cell biology and improve patients' lives.

FACULTY CO-DIRECTORS

Douglas Melton, Ph.D.
Xander University Professor of Stem Cell and Regenerative Biology, Harvard University

Investigator, Howard Hughes Medical Institute

David Scadden, M.D.
Gerald and Darlene Jordan Professor of Medicine, Harvard University

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

Investigator, Howard Hughes Medical Institute

Joseph Bonventre, M.D., Ph.D.
Samuel A. Levine Distinguished Professor of Medicine, Harvard Medical School

Chief, Divisions of Renal Medicine and Engineering in Medicine, Brigham and Women's Hospital

Susan Dymecki, M.D., Ph.D.
Professor of Genetics, Harvard Medical School

Albert Edge, Ph.D.
Eaton-Peabody Professor of Otolaryngology Head and Neck Surgery, Harvard Medical School

Director, Tillotson Cell Biology Unit, Massachusetts Eye and Ear

Jenna Galloway, Ph.D.
Associate Professor of Orthopedic Surgery, Harvard Medical School

Associate Investigator, Center for Regenerative Medicine, Mass General Research Institute

Co-Leader, HSCI Musculoskeletal Program

Carla Kim, Ph.D.
Professor of Genetics and Professor of Pediatrics, Harvard Medical School

Principal Investigator and Stem Cell Program Faculty, Boston Children's Hospital

Co-Leader, HSCI Cancer Program

Jeffrey Macklis, M.D., D.Sc.Tech.
Max and Anne Wien Professor of Stem Cell and Regenerative Biology

Professor of Surgery and Neurology, Harvard Medical School

Faculty Member, Harvard Center for Brain Science

Jerome Ritz, M.D.
Professor of Medicine, Harvard Medical School

Executive Director, Connell and O'Reilly Families Cell Manipulation Core Facility, Dana-Farber Cancer Institute

New Faculty Members

In 2021, HSCI welcomed 19 new faculty members from schools and hospitals across our network.

HSCI PRINCIPAL FACULTY MEMBER AND DIABETES PROGRAM CO-LEADER

Stephan Kissler, Ph.D.
Associate Professor of Medicine, Harvard Medical School

Investigator and Genome Editing Core Co-Director, Joslin Diabetes Center

HSCI PRINCIPAL FACULTY MEMBER

Peter van Galen, Ph.D.
Assistant Professor of Medicine, Harvard Medical School

Assistant Professor of Hematology, Brigham And Women's Hospital

17 HSCI AFFILIATE FACULTY MEMBERS FROM 5 HOSPITALS AND INSTITUTES

Vicki Rosen, Ph.D.
Professor of Developmental Biology and Chair of the Department of Developmental Biology, Harvard School of Dental Medicine

Co-Leader, HSCI Musculoskeletal Program

Lee Rubin, Ph.D.
Professor of Stem Cell and Regenerative Biology, Harvard University

Co-Leader, HSCI Nervous System Diseases Program

Amy Wagers, Ph.D.
Forst Family Professor of Stem Cell and Regenerative Biology and Co-Chair of the Department of Stem Cell and Regenerative Biology, Harvard University

Senior Investigator and Flow Cytometry Core Director, Joslin Diabetes Center

Co-Leader, HSCI Musculoskeletal Program

AWARDS

HSCI faculty are widely recognized as leaders in the fields of stem cell biology and regenerative medicine. Here, we highlight just a few representative examples of the awards that our scientists received in 2021.

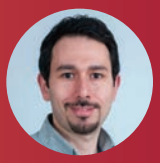
Two HSCI faculty were named Research Professors by the American Cancer Society. **BRADLEY BERNSTEIN, M.D., PH.D.,** will study how tumor formation is affected by epigenetics, heritable changes that do not involve the DNA sequence. **XI HE, PH.D.,** will study how two major biological signaling pathways interact in cancer.

SUSAN BONNER-WEIR, PH.D., received the 8th Helmholtz Diabetes Award for lifetime achievement, in recognition of her accomplishments in furthering our understanding of how the endocrine (hormonal) part of the pancreas grows and functions.

JOSEPH BONVENTRE, M.D., PH.D., was elected as a 2021 Fellow of the American Association for the Advancement of Science. The award recognizes his "scientifically and socially distinguished achievements in the scientific enterprise," particularly his research on kidney injury and development of functional kidney organoids.

BENJAMIN EBERT, M.D., PH.D., received the international Sjöberg Prize for his discovery of how lenalidomide works as a treatment for blood cancer, which could help with the development of new drugs.

NAAMA KANAREK, PH.D., received a grant from the Starr Cancer Consortium, in collaboration with Adrienne Boire, M.D., Ph.D. The researchers will study cancer cells that have metastasized to the tissue that covers the brain and spinal cord (leptomeningeal metastasis), focusing on how the cells adapt to the challenging environment.



MURAT KARABACAK, PH.D., is leading a team that received a grant from the Million Dollar Bike Ride Grant Program. The team will study a rare disease called fibrodysplasia ossificans progressiva, where the muscle and connective tissue are gradually replaced by bone. The researchers will develop a new blood biomarker that can be used in an engineered microfluidics device in order to detect the disease early.

STUART ORKIN, M.D., received the Tobias Lecture Award from the International Society for Stem Cell Research in recognition of his groundbreaking discoveries in blood cell development, which have formed the basis for novel gene therapies for blood disorders including hemoglobinopathies, sickle cell disease and ß-thalassemia. His pioneering genetics research was also recognized by the Gruber Foundation Prize in Genetics

Two HSCI faculty were awarded funding by the Simons Collaboration on Plasticity and the Aging Brain. **LEE RUBIN, PH.D.,** will study how components in the blood can improve the function of the aging brain. **AMAR SAHAY, PH.D.,** will investigate how cognitive function and memory change as the brain ages. Together, these projects will give a better understanding of the mechanisms behind the decline of memory and other cognitive functions during aging, and point the way toward strategies to slow or reverse these processes.

KHALID SHAH, M.S., PH.D., received a Pillars of Excellence Award from Mass General Brigham in the area of "Integrating Diversity, Equity & Inclusion." The award recognizes his contributions to the hospital's mission of serving patients locally, nationally and around the world.

MARC WEIN, M.D., PH.D., received the Stepping Strong Breakthrough Award from Brigham Health. The award will support his research into improving fracture healing caused by serious traumatic injuries.

LEONARD ZON, M.D., was elected as an associate member of the European Molecular Biology Organization, in recognition of his research excellence and outstanding achievements in the field of blood cell development.

DIRECTORS' CALLS

MEETING OUR SCIENTISTS

Throughout the year, Harvard Stem Cell Institute (HSCI) supporters are invited to calls hosted by Co-Directors Douglas Melton and David Scadden. There, supporters have the opportunity to make direct connections with HSCI scientists who are leaders in their field, learning about new advances and asking burning questions. Here, we share highlights from the Directors' Calls of 2021.

DERRICK ROSSI, PH.D.

Co-Founder of Moderna Therapeutics

Former HSCI Principal Faculty member

Question: I don't need to introduce Moderna to people nowadays: many of us have received the benefits of a Moderna COVID-19 vaccine. That is in no small part due to Derrick's imagination about how to use messenger RNA to affect biomedicine. Derrick, I would hazard a guess that you didn't have any idea of the impact that it would have on humanity. What was going through your head at the time?

Answer: The ability to differentiate cells back to stem cells took the world by storm. This project that we were doing was using a modified mRNA to reprogram differentiated cells back to potency.

HSCI is very good at recognizing high-risk science that has potential and funding it. As soon as we made a few dozen human proteins, it became obvious to me what we could use this for: if you could make protein so readily, you had a handle on human disease. Now that has been realized with the vaccine.

Q: You were not necessarily thinking of the applications when you were first doing your work. And yet, something allowed you to be able to move it forward.

A: I happen to be fortunate to be doing my work at Harvard Medical School and within the greater ecosystem of Boston and Cambridge, which is the absolute dead center of biotech enterprise on planet Earth. This concentration of science, business development, intellectual property, venture capital, and philanthropy was critical — the greater the concentration, the better. This might not have happened had it not been for that.

Cross section of muscle fibers showing the dystrophin protein (green) that is affected in Duchenne muscular dystrophy.

A newborn neuron in the hippocampus, the brain region targeted by the exercise hormone irisin. Credit: Wrann Lab

Credit: Harvard University

AMY WAGERS, PH.D.

Harvard University

HSCI Executive Committee member, Musculoskeletal Program Co-Leader, and Principal Faculty member

Q: Amy has done some really beautiful work on identifying ways in which we can correct muscle diseases, particularly the terrible genetic diseases of muscular dystrophy. Can you share what you've been able to figure out?

A: What's really held back the field has been an inability to deliver gene therapies safely, effectively, and *specifically* to the relevant cell types. These approaches have largely made use of adeno-associated viral vectors, or AAVs, which can encapsulate genes and deliver them into the muscle tissue. But they also deliver to other tissues including — particularly problematically — to the liver, which can lead to toxicity.

This is where our work comes in. We made a huge library of randomly modified variants of the virus. Each virus carried a gene to detect the few virus particles among the millions that were actually able to functionally deliver their cargo into muscle. Applying this system in mice, we identified a very large class of muscle-directed AAVs that we named MyoAAVs.

Understanding the mechanism underlying the delivery profile of these vectors enabled their evolution to even more potent forms: the second-generation MyoAAVs showed up to 80-times greater delivery to skeletal muscle and showed remarkably enhanced therapeutic potency. We've also identified third- and fourth-generation MyoAAVs that have robust delivery to primate muscle. We can now test these vectors in models of severe genetic muscle diseases, including Duchenne muscular dystrophy.

Credit: Massachusetts General Hospital

CHRISTIANE WRANN, D.V.M., PH.D.

Massachusetts General Hospital

HSCI Affiliate Faculty member

Q: We all know that exercise is good for you, but Christiane has delved into this deeply to say what is really the molecular basis of improvements. What are the possible mechanisms that link exercise and brain function?

A: The novel exercise hormone that we're interested in is called irisin. This is a molecule that is expressed in skeletal muscle and in the hippocampus, the part of the brain that's important for learning and memory, and also one of the brain regions that first declines in aging and Alzheimer's disease. We have shown that irisin carries the cognitive benefits of exercise.

If you have a very small molecule such as irisin that travels in the bloodstream to the brain, then it is feasible to turn it into a drug. In several mouse models of Alzheimer's disease, we saw a significant improvement in cognitive function of the mice treated with irisin.

Q: It looks like irisin is on the way to being tested in a clinical trial. How do you imagine bringing this forward to patients?

A: We recognize that Alzheimer's disease is very difficult to tackle, however we are optimistic this has some chances. It's possible that Parkinson's is one of the other diseases where irisin has an effect. We feel this is an innovative, different approach which could catalyze the field.

DONOR SPOTLIGHTS

MARTY GRANOFF

HSCI Donor

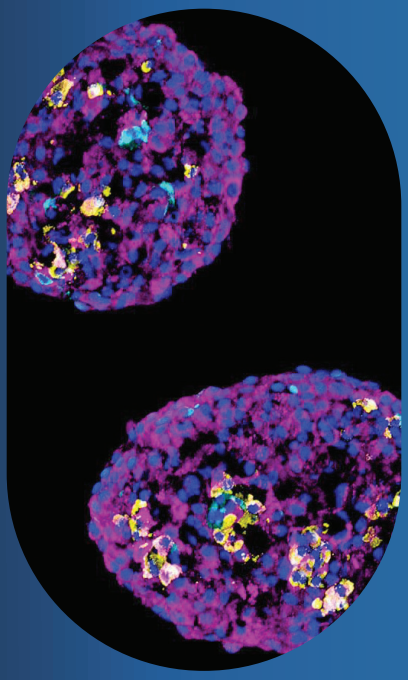
My grandson came down with a very bad case of Type 1 diabetes when he was a teenager. As a biotech investor, I started asking around, who is working on a solution to Type 1 diabetes? Doug Melton's name kept coming up from various people.

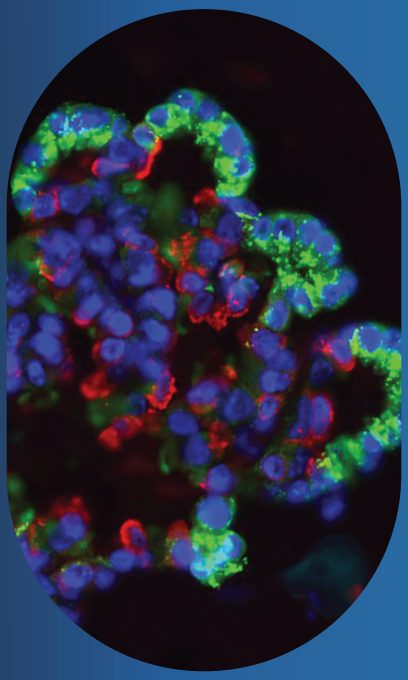
Separately, I noticed in the Wall Street Journal that a firm called Semma Therapeutics was applying for clinical trials, hopefully with a solution to the problem. I looked into the company, and Doug's name was there again. I learned that he was at the Harvard Stem Cell Institute. That's how I came to the institute, in a roundabout way.

I got to meet Doug when he gave a wonderful presentation for my son and grandson. We were inspired by his work, and I decided to give a gift a couple years later.

The results of the clinical trial for beta cell transplants are very exciting. The next step will be to administer the therapy without immunosuppressant drugs. The ramifications of this work go far past just Type 1 diabetes. It could be valuable to other transplant recipients, either for stem cells or organs like the heart and lung.

When my son went into the business world years ago, he asked me if I had any advice. I told him that I would bet not on the deal, but on the person. I feel that way here: I'm betting on the person who's going to come up with a cure for this terrible disease.





Top: Insulin-producing beta cells created from stem cells. Credit: Melton Lab

Bottom: Lab-grown organoids of alveolar cells, the type of cell that forms air sacs in the lung. Credit: Kim Lab

CARLA KIM, PH.D.

Co-Leader, HSCI Cancer Program

Harvard Medical School and Boston Children's Hospital

Most patients with lung cancer are diagnosed when it's "too late". In our lab, we have created a model of early-stage lung cancer to identify the changes happening in those cells, so that we can find ways to intervene early and prevent the disease from progressing.

In our tumor organoid model, we create a three-dimensional system that enables us to mimic the interactions between cells that occur within the lung tissue. After obtaining specific lung cell types, we activate a mutant gene that is most commonly mutated in lung cancer patients. As soon as we turn it on, the cells immediately undergo gene expression changes, earlier than we expected.

Now, with a generous gift from an HSCI donor, we are doing more detailed, single-cell analyses of these organoids. We are now asking precisely which genes are turned on and off within the cells that we know are going to form tumors. Those would be genes you'd want to target and inhibit, and we can see if there's already a drug available. This gift is helping us to test some of those drug candidates in our tumor organoid system.

This project is only possible because I was an HSCI faculty member when I started my lab. Early funding from HSCI helped us develop the organoid system along with feedback from colleagues working on other types of stem cells, and the current donation is critical to taking our work to the next stage.

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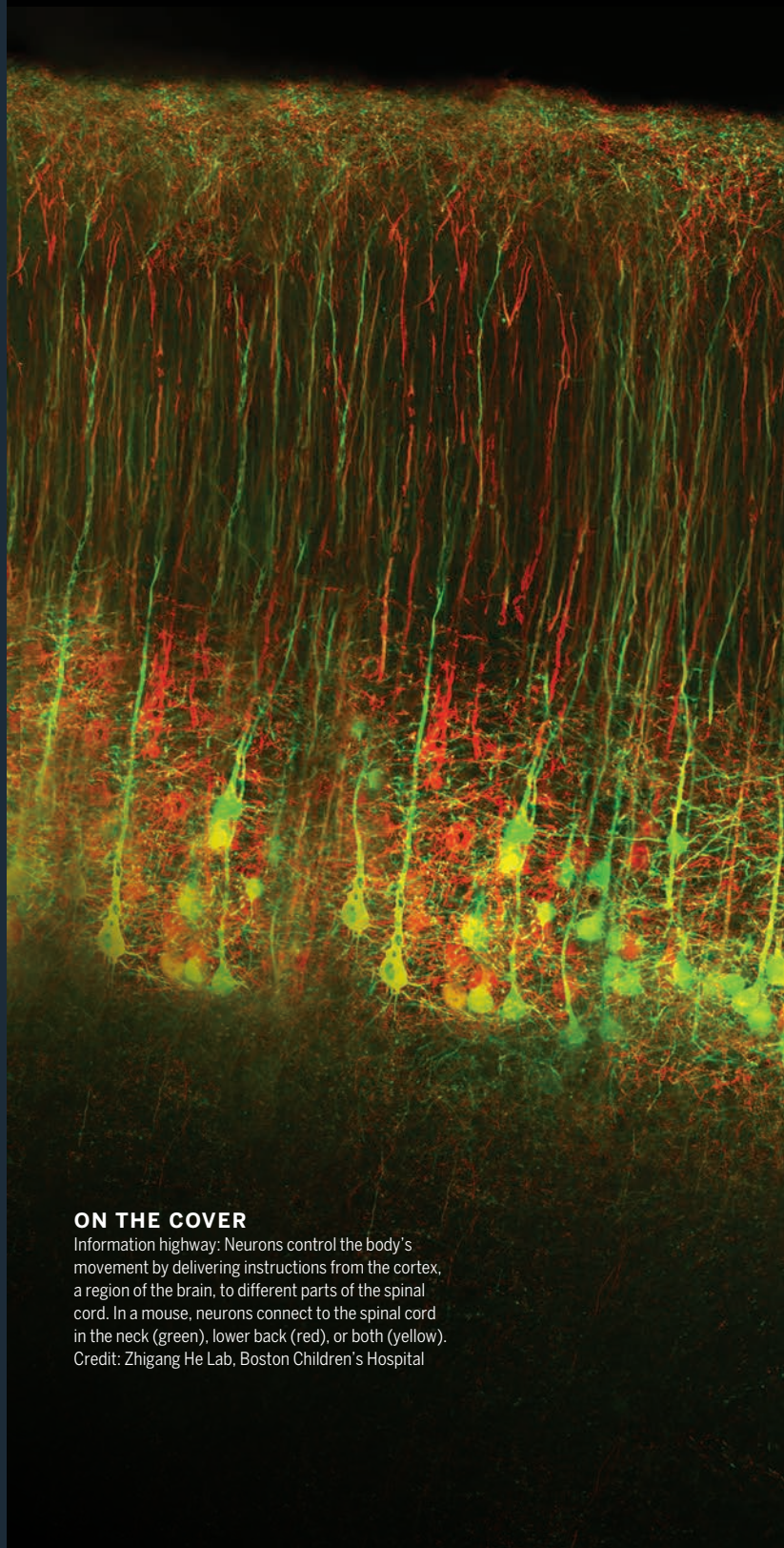

ON THE COVER
Information highway: Neurons control the body's movement by delivering instructions from the cortex, a region of the brain, to different parts of the spinal cord. In a mouse, neurons connect to the spinal cord in the neck (green), lower back (red), or both (yellow). Credit: Zhigang He Lab, Boston Children's Hospital