TRANSITIONS

HSCI
HARVARD STEM CELL INSTITUTE®

ANNUAL REPORT 2022

CONTENTS

DIRECTOR'S MESSAGE

DOUGLAS MELTON, PH.D.

Founding Co-Director

DAVID SCADDEN, M.D.

Founding Co-Director

Every year our Annual Report and more specifically this letter from the leadership team serves as an opportunity to reflect on another successful year from HSCI. As we enter our 20th year, we're also looking towards the future and how we can shift and adapt to where the field is moving. Much has changed since HSCI's establishment in 2005. The field has matured substantially and so have we. HSCI has made tremendous progress in scientific discoveries that have led to clinical applications. We've been able to leverage our unique connection to the Boston biotech ecosystem to mature our projects and commercialize innovations. With Doug Melton and Brock Reeve now spending time within industry while still remaining committed to supporting HSCI's mission, we're in a prime position to more meaningfully connect with communities that have not traditionally been part of academic research.

In the coming year we're excited to embrace a new approach that harkens back to the way we first built this community 20 years ago: namely leveraging expertise across multiple institutions to substantially impact human health. We're doing this by shifting away from a matrixed approach and leaning into verticals through capstone projects that will have a line of sight to a disease program while using technologies directed at solving a specific problem.

Thanks to the support and visionary leadership of Mike Vranos and the Vranos Family Foundation, we kicked off our first capstone project in 2022. This five-year initiative will combine the most advanced experimental methods with a dedicated computational effort to challenge the concept that neurologic functional decline associated with aging is irreversible, aligning expertise from across Faculty of Arts and Sciences and Harvard Medical School.

A $11.5 million grant last year from the National Institutes of Aging to George Murphy, MD, and Markus Frank, MD, the co-leaders of HSCI's Skin Program, also shows the multi-institute, multi-year, disease-specific projects we aim to focus on. Their initiative, which unites laboratories and investigators across six Harvard Institutions, will study defective wound healing as a result of age-related skin stem cell depletion. They seek to define new therapies to replenish cutaneous stem cell health and vitality. This funding helps accelerate their pre-existing program, which had been steadily progressing over the last three years within the HSCI Skin Program.

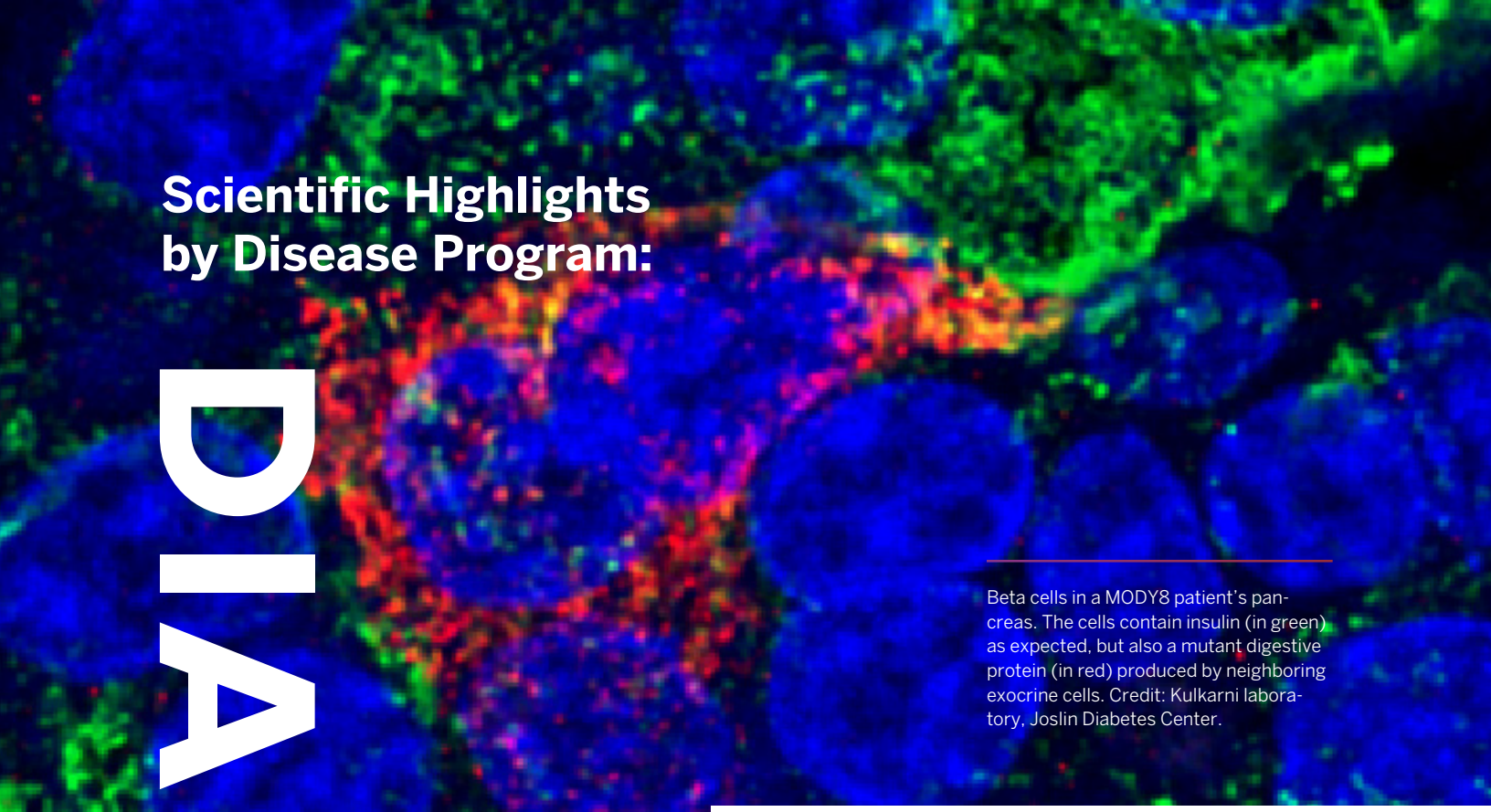
Although we're shifting our approach, our mission remains the same and our philanthropic partnerships continue to be essential to carrying out this mission. We are so thankful for your continued support and leadership, and we hope you share in our excitement in this next chapter. We look forward to working together to meet HSCI's full potential in the years to come.

Sincerely,

Douglas Melton and David Scadden

Scientific Highlights by Disease Program:

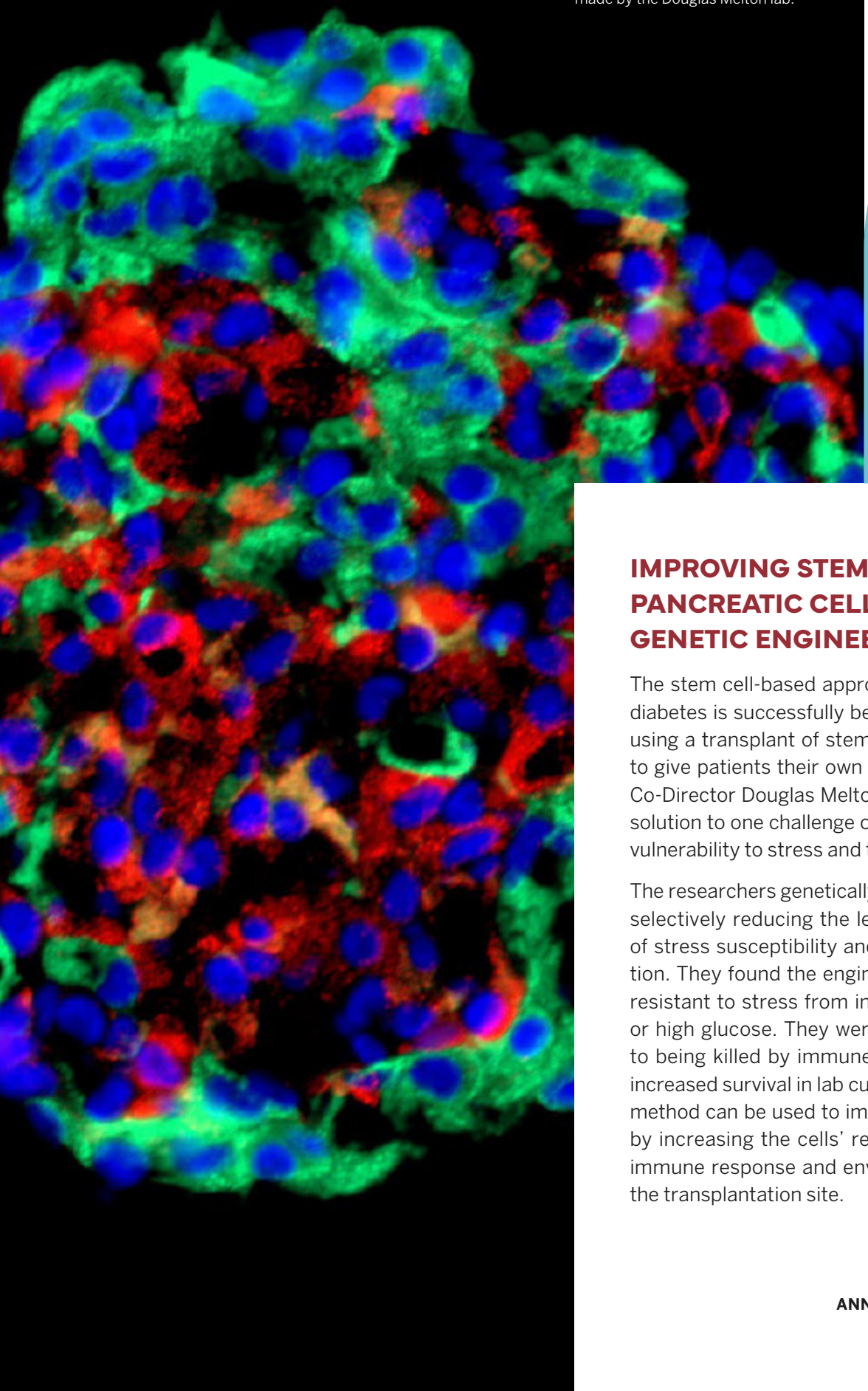
DIABETES



Beta cells in a MODY8 patient's pancreas. The cells contain insulin (in green) as expected, but also a mutant digestive protein (in red) produced by neighboring exocrine cells. Credit: Kulkarni laboratory, Joslin Diabetes Center.

CROSSTALK BETWEEN PANCREATIC CELLS MAY DRIVE RARE FORM OF DIABETES ▶

A rare inherited form of diabetes is "mature onset diabetes of the young type 8," caused by a single gene mutation that disrupts insulin production. A study by HSCI Principal Faculty member Rohit Kulkarni, MD, PhD, identified the mechanism of how this disease develops. Using mouse models and patient samples, the researchers studied the interaction between the two classes of cells in the pancreas: exocrine cells that produce digestive enzymes and endocrine cells that produce hormones including insulin. They found the exocrine cells produced a mutated digestive enzyme, which aggregated in neighboring insulin-producing cells to cause damage. Figuring out the crosstalk between exocrine and endocrine cells can help researchers better understand other forms of diabetes, including type 1 diabetes, leading to potential new therapeutic strategies.



Stem cell-derived beta cells made by the Douglas Melton lab.

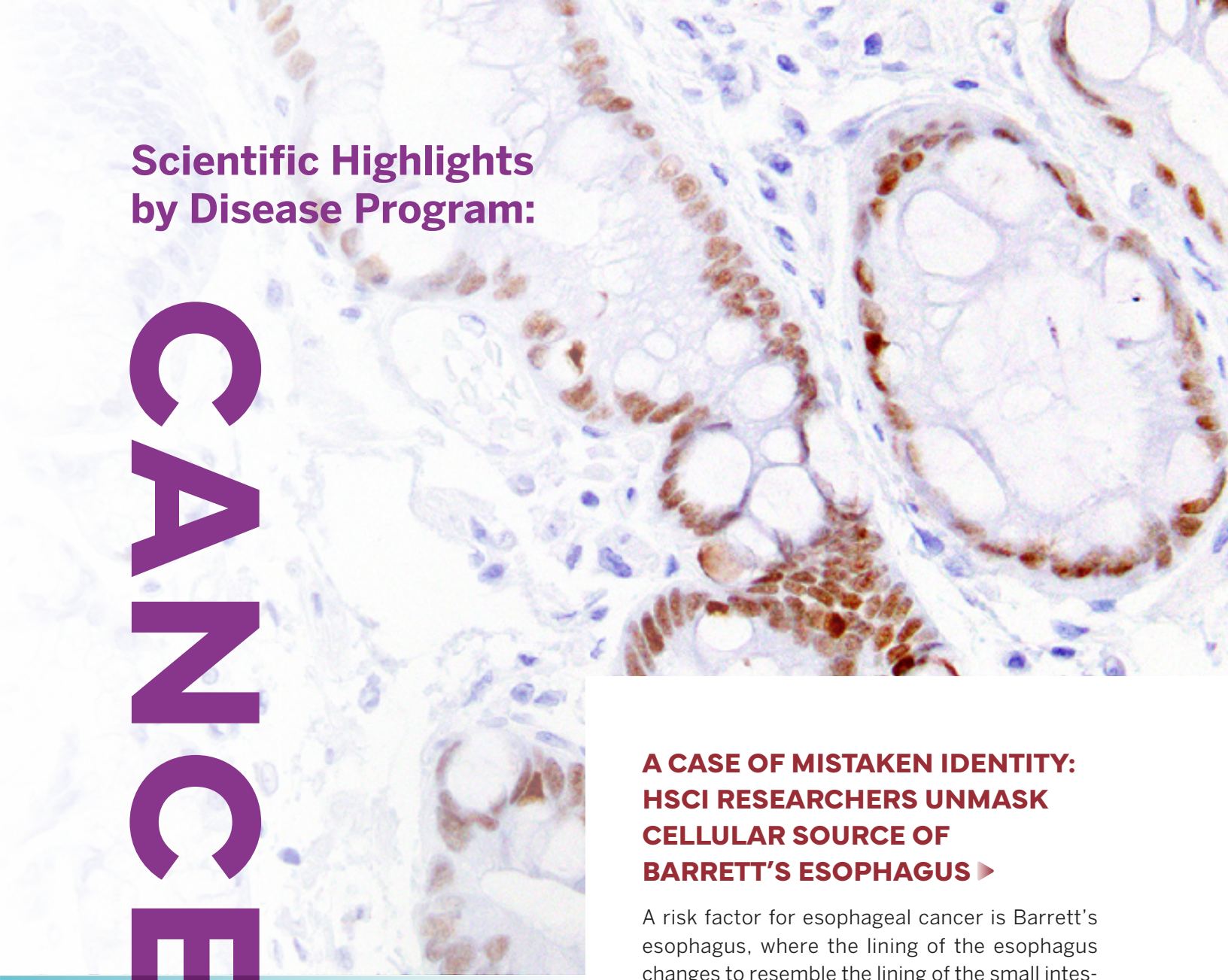
IMPROVING STEM CELL-DERIVED PANCREATIC CELLS WITH GENETIC ENGINEERING

The stem cell-based approach to treating Type 1 diabetes is successfully being tested in the clinic, using a transplant of stem cell-derived beta cells to give patients their own source of insulin. HSCI Co-Director Douglas Melton, PhD, is developing a solution to one challenge of the therapy, the cells' vulnerability to stress and the immune system.

The researchers genetically engineered beta cells, selectively reducing the levels of four mediators of stress susceptibility and immune cell recognition. They found the engineered cells were more resistant to stress from inflammatory molecules or high glucose. They were also less susceptible to being killed by immune cells, showing overall increased survival in lab culture experiments. This method can be used to improve beta cell therapy by increasing the cells' resistance to the body's immune response and environmental triggers at the transplantation site.

Scientific Highlights by Disease Program:

CANCER



A tissue section from a person with Barrett's esophagus shows that the cells express the factor CDX2 (represented in red), which turns on intestinal genes. Credit: Shivdasani laboratory, Dana-Farber Cancer Institute and Harvard Stem Cell Institute.

A CASE OF MISTAKEN IDENTITY: HSCI RESEARCHERS UNMASK CELLULAR SOURCE OF BARRETT'S ESOPHAGUS ▶

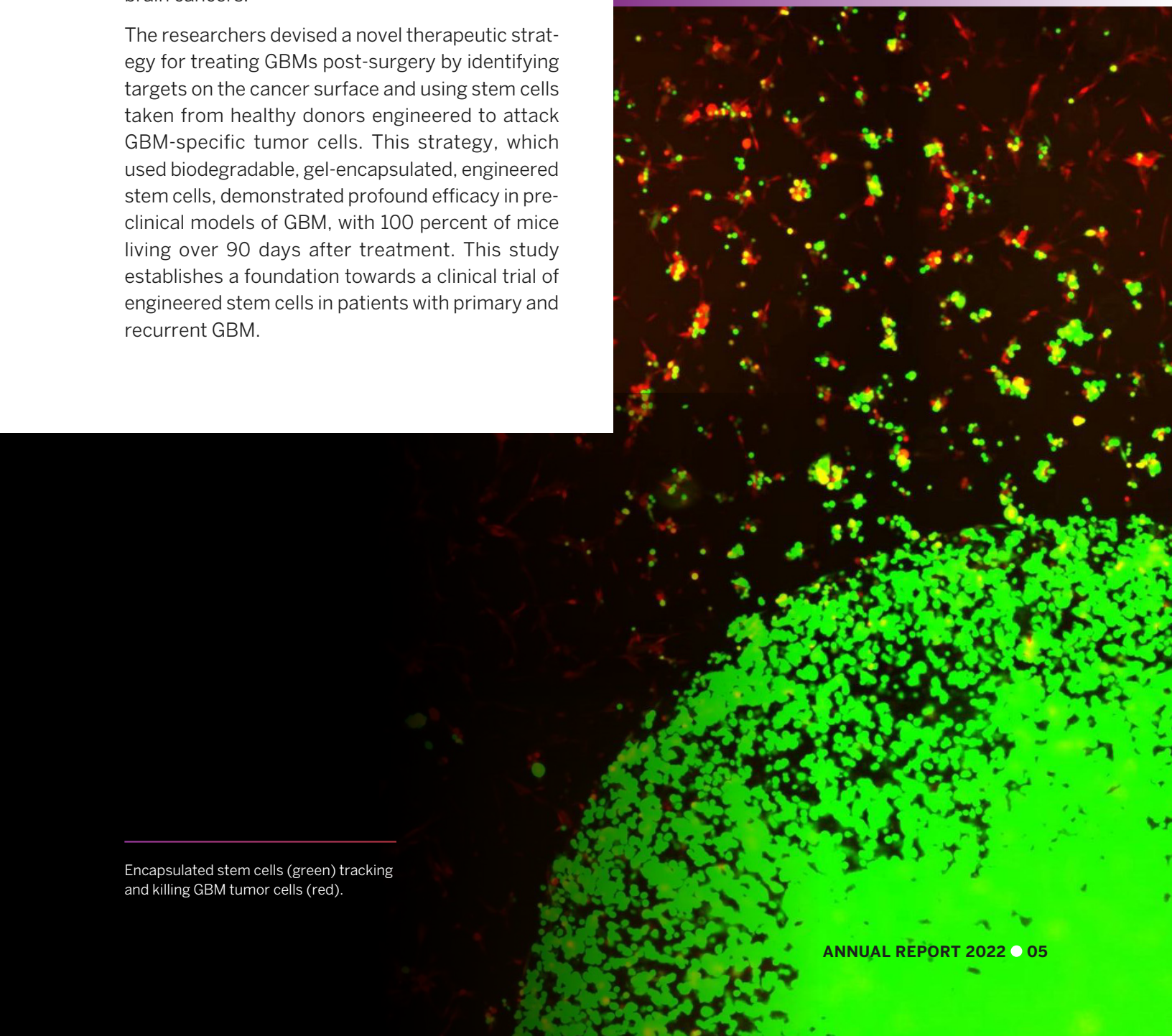
A risk factor for esophageal cancer is Barrett's esophagus, where the lining of the esophagus changes to resemble the lining of the small intestine. Researchers led by HSCI Principal Faculty member Ramesh Shivdasani, MD, PhD, have identified the mechanism of how this switch in cell identity occurs. The researchers studied samples from individuals with Barrett's esophagus, as well as cell and mouse models. They looked at how DNA was organized and which specific proteins were involved.

Unexpectedly, Barrett's esophagus did not involve esophageal cells turning into intestinal cells — instead, stomach cells took on some of the characteristics of intestinal cells. The researchers identified the specific proteins that caused stomach cells to activate intestinal genes. The results open new avenues of investigation for treatment or prevention to lower the risk of esophageal cancer.

ENGINEERED STEM CELLS USED TO TREAT AGGRESSIVE BRAIN CANCER

Glioblastomas (GBMs) are highly aggressive cancerous tumors of the brain and spinal cord. Brain cancers like GBM are challenging to treat, and more than 90 percent of GBM tumors return after being surgically removed, despite surgery and subsequent chemo- and radiation therapy. HSCI Principal Faculty member Khalid Shah, MS, PhD, developed a new strategy to treat these aggressive brain cancers.

The researchers devised a novel therapeutic strategy for treating GBMs post-surgery by identifying targets on the cancer surface and using stem cells taken from healthy donors engineered to attack GBM-specific tumor cells. This strategy, which used biodegradable, gel-encapsulated, engineered stem cells, demonstrated profound efficacy in preclinical models of GBM, with 100 percent of mice living over 90 days after treatment. This study establishes a foundation towards a clinical trial of engineered stem cells in patients with primary and recurrent GBM.



Encapsulated stem cells (green) tracking and killing GBM tumor cells (red).

FIRST-LINE TREATMENTS FOR BONE MARROW DISORDER MAY ACTIVATE DORMANT MUTATED GENE

Hypomethylating agents (HMAs) are currently used as a first-line treatment for patients with myelodysplastic syndrome (MDS)—a group of disorders where there is insufficient production of healthy mature blood cells in the bone marrow. But do these drugs activate a sleeping gene that could potentially cause cancer?

To answer this question, a team including Daniel Tenen, MD, HSCI Principal Faculty and Leader of the Blood Program, analyzed the bone marrow samples of 68 patients with MDS, taken before and after HMA treatment. The scientists discovered that HMAs activate an oncogene known as SALL4 in up to 40 percent of patients with MDS, leading to poor survival outcomes even among those in complete disease remission. This discovery suggests the importance of monitoring SALL4 expression levels in patients receiving HMA therapy and identifying combination therapies that target SALL4.

Scientific Highlights by Disease Program:

NERVOUS SYSTEM DISEASES

Microscopy image of a brain organoid showing neuron precursors (magenta) and deep-layer projection neurons (green), which are one of the cell types affected by autism risk gene mutations. Credit: Paola Arlotta laboratory at Harvard University and Kwanghun Chung laboratory at MIT.

DIFFERENT AUTISM RISK GENES, SAME EFFECTS ON BRAIN DEVELOPMENT ▶

Autism spectrum disorder has been associated with hundreds of different genes, but how these distinct genetic mutations converge on similar symptoms in patients has remained a mystery. HSCI Principal Faculty member Paola Arlotta, PhD, studied three autism risk genes whose exact functions have been unclear. Arlotta's lab created miniature 3D models, or "organoids," of the human cerebral cortex, the part of the brain responsible for cognition, perception, and language. The organoids contained a mutation in one of the autism risk genes. They found that the three different risk genes affected similar aspects of development and the same types of neurons, although each gene acted through unique molecular mechanisms. Additionally, a person's specific genetic background fine-tuned the genes' effects. These results advance our understanding of autism spectrum disorder and are a first step toward finding treatments for the condition.

SCIENTISTS DISCOVER A DUAL FUNCTION OF A KEY PROTEIN PARKINSON'S DISEASE PROTEIN

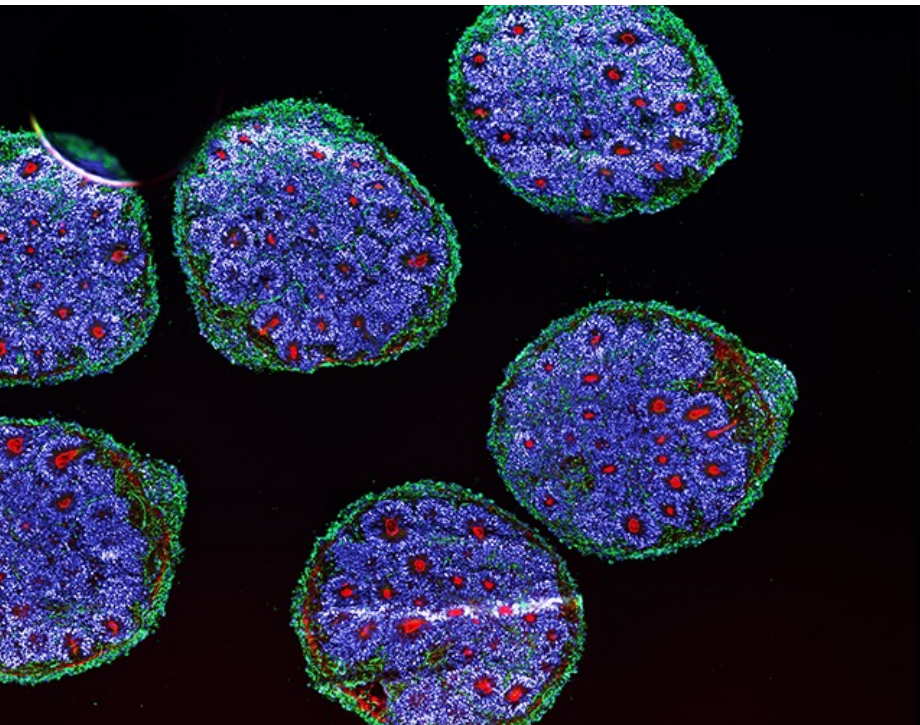
One of the hallmarks of Parkinson's disease (PD) is the accumulation in the brain of a protein known as alpha-synuclein. But alpha-synuclein's function is not well understood. New research from HSCI Principal Faculty member Vikram Khurana, MD, PhD, uncovered a new function for the protein with relevance for PD and related conditions.

The researchers studied neurons with alpha-synuclein gene mutations and post-mortem brain tissue samples from PD patients to learn more about the protein's function. The team discovered that alpha-synuclein is involved in the expression of certain genes. It appears the protein acts as a "toggle switch" that regulates two very distinct functions: transport of vesicles (previously known) and gene expression (a new discovery). In disease states, the balance is broken. Patients who had an accumulation of mutated genes appeared to be at higher risk for PD. This discovery provides new insights for treatment of the disease.

BRAIN ORGANOIDS REPLICATE KEY EVENTS IN HUMAN BRAIN DEVELOPMENT

Organoids are carefully grown collections of cells in a dish, designed to mimic organ structures and composition better than conventional cell cultures and give researchers a unique view into how organs such as the brain grow and develop. HSCI Principal Faculty Paola Arlotta, PhD, has found that human brain organoids replicate many important cellular and molecular events of the developing human cortex and can be used to study important brain processes.

The Arlotta lab grew brain organoids from stem cells and closely studied their growth over a six-month period at a single-cell level. They then constructed an "atlas" characterizing more than 600,000 cells from organoids that were sampled as they developed and matured. The team found that after the first month, in each organoid they made, the same types of cells developed in the same order and expressed the same genes as cells in the developing human embryo. Because these organoids are reasonably accurate models of early brain development and can be grown in relatively large numbers in the lab from just a small pool of stem cells, these models could help accelerate research on brain health and neurodevelopmental disorders.



Human brain organoids showing neurons and their dendrites (green), telencephalic (forebrain) cells (blue), and a kind of cell-cell contact called tight junctions (red). Image credit: Noelia Anton Bolanos and Irene Faravelli.

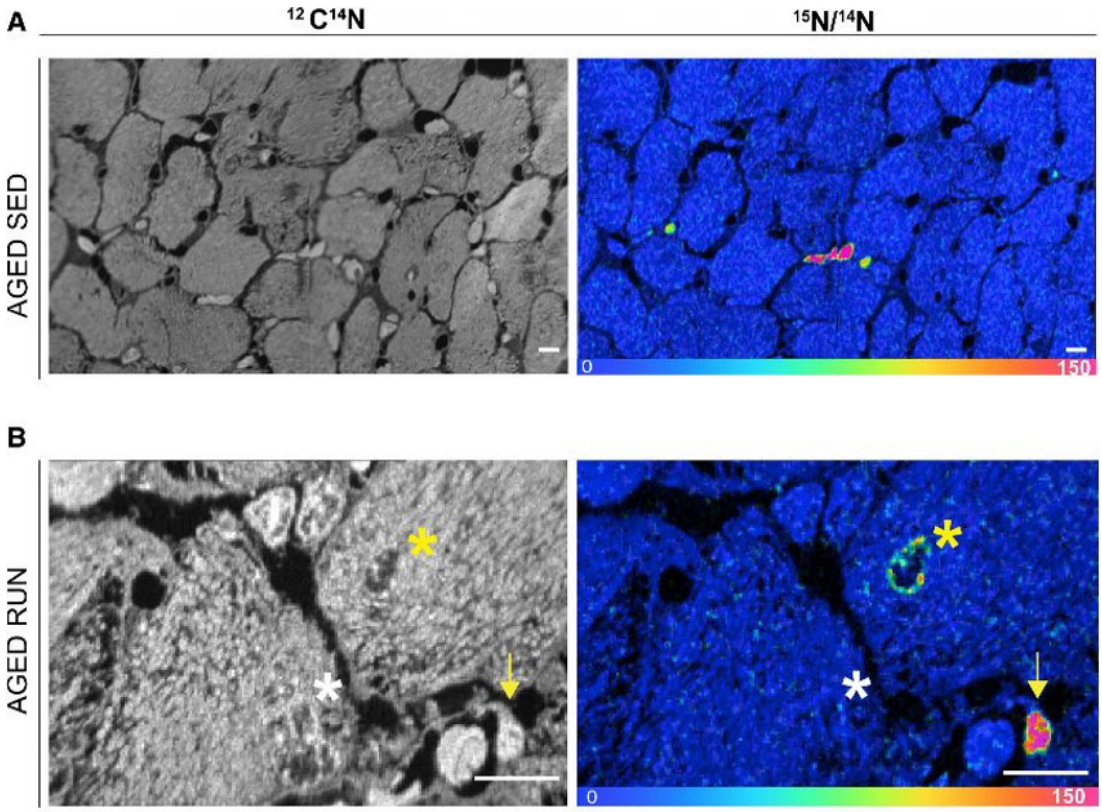
Scientific Highlights by Disease Program:

CARDIO-VASCULAR DISEASES

BIOHYBRID FISH MADE FROM HUMAN CARDIAC CELLS SWIMS LIKE THE HEART BEATS ▶

Lab models are an important tool to study heart disease and work toward building an artificial replacement heart, but most of them replicate either the heart's simple beating or basic structure. HSCI Principal Faculty member Kevin Kit Parker, PhD, created a more complex bioengineered device to study the biophysical properties of the heart.

Inspired by the swimming motion of zebrafish, researchers grew two layers of heart muscle cells that were made from stem cells, one on each side of the device's tail fin. When one side contracted, the other one stretched, automatically triggered by a protein that is sensitive to mechanical forces. The researchers also added a pacemaker to control the frequency and rhythm of the contractions. They found the bioengineered system propelled the fish's movement for over 100 days, with the muscle contractions and coordination improving over time. By modeling the mechanical and electrical signals of the pumping heart, researchers are one step closer to developing a more complex artificial muscular pump, as well as a platform to study heart diseases like arrhythmia.



A) Representative images of the myocardium in sedentary aged mouse hearts, labeled with15N-thymidine. B) Representative image of 15N-thymidine–labeled cardiomyocyte (yellow asterisks), together with 1 nonlabeled cardiomyocyte (white asterisk) and 1 labeled noncardiomyocyte (yellow arrow) in the myocardium of an aged runner. The scale ranges from blue, where the ratio is equivalent to natural ratio, to red, where the ratio is 150% above natural ratiol.

EXERCISE MAY MAKE OLD HEARTS YOUNGER

A research collaborative co-led by Richard Lee, MD, HSCI Principal Faculty and Leader of the Cardiovascular Diseases Program, has discovered that exercise appears to restore an aged heart's ability to create new heart muscle cells, or cardiomyocytes, a process that usually ends by middle age.

The researchers compared cardiomyocytes in sedentary aged mice to those in exercised adult mice, using multi-isotope imaging mass spectroscopy to determine when new cells were born. They discovered that exercise stimulated production of new heart cells in older mice at an annual rate of 2.3% new cardiomyocytes. They also found changes in the heart's circadian rhythm pathway. Understanding the pathways involved in exercise-induced cardiomyogenesis may provide additional insights into stimulation of new heart cells for aged hearts.

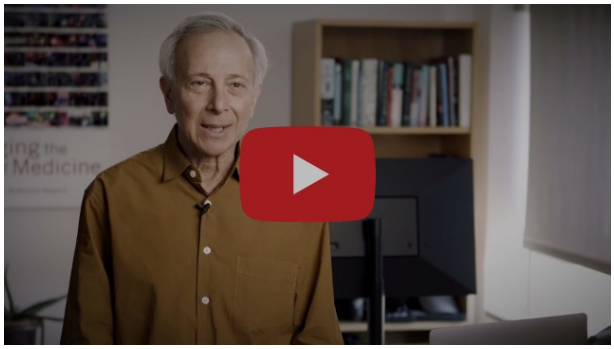
Scientific Highlights by Disease Program:

OTHER RECENT DISCOVERIES

STUDYING ZEBRAFISH SOCIAL PATTERNS REVEALS CLUES ABOUT PSYCHIATRIC DISEASE IN HUMANS

Psychiatric diseases, like autism and schizophrenia, are marked often by deficits in social interaction. To learn more about the connection between genes and social behavior, internationally recognized geneticist and HSCI Principal Faculty member Mark Fishman, MD, uses zebrafish to understand how genetic changes in individuals affect how groups form and behave. The hope is that by understanding the genetics of social behavior in an animal that is genetically related to humans but much more easily studied, researchers could ultimately find new therapeutics for disorders like autism and schizophrenia.

The Fishman lab introduced several different types of mutations into the genes of zebrafish — those known to be associated with autism, schizophrenia, and addiction — and studied their individual and collective behavior. Their studies revealed that the mutations introduced into a single zebrafish led to different behaviors within the group; some mutations caused the fish to scatter; others led them to collectively huddle. The results showed that making certain genetic modifications predicted how an animal will interact in a group. The research team hopes this discovery may lead to a better understanding of the synaptic circuitry that underlies autism, schizophrenia, and other diseases and ultimately to new therapies in the field of psychiatry.



RESTORING HEARING LOSS THROUGH REGENERATIVE MEDICINE

Approximately 15% of American adults aged 18 and over report some trouble hearing. Jeff Karp, PhD, HSCI Principal Faculty member, is working to find a solution to hearing loss by directly targeting stem cells and progenitor cells — cells that eventually become other types of cells — by delivering combinations of small molecules directly into the area affected.

The concept grew from Karp's research into the lining of the intestine. While stem cells in the gut constantly divide, progenitors in the mammalian inner ear do not divide after birth. Karp's team found that the molecules they initially discovered in their studies of the intestine could promote the proliferation of inner ear progenitor cells and grow new hair cells.

Karp has co-founded a commercial company called Frequency Therapeutics to take this approach to clinic. The company's lead drug candidate, FX-322, has now completed five clinical studies in a total of about 200 patients. Trial results to date show striking improvements in speech perception in as little as 90 days after treatment with some individuals maintaining results for two years or more. Frequency recently completed enrollment of a Phase 2b study of 142 patients at more than two dozen sites in the US, with data anticipated soon.

GRANTS

HSCI GRANT RECIPIENTS IN 2022

DISEASE PROGRAM PILOT GRANTS

MUSCULOSKELETAL (MSK) PROGRAM

Investigation into MEST as a pro-regenerative factor for composite tissue regeneration
Jessica Lehoczky, PhD

CARDIOVASCULAR PROGRAM

Nanofibers for Cardiac Regeneration
Rich Lee, MD, & Kit Parker, PhD

NERVOUS SYSTEM DISEASES PROGRAM

Proteomic profiling of blood-brain barrier cells from the postmortem human brain and iPSC-derivates
Tracy Young-Pearse, PhD

Neuropeptide-based strategy to promote optic nerve regeneration
Anne Jacobi, PhD

Full length optic nerve regeneration and novel growth factor screening
Yuqin Yin, MD, PhD

CANCER PROGRAM

Mapping of stemness-associated immunotherapeutic targets in adrenocortical carcinoma
David Breault Lab, BCH, & Robert Manguso Lab, MGH

Tolerance against normal and malignant stem cells
Joji Fujisaki, MD, PhD, & Ioannis Vlachos, PhD

DIABETES PROGRAM

A novel biologic and therapeutic target for diabetes
Jose Rivera-Feliciano, PhD

BARRY FAMILY HSCI INNOVATION AWARD FOR EARLY INVESTIGATORS

Decoding the tendon matrisome to promote regeneration
Jenna Galloway, PhD

HSCI LEADERSHIP

The Harvard Stem Cell Institute (HSCI) is led by Faculty Co-Directors Douglas Melton and David Scadden. 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, PhD
Xander University Professor of Stem Cell and Regenerative Biology, Harvard University

Investigator, Howard Hughes Medical Institute

David Scadden, MD
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

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Grousbeck Professor of Pediatrics, Harvard Medical School

Director, Stem Cell Program, Boston Children's Hospital

Investigator, Howard Hughes Medical Institute

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Director, Tillotson Cell Biology Unit, Massachusetts Eye and Ear

Jenna Galloway, PhD
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Associate Investigator, Center for Regenerative Medicine, Mass General Research Institute

Co-Leader, HSCI Musculoskeletal Program

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

Co-Leader, HSCI Cancer Program

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Faculty Member, Harvard Center for Brain Science

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

Vicki Rosen, PhD
Professor of Developmental Biology and Chair of the Department of Developmental Biology, Harvard School of Dental Medicine

Co-Leader, HSCI Musculoskeletal Program

Lee Rubin, PhD
Professor of Stem Cell and Regenerative Biology, Harvard University

Co-Leader, HSCI Nervous System Diseases Program

Amy Wagers, PhD
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 2022.

VIJAY SANKARAN, MD, PHD, received the 2022 E. Mead Johnson Award from the Society for Pediatric Research. The award recognizes his research that uses human genetic variation to advance our understanding of blood cell production, as well as how the process goes wrong in disease. His findings have led to clinical advances for children with blood disorders.

STUART ORKIN, MD, received the 2022 Canadian Gairdner International Award for the discovery of the molecular mechanism responsible for the switch from fetal to adult hemoglobin gene expression during human development and translating that knowledge into a novel treatment for the hemoglobin disorders — sickle cell disease and beta-thalassemia.

Two HSCI faculty were elected to the National Academy of Sciences. **LEONARD ZON, MD,** for his pioneering work in stem cell biology and cancer genetics, and **KORNELIA POLYAK, MD, PHD,** for her work documenting the clinical and functional relevance of intratumoral cellular heterogeneity.

CARLA F. KIM, PHD, was appointed the Boston Children's Hospital Professor of Pediatrics in the Field of Regenerative Medicine at Harvard Medical School. Dr. Kim's Chair appointment reflects her excellent scientific accomplishments over the past 17 years in the Stem Cell Program at Boston Children's Hospital and her commitment to the Boston Children's Hospital research community.

DANIEL BAUER, MD, PHD, was appointed the Donald S. Fredrickson, MD Associate Professor of Pediatrics as the inaugural incumbent of this endowed chair.

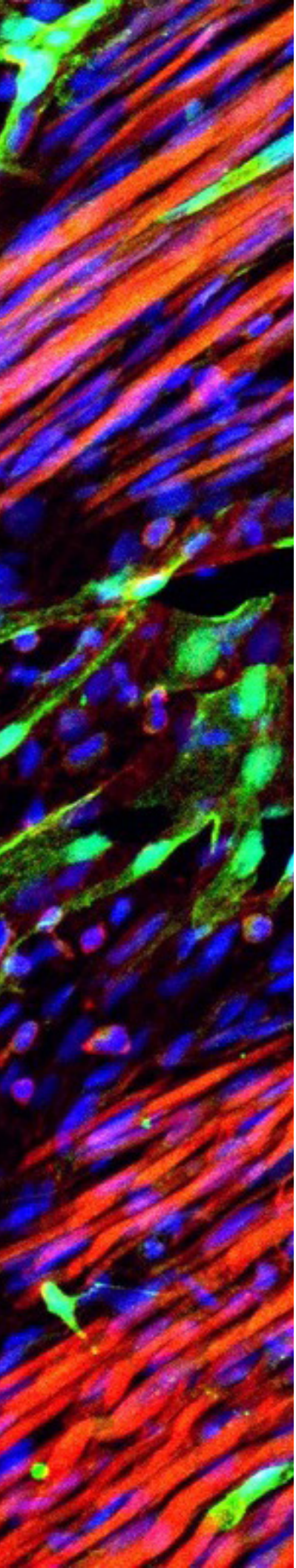
PATRICIA DONAHOE, MD, was elected to the National Academy of Inventors. NAI was established to highlight academic inventors who have demonstrated a prolific spirit of innovation in creating or facilitating outstanding inventions that have made a tangible impact on quality of life, economic development and the welfare of society. Election to NAI Fellow status is the highest professional distinction accorded solely to academic inventors.

CHRISTOPHER WALSH, MD, PHD, received the Kavli Prize in Neuroscience for "pioneering the discovery of genes underlying a range of serious brain disorders." The Kavli Prize in Neuroscience is awarded for outstanding achievement in advancing our knowledge and understanding of the brain and nervous system, including molecular neuroscience, cellular neuroscience, systems neuroscience, neurogenetics, developmental neuroscience, cognitive neuroscience, computational neuroscience, and related facets of the brain and nervous system.

Two HSCI faculty, **JOSÉ ORDOVÁS-MONTAÑÉS, PHD**, and **CHRISTOPHER WALSH, MD, PHD,** received a gift from the Manton Foundation to establish a new Cell Discovery Network at Boston Children's Hospital. The goal of the network is to build communities of biologists, computational experts, and clinicians to leverage the concepts and principles of single-cell biology to understand pediatric health and disease.

MARC WEIN, MD, PHD, received the Smith Family Foundation Odyssey Award for a project titled "Trafficking and translation of mRNA in osteocyte dendrites." The award supports the pursuit of high impact ideas to generate breakthroughs and drive new directions in biomedical research. The award funds high-risk, high-reward pilot projects solicited from the brightest junior faculty in the Greater Boston area.

RYAN FLYNN, MD, PHD, was named a 2022 Rita Allen Foundation Scholar to support his efforts in exploring glycoRNA biology.



DIRECTOR'S CALL

BARRY FAMILY HSCI INNOVATION AWARD RECIPIENTS

In April 2022, Douglas Melton and David Scadden hosted a Director's Call with Jessica Whited and Jason Buenrostro, the first two recipients of the Barry Family HSCI Innovation Award — an award supporting innovative ideas from junior faculty. Jessica spoke about how her work in understanding repair processes in highly regenerative animals is leading to new therapeutic strategies for peripheral nerve repair. Jason spoke about how he has developed new tools to understand how cells acquire and reverse epigenetic changes and how these changes lead to disease. This understanding is being used to develop to new approaches to improve the success rate for cell transplant therapies. Here we share highlights from the call.

Transgenic axolotl limb tissue expressing EGFP in vascular endothelial cells, counterstained with phalloidin in red (labels F-actin) and DAPI in blue (labels cell nuclei). Image credit: Whited lab

JESSICA WHITED, PHD

Harvard University
HSCI Principal Faculty member

Question: Having the ability to compare between regenerative animals, mice, and humans is fantastic. What happens when you find things that are different? How will you actually test whether those differences are meaningful and what are the steps necessary to ultimately get to a point where findings can be applied to people?

Answer: There are multiple approaches to this. One is shorter-term in vitro, comparing differences between axolotls and humans. For example, we could culture human cells that display similar properties then take these genes and diminish their expression in axolotls to find out if they're using these genes to grow the structure out, set up a neuromuscular junction, etc. If that checks out, then we may ask, If this isn't getting turned on in the human, can we give them a boost of that particular gene to regenerate better in vitro?

Ultimately we want to go into a mammalian system, so we might use transgenic mouse strategies to conduct experiments and see if, for example, turning a gene on in a mouse neuron or in a support cell gets a better outcome. Or if some of the genes in salamanders actually need to be turned down to get a better outcome, we might be able to inhibit them in the mouse setting to see if you can get better peripheral nerve regeneration.

Those studies obviously are going to be required in a foundational setting if we're ever going to take the findings and go into a person. In humans, we might think about piggybacking on nerve transplants that surgeons can do which basically provides a tiny bridge for the nerves to crawl across. These bridges can be loaded with molecules, so instead of just a physical bridge, you can load it up with some peptides, which are parts of proteins that were inspired by the salamander work. That's really how we see it in the short, middle, and long term.

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JASON BUENROSTRO, PHD

Harvard University
HSCI Principal Faculty member

Q: Do primed regenerative cells divide to give one daughter that differentiates and maintains its stem cell-like property, or do you create a pile of regenerative cells that divide twice and then all their daughters differentiate?

A: I don't think we know that yet. There's a lot of interesting things to consider. Do the differentiated daughter cells retain that prime state? In the context of wounding in the gut, there's a lot of really complex changes to cells, where differentiated cells can de-differentiate and therefore be regenerative as well. So one thing that we're hoping to tackle is the program for regeneration, because we think it might be not just specific to the stem cell but also retained into some of the differentiated cells. But we'll find out as we get better tracing.

Q: When you enter the gut, this signal that there's a problem, a wound, only goes so far. How does the top of the gut know that it doesn't need to regenerate, that the bottom of the gut where you injured it is where the problem is? How is that signal propagated and limited?

A: There's a complex web of neurons that innervate and also play a role in this process. There are diffusible signals that can modulate the repair process. In our case, we're mostly interested in the cell's intrinsic programs, because what we find in terms of the breaks is that DNA that's too closed or too compacted can be hard to made open. When you reach a bad level of closeness, of compaction, that really puts the brakes on being able to change into regenerative outcomes.

Q: We now know that all of us accumulate genetic injuries over time to different cells. Some people who get those injuries develop a malignancy, and for others it doesn't matter at all. We don't know how to distinguish the two until it's too late. How does your identification of cell states give us information about the relative risk based on those state definitions that you're coming up with?

A: As we gain a more immense appreciation for all the different flavors of types and states of cells, we start to realize that they are really instructive in the progression of disease. We've found that there are states that proceed or come before those genetic mutations. Overall, I think this idea that cells can get prepared and primed for future outcomes, sometimes in a disease context, sometimes in a regeneration context, is something that we're learning a lot about.

DONOR SPOTLIGHT

SUSAN STOCKER

HSCI Donor

"I first learned about Doug Melton in 2020 from a friend. My husband had recently passed away and as a type 1 diabetic since age 65, I knew I wanted to support advances in diabetes as part of my trust. My friend is a physician and passed along Doug's name. When we connected, I was instantly impressed by his dedication to finding a cure for type 1 diabetes and our shared personal connection to the topic.

I was also impressed by HSCI's cooperative approach. To tackle big problems, we need to work together. HSCI is using cross-institute and cross-sector collaboration and their progress made to date has been remarkable. The use of transplanted stem cell-derived beta cells holds so much promise as an alternative to insulin injections. My hope for HSCI is to extend the life of these SC-beta cells to create a permanent solution for patients with type-1 diabetes to improve quality of life.

Long-term, I'd also love to see these discoveries lead to successes in other disease areas such as cancer or even hearing loss. It's extremely exciting to see these fields mesh together, with Harvard at the center. As a retired schoolteacher, I find it so rewarding to learn about the science behind HSCI's research and feel truly fortunate to be able to support such a worthy cause."

2022 DONORS

Anonymous (7)

Harriet Abramson

Edward Adam

Ronald C. Agel and
Yvette Agel-Stenzel

Linda Baer and Alvin W. Lee

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