ACCELERATING

Contents

The dictionary defines accelerating as "[causing] to develop or progress more quickly." It is therefore the ideal theme for this year's annual report, as the Harvard Stem Cell Institute is causing stem cell research to progress at a faster pace than anyone could have imagined when the institute was founded six years ago. For example:

— through significant scientific advances by our researchers and innovative alliances with industry, we are accelerating the process of translating basic stem cell discoveries from the laboratory to the clinic where they may benefit patients;

— through our ongoing support of the research and training of early-career basic scientists and clinician-scientists, we are accelerating the point at which they can start making significant contributions to finding treatments and cures for a host of diseases;

— through our many community-building events and programs, we are accelerating the development of new collaborations and sparking new ideas and approaches, which are vitally important to tackling complex challenges;

— through strategic investments in our shared core facilities, some of which are unique in an academic setting, we are accelerating the process of using stem cells to reveal information about diseases and as tools of drug discovery, as well as the source of regenerative therapies.

Accelerating the pace of our work in these and other areas is imperative, as there is no time to waste. As we all know, virtually every day another child is diagnosed with diabetes, another adult in the prime of life learns he or she has cancer, another person is paralyzed, another infant is born with a fatal genetic condition.

The Harvard Stem Cell Institute was established six years ago with a straightforward yet audacious mission—to fulfill the promise of stem cell biology as the basis for cures and treatments for a host of diseases that affect so many people. We are not there yet. But by tackling challenges collaboratively, creatively, and with conviction, we are accelerating the day when our mission will become reality.

"I've been involved with and followed diabetes research since our son, Ryan, now 27, was diagnosed with type 1 diabetes at age 16, so I'm not naive about the complexity of the challenges posed by this insidious disease. But I'm convinced that the work being done by Harvard Stem Cell Institute scientists is accelerating to the point where it will result in a cure for diabetes—and likely other terrible diseases—within our son's lifetime."

—Stephen O'Connor,
father and HSCI supporter

is accelerating the pace of discovery by meeting the rapidly growing demand from the entire research community for iPS cells for many diseases and conditions.

Last year, we also expanded our successful disease program think tanks. Now all of our programs hold these events, which accelerate scientific progress by bringing together researchers from across HSCI and the broader scientific community to define the most promising avenues of disease-specific stem cell research.

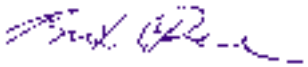
Our relationships with industry are yet another example of how HSCI is accelerating the transition from the laboratory to the clinic. Experts from academia and industry increasingly agree that the fastest, most efficient way to get new, better treatments to patients is through close collaboration, with each sector doing what it does best.

Specifically, we recently concluded the second year of our very successful five-year alliance with GlaxoSmithKline with an all-project team meeting that included launching some new projects, which are described later in this report. Building on our experience in making industry alliances productive at scale, we are exploring similar relationships with other pharmaceutical companies, who increasingly understand the value of stem cell research for developing new therapeutics.

Accelerating science means accelerating the scientists. This year we expanded our Clinician-Scientist Program to accelerate the career trajectories and eventual scientific contributions of clinician-scientists in the critical years directly following completion of their joint medical/doctoral degrees.

More broadly, accelerating our work cannot be done by us alone. This year we established an HSCI Advisory Board to work with us on strategic and operational issues. The board's members have contributed their time, talents, and resources to HSCI for years but are now engaged more programmatically. As with the members of our longstanding Scientific Advisory Board, these committed individuals play an important role in helping us achieve our mission.

In the end, it all comes back to our mission—to cure diseases. Certainly we have a long way to go. But by accelerating our work and with your continued support, we will reach our destination that much sooner.



Brock C. Reeve, MPhil, MBA
Executive Director
Harvard Stem Cell Institute

(From left): Douglas A. Melton, PhD, Brock C. Reeve, MPhil, MBA, and David T. Scadden, MD

ACCELERATING RESEARCH THROUGH *Scientific Programs*

The Harvard Stem Cell Institute's mission is to find treatments or cures for many intractable conditions, both common and rare, that cause suffering for millions of people worldwide.

Accordingly, a large body of the institute's research is organized within disease-specific programs, which bring together stem cell scientists across institutions, departments, and laboratories to focus intensely and collaborate on a specific medical challenge. These six programs are complemented by HSCI's Scientific Programs, such as our Junior Faculty Programs and Translational Research Program, which pertain to all diseases.

This spring, which marked our sixth anniversary and inaugurated "phase two" of our operations, the institute welcomed several new leaders, including some junior faculty members, to our disease programs. Like their predecessors, the new leaders were chosen for their scientific excellence, collaborative approach to research, and commitment to our mission.

Now co-leading the Cancer Program are Scott Armstrong, MD, PhD, of Children's Hospital Boston/Dana-Farber Cancer Institute, and Ramesh Shivdasani, MD, PhD, of Dana-Farber Cancer Institute. Richard Lee, MD, of Brigham and Women's Hospital, is leading the Cardiovascular Program. The Kidney Program is now co-led by Benjamin Humphreys, MD, PhD, of Brigham and Women's Hospital, and Andrew McMahon, PhD, of Harvard's Faculty of Arts and Sciences and head of HSCI's Genome Modification Facility.

Also this year HSCI's Executive Committee, which is responsible for guiding the institute's overall direction, research, and programs, welcomed four HSCI faculty to its ranks. Now serving a three-year, renewable term are Joseph Bonventre, MD, PhD, former leader of HSCI's Kidney Program; Carla Kim, PhD, leader of HSCI's Stem Cell Regulation Project; Andrew McMahon, PhD, head of HSCI's Genome Modification Facility and co-leader of HSCI's Kidney Program; and Ramesh Shivdasani, MD, PhD, co-leader of HSCI's Cancer Program.

THINK TANKS

In 2006, HSCI held its first disease program think tank. This event brought together international leaders in the nervous system diseases scientific community to assess the state of the science relating to Parkinson's disease and, building on that knowledge, to define research priorities going forward. The inaugural think tank was so fruitful that other HSCI disease programs began to adopt the idea over the ensuing years; this year most of the disease programs have held or plan to hold at least one think tank.

While every think tank is different—reflecting each program's unique scientific priorities, challenges, and community—all share a common purpose: to regularly revisit and rethink the program's focus to capitalize on the latest scientific knowledge, to solicit input from the broad HSCI community, and to foster collaborations and sharing of ideas and research tools that will accelerate scientific progress. This spring, four of the six disease programs—Cancer, Cardiovascular, Diabetes, and Kidney—convened their annual think tanks. The Nervous System Diseases Program think tank is planned for the fall.

The Cancer Program think tank, held in May, included a symposium with an invited speaker (John Dick, PhD, from the University of Toronto) followed by a roundtable discussion among the program's principal investigators to address future challenges and priorities.

Among the outcomes of this gathering was the decision to concentrate the program's efforts on identifying genes or pathways that distinguish normal from cancer-initiating stem cells. To encourage this research, a request for proposals was recently announced for one- to two-year pilot grants within the program. It is anticipated that these pilot projects will generate significant new findings and enable additional HSCI or external funding.

The Kidney Program think tank encompassed two well-attended meetings in March and April that focused on several high-priority areas of HSCI's kidney research. From these meetings came the decision to fund up to eight small short-term (mostly six month) pilot grants a year. These grants will support innovative, high-impact projects involving research on the proximal tubule, the segment of the nephron (the functional units of the kidneys) that are most amenable to regenerative therapies. As with the Cancer Program's pilot grants, these are expected to cast a wider net for innovative ideas within the HSCI community and generate a critical mass of data that can be leveraged for additional funding.

HSCI Disease Programs

Blood Diseases
Cancer
Cardiovascular Disease
Diabetes
Kidney Disease
Nervous System Diseases

Other HSCI Scientific Programs
- Junior Faculty Programs
  - -Cell Development
  - -Epigenetics of Stem Cell Function and Aging
  - -Regenerative Therapeutics
  - -Stem Cell Regulation
  - -Tissue Regeneration and Repair
- Translational Research

The Cardiovascular Program's think tank, held in April, was designed primarily as a community-building event to introduce the many cardiovascular investigators within HSCI and their work to each other. Attendees also learned about two multi-investigator projects recently funded by HSCI, the focus of which arose from the 2009 think tank. The first of these projects seeks to clarify which factors are involved in cardiogenesis and at what stage; the second aims to understand which factors promote the expansion of heart progenitor cells *in vitro*.

Held in May, the Diabetes Program's think tank involved discussions about where to focus the research across the three key areas of immunology, beta cells, and obesity. While collaboration among researchers in these areas will continue, it was decided to hold two separate follow-up think tanks during the summer to further define the program's research priorities. One of these meetings will address the first two areas of research, which pertain to type 1 diabetes; the other will focus on obesity research, which is relevant to type 2 diabetes.

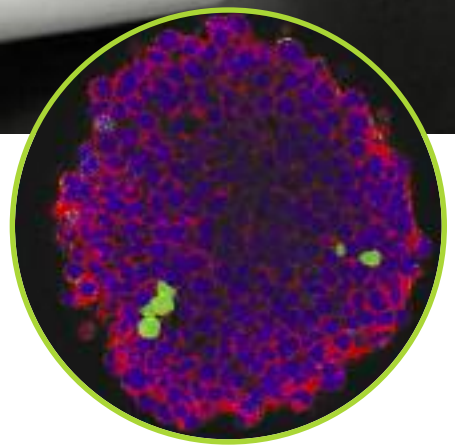
TRANSLATIONAL RESEARCH/CENTER FOR HUMAN CELL THERAPY

There are many steps between the discovery in a laboratory of a potential stem cell-based therapy and its introduction into clinical practice—from grappling with technical issues and designing clinical trials to working with regulatory agencies.

The Center for Human Cell Therapy (CHCT), led by Leslie Silberstein, MD, of the Immune Disease Institute, is a cross-institutional core facility available to all HSCI researchers that provides the specialized expertise and resources to guide researchers along these steps and, in so doing, accelerates the complex process of bringing basic laboratory discoveries to patients.

HSCI affiliated faculty member and pediatric surgeon Dario Fauza, MD, is among those who have taken advantage of the CHCT's resources to bring his novel "amniotic mesenchymal stem cell (aMSC)-based patch" into clinical trials for newborns with congenital diaphragmatic hernia (CDH).

CDH is a condition in which the diaphragm does not close completely during fetal development, allowing some organs to migrate into the chest cavity. Currently, the only option for infants with CDH is an artificial patch that, unlike the engineered aMSC-based version, often must be surgically replaced as the child



grows. It is hoped that patients will start being enrolled in these trials within a year. Fauza's group has also been engineering a variety of other grafts from aMSCs, which may eventually be used in the treatment of other congenital anomalies.

Other stem cell researchers have also benefited from the resources of the CHCT. One is Rona Carroll, PhD, a 2006 HSCI seed grant recipient whose institute-funded project is focused on glioblastoma, an especially lethal type of brain tumor. Carroll and her colleagues are using genetically modified human mesenchymal stem cells, which have the ability to migrate to tumors in the brain, as vehicles to deliver complementary therapeutic compounds directly to tumors in animal models with human glioblastomas. Currently, Carroll is completing the necessary studies to apply for clinical trials in patients.

Another scientist who has tapped the resources of the CHCT is Leonard Zon, MD, chair of HSCI's Executive Committee, whose work led to HSCI's first clinical trial to evaluate a drug that expands blood stem cells in umbilical cord blood (see sidebar, page 7).

In January, the CHCT was awarded a five-year, $14.5 million Production Assistance for Cellular Therapies (PACT) contract by the National Institutes of Health. The purpose of the award is to advance research of cell-based therapy across broad areas, including immunotherapy for cancer and stem cell therapy, with applications for tissue engineering and the treatment of congenital and acquired disorders.

As a member of the PACT group, CHCT will partner with the PACT steering committee to identify basic research scientists who have developed successful cell-based therapies in preclinical (non-human) models and provide the necessary support to transition these new approaches to clinical trials. In addition to supporting investigators in translational research, the PACT group will also offer educational resources for the cell therapy research community.

From Zebrafish to Patients

The treatment of some types of blood cancers, such as leukemia, requires high-dose chemotherapy, which kills cancer cells but also wipes out the patient's bone marrow, the source of blood cells. This is rebuilt using blood stem cells harvested, in most cases, from a relative whose immune system closely matches the patient's.

Unfortunately, many patients lack a closely matched donor. For these individuals, blood stem cells harvested from umbilical cords, which do not trigger as robust an immune response, can be lifesaving.

A single umbilical cord provides sufficient quantities of blood stem cells for a child, but an adult patient requires two cords. However, for several reasons it is better for the patient to receive blood stem cells from just one cord.

Confronted with this clinical challenge, HSCI researchers have been searching for ways to amplify blood stem cells in cord blood so that adult patients could be effectively treated with cells from just one umbilical cord. In studies using zebrafish and mice, Leonard Zon, MD, Trista North, PhD, Wolfram Goessling, MD, PhD, and colleagues found a derivative of an FDA-approved drug that triggered a four-fold increase in the number of blood stem cells in cord blood.

After receiving FDA approval in early 2009, this drug is now being evaluated for safety in a phase 1 clinical trial of 12 adult cancer patients. While the outcomes of this study are not yet known, it is hoped that this drug will benefit many patients undergoing stem cell transplantation.

"Although many people contributed to this effort, the resources provided by the Center for Human Cell Therapy were absolutely critical to our being able to get this drug into a clinical trial," says Zon. "We were able to go from publication of our paper [in *Nature*] in early 2007 to phase 1 clinical trials and subsequent NIH funding in only 36 months. We couldn't have done it without them."

Scientific Programs

JUNIOR FACULTY PROGRAMS

In today's fiscal environment, obtaining research funding from traditional sources like the National Institutes of Health (NIH) is a challenge for all scientists, even those with a long, strong track record.

But for early-career scientists who are just getting out of the gate and whose research may lack supporting data, it is especially difficult. Yet it is the new generation of scientists—with fresh, bold ideas and a willingness, even eagerness, to work together to tackle big questions—that often achieves the significant breakthroughs that accelerate scientific progress.

Recognizing this, for the past several years HSCI has provided significant, vital support to small groups of junior faculty with complementary interests and expertise who, on their own initiative, have banded together across institutional boundaries to work collaboratively on an important aspect of stem cell research.

Through its Junior Faculty Program, HSCI provides these collaborative teams with three years of funding and access to all the varied resources of HSCI, including its core facilities and many community-building events. Thus far, five groups totaling 30 investigators from many HSCI-affiliated institutions have received support from Junior Faculty Program grants.

HSCI's investment in the young scientists supported through this program has paid off in innumerable ways: major research breakthroughs and resulting scientific papers; additional funding from the federal government, industry, and other sources; new intellectual property; and further collaborations within and beyond HSCI that may lead to more discoveries.

To cite just one example, the Cell Development Project—the first and the model for all subsequent Junior Faculty projects—led to major advances in cell reprogramming, millions of dollars in additional funding, international recognition, and fruitful new collaborations.

This year, with a mind toward accelerating promising translational research, HSCI opted to fund two, rather than one, Junior Faculty Program projects (see sidebar, right). Consistent with HSCI's commitment to bring basic discoveries into the clinical setting, both of these projects are focused on regenerative medicine.

HSCI Junior Faculty Programs, 2007-Present

Cell Development Project*, 2007-2010
Mission: To elucidate the biochemical pathways that control reprogramming and regeneration in tissue specification and repair.
Faculty: Amy Wagers, PhD (Project Leader), Chad Cowan, PhD, Alan Davidson, PhD, Kevin Eggan, PhD, Niels Geijsen, PhD, Konrad Hochedlinger, PhD, Laurie Jackson-Grusby, PhD, Jianlong Wang, PhD
Institutions: Children's Hospital Boston, Harvard University, Joslin Diabetes Center, Massachusetts General Hospital

Stem Cell Regulation Project*, 2008-2011
Mission: To understand the molecular regulation of stem cell identity, maintenance, and differentiation in normal development and disease.
Faculty: Carla Kim, PhD (Project Leader), Paola Arlotta, PhD, Chad Cowan, PhD, Hanno Hock, MD, PhD, Richard Gregory, PhD
Institutions: Children's Hospital Boston, Massachusetts General Hospital

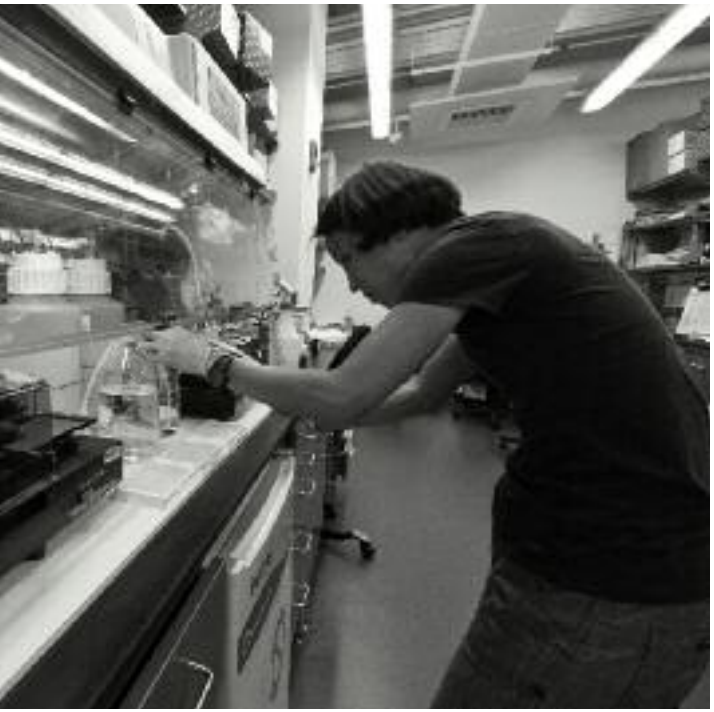
Epigenetics of Stem Cell Function and Aging Project*, 2009-2012
Mission: To gain novel insights into the molecular mechanism of stem cell aging, regenerative capacity, and pluripotency.
Faculty: Alexander Meissner, PhD (Project Leader), Andrew Brack, PhD, Caroline Burns, PhD, Benjamin Ebert, MD, Derrick Rossi, PhD
Institutions: Brigham and Women's Hospital, Broad Institute, Harvard University, Immune Disease Institute, Massachusetts General Hospital

Tissue Regeneration and Repair Project, 2010-2013
Mission: To understand the intrinsic regenerative potential of tissues injured in human disease and harness this for organ regeneration and repair.
Faculty: David Breault, MD, PhD, and Benjamin Humphreys, MD, PhD (Project Co-Leaders), Akio Kobayashi, PhD, Jay Rajagopal, MD, Thomas Serwold, PhD, Yu-Hua Tseng, PhD
Institutions: Brigham and Women's Hospital, Children's Hospital Boston, Joslin Diabetes Center, Massachusetts General Hospital

Regenerative Therapeutics Project, 2010-2013
Mission: To identify signaling pathways critical to the growth and repair of multiple organs and translate these findings into small molecule (drug)-based therapies to enhance organ regeneration.
Faculty: Trista North, PhD (Project Leader), Fernando Carmago, PhD, Wolfram Goessling, MD, PhD, David Langenau, PhD, Jeffrey Karp, PhD, Qiao Zhou, PhD
Institutions: Beth Israel Deaconess Medical Center, Brigham and Women's Hospital, Children's Hospital Boston, Dana-Farber Cancer Institute, Harvard University, Massachusetts General Hospital

** To watch a video that features the leaders of each of these projects discussing their work, visit the HSCI website at www.hsci.harvard.edu.*

Scientific Programs



INDUSTRY COLLABORATIONS AND START-UPS

HSCI's mission is to accelerate the translation of laboratory research into treatments that will benefit patients suffering from a broad range of diseases. But no research organization can do this entirely on its own. This process is greatly accelerated by our collaborations with industry and our faculty's participation in the formation and governance of start-up companies that were created to develop and introduce treatments based on HSCI's discoveries into clinical practice.

Industry Collaborations

Now entering its third year, HSCI's alliance with the pharmaceutical company GlaxoSmithKline (GSK) continues to be a very productive, successful partnership.

In 2008, HSCI and GSK entered into a five-year, $25 million-plus collaborative agreement to capitalize on the unique, complementary strengths of each organization with the goal of accelerating the development of treatments for a select range of diseases. Already this alliance between academia and industry, one of the first such investments by a major pharmaceutical company, has led to several joint intellectual property filings.

Jointly led and defined, with active involvement by scientists and staff from both organizations, the HSCI/GSK alliance focuses on specific projects in six major areas: cancer, cardiovascular, muscle, type 1 diabetes, obesity, and selected neurological diseases across several HSCI-affiliated institutions.

The HSCI/GSK alliance was structured to allow the flexible incorporation of new projects. For example, new projects include three in the cancer area. The first, led by Sarah Thayer, MD, PhD, of Massachusetts General Hospital (MGH), will focus on identifying and validating potential therapeutic targets that play a key role in the survival and self-renewal of cancer stem cells in the most common form of pancreatic cancer, an especially lethal type of cancer.

The second, led by Rosemary Foster, PhD, and Bo Rueda, PhD, also from MGH, aims to identify and validate potential therapeutic targets in ovarian cancer stem cells and determine the effect that inhibiting certain pathways has on tumor-forming capacity.

The third, led by Gregory Verdine, PhD, from Harvard's Department of Stem Cell and Regenerative Biology, will investigate alternative drug design (specifically nucleic-acid based pharmaceuticals) with the goal of attacking traditionally "non-druggable" disease targets.

The Novartis Institutes for Biomedical Research recently initiated a multi-year project with a group at HSCI headed by Lee Rubin, PhD, HSCI's Director of Translational Research. The initial focus is to use small molecule modulators to understand a group of neuromuscular disorders, with the ultimate aim of finding effective therapeutics. This is Novartis's first academic collaboration with Harvard in the stem cell and regenerative medicine area; it is anticipated that additional HSCI scientists will be involved in the future.

Additionally, various HSCI labs are currently engaged in projects with Astra Zeneca, Eli Lilly, Roche, Sanofi-Aventis, and Vertex Pharmaceuticals, among other companies.

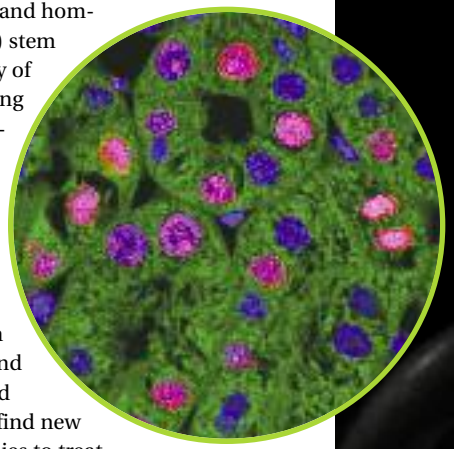
Start-Ups

In 2007, HSCI faculty helped found Fate Therapeutics, a California company that is applying iPS (induced pluripotent stem) cell technology to develop stem cell modulators—small molecules and

HSCI Accelerates Research Nationwide

HSCI is accelerating stem cell research nationwide by contributing large numbers of human embryonic stem cell lines to the National Institutes of Health (NIH) stem cell registry. In fact, nearly two-thirds of the 75 human embryonic stem cell lines currently in the NIH registry came from HSCI labs. Stem cell lines from the NIH registry are eligible for use in NIH-funded projects, making them a valuable resource for U.S. stem cell scientists.

biologics that guide cell fate in patients for therapeutic purposes. Fate Therapeutics now has a drug (FT1050) in clinical trials that enhances the proliferation and homing of hematopoietic (blood-forming) stem cells, thereby increasing the efficiency of transplantation for patients undergoing treatment for blood cancers (see sidebar, page 7). The company is also focusing on stem cell modulators that may have therapeutic applications in other diseases.



Last year, HSCI faculty helped found iPierian, a California-based biopharmaceutical company. iPierian is applying cellular reprogramming and differentiation, including iPS (induced pluripotent stem) cell technology, to find new molecular targets and develop therapies to treat specific nervous system diseases, including Parkinson's disease, spinal muscular atrophy, and amyotrophic lateral sclerosis (ALS, or Lou Gehrig's disease).

More recently, the Cambridge, Mass. company, Provasculon, was founded by Richard Lee, MD, head of HSCI's Cardiovascular Program, based on his research of a protein called Stromal Cell-Derived Factor-1 (SDF-1). SDF-I has long been known to have an important role in harnessing stem cells to assist in repairing tissue and generating new blood vessels, but its therapeutic use has been limited because it is inactivated by enzymes in injured tissue. Lee's laboratory discovered new forms of SDF-1 that resist this inactivation. These new forms represent potential therapies for patients suffering tissue damage following a heart attack as well as other conditions that involve tissue damage and reduced blood flow, such as peripheral vascular disease and diabetic foot ulcers.

Many HSCI faculty also actively advise companies in the stem cell field. For example, four HSCI scientists are on the Scientific Advisory Board of Stemgent, a company formed a few years ago specifically to provide tools and reagents to stem cell researchers. Companies like Stemgent plan to capitalize on and accelerate the growth of the field by focusing specifically on the needs of the research community in both the academic and commercial sectors.

2009-2010 RESEARCH ADVANCES

Following, in chronological order, is a sampling of important research breakthroughs that took place during fiscal year 2009-2010. More information about these and many other significant research findings is available on the HSCI website at www.hsci.harvard.edu.

▶ *Generating iPS cells from patients with diabetes*

An HSCI team created iPS cells from the skin cells of patients with type 1 diabetes using a cocktail of three genes, then coaxed these cells into becoming insulin-producing beta cells, the cells that are destroyed in type 1 diabetes. This achievement provides scientists with the first *in vitro* model of diabetes in humans for studying what causes this disease and for testing drug therapies, bringing the science a step closer to potential cell replacement therapy. *Douglas Melton, PhD, and colleagues*

▶ *Making safer iPS cells*

A team of HSCI researchers used a single chemical to replace two of the four genes needed to reprogram adult skin cells to an earlier pluripotent state. The drug, dubbed RepSox in honor of another Boston team, replaces Sox2 and cMyc, two genes associated with cancer. Finding ways to efficiently create safe induced pluripotent stem (iPS) cells is necessary for regenerative medicine to become a reality. *Kevin Eggan, PhD, Lee Rubin, PhD, and colleagues*

▶ *Creating functioning heart muscle*

Using a novel technology developed by an HSCI bioengineer and cells identified by an HSCI biologist, an interdisciplinary HSCI team isolated and used human ventricular heart stem cells to create a two-dimensional, fully functioning strip of ventricular muscle. This advance paves the way for using stem cells in humans to repair heart muscle damaged by a heart attack or other types of heart disease. *Kenneth Chien, MD, PhD, Kevin Kit Parker, PhD, and colleagues*

▶ *Blood tells old cells to act young*

HSCI scientists demonstrated that blood stem cells of old mice exposed to certain factors present in blood of young mice begin to act like young stem cells, with the process driven by signals from another type of cell—bone-forming osteoblasts—in the local bone marrow environment. Even the tissues of the old mice appeared more youthful. This research advances scientists' understanding of the aging of hematopoietic (blood-forming) cells and suggests ways to treat age-related ailments via the blood. *Amy Wagers, PhD, and colleagues*

▶ *iPS cells from patients shed light on a host of conditions*

Induced pluripotent stem (iPS) cells created by an HSCI team from the skin cells of patients with a premature aging disorder led to the discovery that the reprogramming process reactivates an enzyme (telomerase) that maintains telomeres—the caps on the ends of chromosomes that prevent a cell from aging and allow it to divide and replicate. In addition to suggesting ways to treat this rare aging disorder, this finding also has broad implications for understanding cell pluripotency, normal aging, and cancer, which is thought to rely on telomerase to maintain immortality and uncontrolled cell replication. *George Daley, MD, PhD, and colleagues*

▶ *Key to stem cell hibernation*

HSCI researchers found that a protein, Sprouty1, plays a key role in the process by which muscle stem cells enter and exit a state of hibernation following a period of repair. Called reversible quiescence, this process allows stem cells to avoid exhaustion; without Sprouty 1, the muscle stem cell pool is rapidly depleted after repairing an injury. This discovery has particular relevance to diseases such as muscular dystrophy, which places a high demand on muscle stem cells to replenish tissue. *Andrew Brack, PhD, and colleagues*

▶ ***Bad environment influences good cells***

An HSCI team found that the local microenvironment, or niche, in which normal blood stem cells reside influences whether they will become cancerous. When researchers made a particular genetic alteration to bone cells in mice, the neighboring normal blood stem cells developed genetic changes that led the mice to develop myelodysplasia, which is often a precursor to acute myelogenous leukemia, a usually fatal form of cancer. These findings suggest new targets for therapies. *David Scadden, MD, and colleagues*

▶ ***New leukemia target***

Acute myelogenous leukemia (AML) is caused by leukemia stem cells—endlessly self-renewing cancer cells that are resistant to conventional cancer treatments. A study in mice conducted by HSCI scientists found that leukemia stem cells cannot develop and thrive without a particular cell-signaling pathway known as the Wnt/beta-catenin pathway. This discovery suggests that selectively targeting this pathway could prevent the growth of these stem cells and, thus, AML. *Scott Armstrong, MD, PhD, and colleagues*

▶ ***Improving reprogramming***

HSCI researchers identified a cluster of genes (in mice) that is silenced in many induced pluripotent stem (iPS) cells, which limits the overall developmental potential of those cells and, consequently, their use in therapeutic applications. In iPS cell lines in which these genes were normally activated, the cells functioned like embryonic stem cells—still the gold standard—in the most rigorous test: producing live animals, which is believed to be the first time this has been achieved using only iPS cells. Being able to create and identify iPS cells of the highest quality is essential for the development of therapeutic applications. *Konrad Hochedlinger, PhD, and colleagues*

StemBook: HSCI's Online Textbook

The number of citations in scientific journals containing the terms "stem cell" and "regenerative medicine" has grown exponentially over the past few years, reflecting the enormous and continually growing interest in this exciting area of research.

Keeping abreast of such a broad, rapidly evolving field—in which it is not unusual for significant advances to be announced almost monthly—presents a significant challenge to scientists worldwide.

In the fall of 2008, HSCI addressed this challenge with the launch of *StemBook*, an online, freely accessible open-access "textbook" of peer-reviewed chapters covering a comprehensive range of topics related to stem cell biology.

Overseen by an international editorial board of prominent scientists, *StemBook* encompasses a collection of chapters on diverse areas of stem cell research written, by invitation, by leading scientists around the world. *StemBook* began with 16 chapters; it now has more than 50, with a total of 80 commissioned. *StemBook* chapters are indexed on MEDLINE, a freely accessible online database of biomedical journals used by researchers worldwide.

There are many advantages to *StemBook*'s online, highly interactive format. These include links to sources, terms, and many other useful resources; multiple types of media, such as videos and complex images; and networking tools that encourage dialogue among users. *StemBook* can also be updated quickly and is available to anyone with Internet access.

The value of *StemBook* is reflected in the growing number of researchers who use it. As of early 2010, there have been close to 10,000 page requests.

TEAM SCIENCE

In biomedical research as in many other fields, when the problems are big and the stakes are high, bringing leading experts together to focus collectively on finding a solution invariably yields faster, better results than when they work separately.

Recognizing the enormous value of collaborative research, federal research-funding agencies are increasingly supporting projects that involve cross-institutional, interdisciplinary teams of scientists working together toward a common goal. As an enterprise structured since its inception on this "team science" research model, last year HSCI was the recipient of three major multi-institutional grants, described below.

Grand Opportunities Grant

Five HSCI faculty from three HSCI-affiliated institutions—Dana-Farber Cancer Institute, Children's Hospital Boston, and the Harvard School of Public Health—recently received a National Institutes of Health Grand Opportunities (GO) grant that will enable them to focus on several areas of research involving cancer stem cells. Created as part of the American Recovery and Reinvestment Act of 2009, the new GO grants program supports high-impact ideas that lend themselves to short-term (two-year) funding and may lay the foundation for new fields of investigation. The HSCI GO grant recipients are principal investigators Ramesh Shivdasani, MD, PhD, Scott Armstrong, MD, PhD, Stuart Orkin, MD, Ronald DePinho, MD, and Winston Hide, PhD.

Among the aims of HSCI's GO Grant is understanding the relationship between tumor-initiating stem cells and stem cells found in normal tissue, since key differences between them might be exploited for therapeutic benefit. The studies proposed in this project will provide vital information that could aid in the development of therapies to target cancer stem cells while sparing their normal counterparts.

Ovarian Cancer Development Award

In 2008, the Department of Defense (DOD) announced that it would fund a major, multi-institutional research effort focused on identifying and characterizing early changes of disease associated with ovarian cancer. Due to the complexity of creating a strong proposal, DOD first awarded four one-year "development awards" to provide funding for convening the ovarian cancer community, developing plans, and working out the details of implementation. Last year, HSCI was one of four organizations to receive this award.

Under the direction of principal investigators George Daley, MD, PhD, of Children's Hospital Boston, and Stephen Cannistra, MD, of Beth Israel Deaconess Medical Center, approximately 20 researchers and physicians from six institutions in Boston and elsewhere have been meeting to refine their scientific focus and work out the details of creating a consortium that will achieve DOD's goals. This fall, HSCI will compete for the single Ovarian Cancer Award—totaling between $6 to $12 million—which will be announced in early 2011.

NHLBI Progenitor Cell Biology Consortium Award

The National Heart, Lung, and Blood Institute (NHLBI) Progenitor Cell Biology Consortium was established in 2009 to fund collaborative research aimed at developing stem cell and progenitor cell-based tools and treatments for the understanding and treatment of cardiovascular and blood disorders. The consortium consists of nine research hubs across the nation, each comprising multidisciplinary teams from two academic medical centers. Under the program, these 18 research groups are receiving a total of $170 million, which represents the single largest amount of federal funding for stem cell research. Three teams of HSCI researchers are slated to receive $9 million each, or a total of $27 million, over a period of seven years.

The Boston hub is led by principal investigators and HSCI Executive Committee members George Daley, MD, PhD, of Children's Hospital Boston, and Kenneth Chien, MD, PhD, of Massachusetts General Hospital. Other HSCI faculty included in this hub are HSCI Co-Directors Douglas Melton, PhD, and David Scadden, MD, and principal faculty members Ibrahim Domian, MD, PhD, Carla Kim, PhD, Stuart Orkin, MD, Kevin Kit Parker, PhD, Amy Wagers, PhD, Sean Wu, MD, PhD, and Leonard Zon, MD.

ACCELERATING RESEARCH THROUGH *Core Facilities*

Since its inception, HSCI has made significant investments in core facilities that are available to all HSCI researchers. These resources (see sidebar, below) provide the highly specialized expertise and often costly cutting-edge technologies that would be beyond the reach of any single institution or laboratory, but that are critical to accelerating the rate of basic research or its translation to the clinical setting. Because these facilities are at the intersection of many HSCI scientists' projects, they are also incubators for collaboration, which further accelerates the pace of discovery.

While all of the cores are valuable to HSCI's stem cell scientists, two in particular—the iPS Core Facility and the Therapeutic Screening Center—are unique in an academic setting and play essential roles in accelerating the pace of research. In recognition of their importance, both were recently renovated and expanded to meet the growing demand for their services, and are now located next door to each other on the Harvard University campus.

iPS CORE FACILITY

Conventional drug discovery and testing is a slow, expensive, and risky business that also poses ethical issues. With the recent advent of cell reprogramming—a rapidly evolving field with several HSCI faculty at its forefront—a new, better option now exists.

Scientists can now take mature cells (typically skin, hair, or blood cells) from a patient with a specific disease and, in the laboratory, return those cells to an earlier, embryonic-like (pluripotent) state and create large numbers of them. These disease-specific induced pluripotent stem (iPS) cells, the first of which were created by HSCI researchers in 2007, are valuable tools that, among other existing and potential uses, serve as "diseases in a dish." As a result, scientists now have a better tool for understanding how a disease develops as well as the basis for a new way to screen compounds that might be safe and effective.

As a pioneer and leader in iPS cell technology, in 2008 HSCI established the first iPS Core Facility in the world. Overseen by a committee of HSCI's world-renowned cell reprogramming experts, the iPS Core generates new disease-specific iPS cell lines for the HSCI community using existing and new technologies emerging from HSCI laboratories. This core also serves as a repository for HSCI's existing iPS cell lines and distributes these valuable resources to scientists worldwide. While top priority and a period of exclusivity is given to HSCI-affiliated scientists, thus far iPS cell lines of multiple diseases have been distributed to scientists throughout North America, Asia, and Europe.

In early 2010, the iPS Core Facility moved from its original quarters at Massachusetts General Hospital to a larger, newly renovated space on the Harvard University campus. The new location offers many advantages, including five times the bench space, which will enable the iPS Core to expand its capacity to meet the ever-growing demand for iPS cells. The facility also now has three separate cell-culture rooms, which ensures better

HSCI Core Facilities

Flow Cytometry Core Facilities – offer high-speed cell sorters, cell analyzers, data-analysis computers, and other scientific instruments at four HSCI-affiliated institutions.

Genome Modification Facility – develops genetically modified mouse models for HSCI researchers.

iPS Core Facility – generates new disease-specific induced pluripotent stem (iPS) cell lines, stores iPS cells produced by HSCI scientists, and distributes iPS cell lines to HSCI researchers and the broader academic scientific community.

Therapeutic Screening Center – provides expertise and technologies to identify factors that direct stem cells to differentiate and proliferate, and to screen cells for the understanding of disease mechanisms and the identification of potential therapeutic agents.

quality control during the painstaking, many months-long process of creating a new iPS cell line.

Another advantage is the facility's close proximity to and relationship with HSCI's Therapeutic Screening Center and cell reprogramming experts within Harvard's Department of Stem Cell and Regenerative Biology, who are continually working on developing new methods to further improve the efficiency of cell reprogramming while also making them "safer" (non-cancer causing). All this, plus HSCI's access to large populations of patients with both prevalent and rare diseases of interest, creates a unique capability that has recently attracted the attention of the pharmaceutical industry, which is eager to tap into the iPS Core's broad expertise and services.

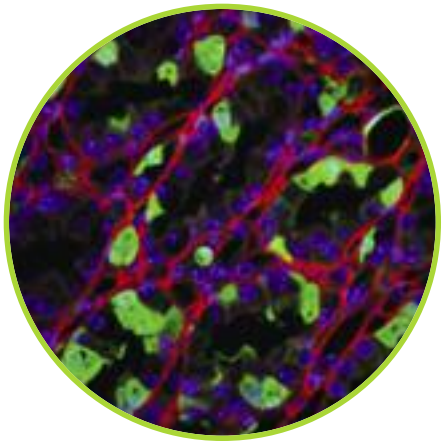
THERAPEUTIC SCREENING CENTER

Since its opening in 2006, the Therapeutic Screening Center has been a vital resource to HSCI's research community, providing the institute's scientists with access to highly specialized expertise and technologies. This unique capability has not only accelerated HSCI scientists' research in innumerable ways, but has also enabled HSCI to attract significant funding from disease foundations, the federal government, and industry.

The Therapeutic Screening Center uses sophisticated high-throughput, high-content, cell-based screening technologies for several purposes: to search for compounds that might safely treat disease, to better understand underlying disease mechanisms, and to identify factors that direct stem cells to differentiate and proliferate to create assays that could eventually lead to new therapies. For the first time, this work can be done with human cells—both those that are normal and those that are affected in a particular disease.

Serving the entire HSCI community, the Therapeutic Screening Center is involved in collaborative projects focused on a wide range of disorders, including diabetes, Parkinson's disease, amyotrophic lateral sclerosis (ALS, or Lou Gehrig's disease), Huntington's disease, and neuropathy, as well as cell reprogramming. For example, working collaboratively with HSCI's cell reprogramming experts, the Therapeutic Screening Center has helped identify molecules to replace the essential cell reprogramming factors, an important step toward eventual regenerative therapies.

In particular, the Therapeutic Screening Center has a special interest in orphan nervous system disorders. With critical support from leading disease foundations, the center has made significant progress in several areas, most notably spinal muscular atrophy (SMA), an inherited, usually fatal, childhood neuromuscular disorder. Based on the center's work, it is conceivable that a drug for SMA could enter clinical trials in the foreseeable future.



'Diseases in a Dish'

From affected patients' mature (skin) cells, HSCI's iPS Core has derived lines of induced pluripotent stem (iPS) cells for a long and growing list of diseases, some of which are listed at right. These "diseases in a dish" are being used to learn how diseases develop and to screen for potential therapeutics.

- amyotrophic lateral sclerosis (ALS)
- bipolar disorder
- type 1 diabetes
- Down syndrome
- Huntington's disease
- muscular dystrophy
- Parkinson's disease

ACCELERATING RESEARCH THROUGH *Seed Grants*

SEED GRANT PROGRAM

For the sixth consecutive year, HSCI awarded seed grants to scientists throughout the HSCI community to provide critical early funding for stem cell research. In 2010, 10 seed grants totaling more than $1.8 million were awarded to investigators selected from a large pool of applicants across HSCI-affiliated institutions.

HSCI's Seed Grant Program provides two years of funding (totaling $180,000 each) for projects in diverse areas of stem cell research that will advance HSCI's mission. A multi-institutional panel conducts a rigorous review process with the difficult task of selecting the most promising projects from many superbly qualified applications. Highest priority is given to projects that are difficult to fund from other sources because they are early stage, high risk, or lack sufficient preliminary data. HSCI's seed grants are primarily intended to support junior faculty in the early stages of their independent careers, but sometimes more senior faculty entering the field of stem cell research receive awards.

To date, HSCI has awarded 63 seed grants totaling just over $11 million. This investment has paid off in numerous ways, not the least of which is the ability for recipients to compete successfully for subsequent major funding from the National Institutes of Health, disease foundations, and industry. Because they are by definition risky, some projects fail. But of the seed grant-funded projects that are successful, an internal survey last year showed that, on average, recipients have received three times HSCI's initial investment in follow-on funding.

This year's grants will support stem cell research in a variety of targeted disease areas such as breast cancer; diabetes; Duchenne muscular dystrophy; and heart, kidney, and lung diseases. The grants will also support research of broadly applicable areas of stem cell biology such as stem cell homeostasis, markers of differentiation, and stem cell regulation at the molecular level.

2010 SEED GRANT RECIPIENTS

Andrew Brack, PhD
Massachusetts General Hospital
Geoffrey Burns, PhD
Massachusetts General Hospital
Cassandra Extavour, PhD
Harvard Faculty of Arts and Sciences
Richard Gregory, PhD*
Children's Hospital Boston
Craig Hunter, PhD
Harvard Faculty of Arts and Sciences
Akio Kobayashi, PhD
Brigham and Women's Hospital
Andrew Lassar, PhD
Harvard Medical School
Zhe Li, PhD
Brigham and Women's Hospital
Jayaraj Rajagopal, MD
Massachusetts General Hospital
Judith Steen, PhD
Children's Hospital Boston

* In 2007, the Millipore Foundation made a gift of $500,000 to the HSCI Seed Grant Program. Richard Gregory, PhD, was named HSCI's second Millipore Foundation Seed Grant Fellow. The first fellow was 2008 Seed Grant recipient Sangeeta Bhatia, MD, PhD.

2009 SEED GRANT RECIPIENTS

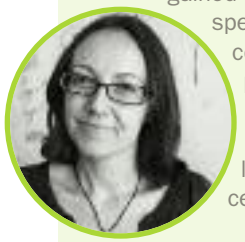
Wolfram Goessling, MD, PhD**
Brigham and Women's Hospital
Mark Damone Johnson, MD, PhD
Brigham and Women's Hospital
David Langenau, PhD
Massachusetts General Hospital
Trista North, PhD**
Beth Israel Deaconess Medical Center
Sharad Ramanathan, PhD
Harvard Faculty of Arts and Sciences
Derrick Rossi, PhD
Immune Disease Institute
Yu-Hua Tseng, PhD+
Joslin Diabetes Center
David Weinstock, MD
Dana-Farber Cancer Institute
Paul Yu, MD, PhD
Massachusetts General Hospital

*** Collaborators on a joint Seed Grant*

+ As part of its collaborative agreement with HSCI, in 2009 GlaxoSmithKline supported seed grant recipient Yu-Hua Tseng, PhD.

For One Seed Grant Recipient, HSCI is 'Priceless'

In early 2008, Paola Arlotta, PhD, learned that she was the recipient of an HSCI Seed Grant to fund her project, "Directed Differentiation of Neural Progenitors and iPS Cells into Corticospinal Neurons." The young HSCI neuroscientist was excited and also a bit relieved, because she knew traditional funding sources would probably not even consider funding such a risky project.



With her Seed Grant funding and applying the knowledge she and others had gained about generating corticospinal motor neurons (CSMNs)—the specific nerve cell type that connects the brain to the spinal cord—Arlotta set out to discover if she could direct neural progenitor cells in the developing mouse brain to become CSMNs. These cells are of great interest because they are one of the two neuronal cell types that die in amyotrophic lateral sclerosis (ALS, or Lou Gehrig's disease) and are the cells permanently damaged in spinal cord injury.

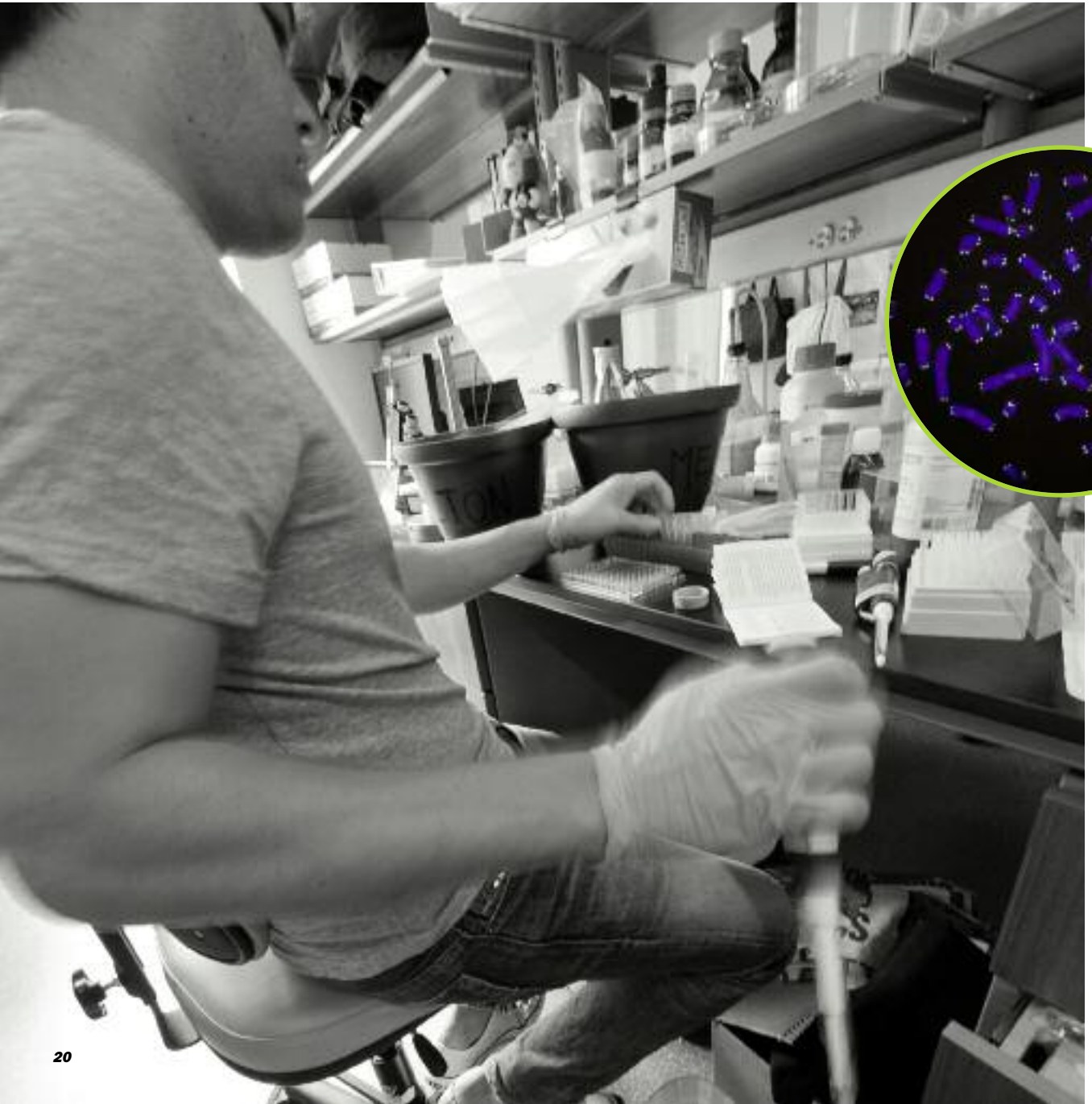
Indeed, Arlotta's Seed Grant-funded work has shown that using the right genes, it is possible to very precisely instruct neural progenitors inside the developing brain to change their fate and generate cortical neurons that resemble CSMNs.

"While further work is required to precisely characterize these neurons, the success of the experiments with neural progenitors gives us reason to believe we will be able to create CSMNs from pluripotent stem cells in a dish," says Arlotta. "Our initial results are very promising and support this prediction."

The implications of these findings are significant because vast numbers of CSMNs are needed to conduct large-scale screening of drugs that might be used to treat a number of movement disorders. As there is currently no way to obtain sufficient quantities of these cells from mice or humans for drug-screening purposes, generating CSMNs from induced pluripotent stem cells from both provides a much-needed solution.

Arlotta credits not only the Seed Grant Program for her accomplishment and the subsequent major NIH and foundation funding it enabled, but also the many other resources that HSCI offers. "This work has benefited immensely from the ability to draw on the expertise of other HSCI scientists, and the support of the HSCI's core facilities has made it move foreword very fast," says Arlotta. "In terms of my research, being part of the HSCI community is priceless."

ACCELERATING RESEARCH THROUGH *Training*



HSCI INTERNSHIP PROGRAM

Every year, hundreds of bright undergraduates from around the world vie for the chance to participate in the HSCI Internship Program (HIP). This program offers students a unique opportunity to spend the summer conducting a stem cell research project in a world-class laboratory under the mentorship of an HSCI stem cell scientist.

Only 35 fortunate students are selected to participate in HIP, which recently completed its sixth year. Since 2005, 200 college undergraduates from Harvard and many other colleges and universities around the globe have participated in this hands-on experience, which one intern described as "life-changing."

Over the summer HIP interns get a taste of what it is really like to be a scientist: they design and conduct experiments, learn to read and critically assess scientific literature, create a scientific poster, and present their research findings to their mentors and peers at the HIP symposium at the end of the summer. They also participate in a weekly seminar series and course and attend numerous other HSCI events. In short, they develop skills that are essential not only for a career in stem cell research, which many pursue, but are also important in science or, more broadly, any profession.

This year, more than 200 students applied for the paid, 10-week HIP internship, which is twice the number who applied the first year. In addition to Harvard undergraduates, this year's HIP group included students from colleges and universities throughout the United States as well as students from universities in Canada, Central America, Pakistan, and the United Kingdom.

CLINICIAN-SCIENTIST PROGRAM EXPANDS

Through its Clinician-Scientist Program, since 2005 HSCI has provided critical support to an MD/PhD student anticipating a career involving stem cell research. The program provides a stipend and tuition support for the final two years of the recipient's MD degree.

Thanks to an infusion of new funding from the estate of longtime HSCI donor Ruthe B. Cowl and the pharmaceutical company GlaxoSmithKline, last year HSCI expanded the program to include Postdoctoral Fellowships and Instructor Development Awards. Designed to complement the existing MD/PhD fellowships, the

"The HSCI Training Program enabled me to attend a major week-long stem cell conference this year, which would not have been possible otherwise. Having the opportunity to listen and talk to stem cell scientists from around the world was an incredibly valuable learning experience."

—Graduate student and HSCI Training Program trainee Gabriella Boulting

new awards support clinician-scientists in the critical years that directly follow completion of their joint medical/doctoral degree.

Specifically, the Postdoctoral Fellowships provide two years of support to individuals who have just completed their MD/PhD programs, are beginning their clinical training, and need salary and/or research support. The Instructor Development Awards provide two years of support for individuals who are within three years of the completion of their MD/PhD and, as newly or soon-to-be appointed instructors, are beginning to build their own labs.

In 2009, the HSCI Clinician-Scientist Program, which is under the direction of HSCI principal faculty member Kenneth Chien, MD, PhD, awarded an MD/PhD Fellowship, three Postdoctoral Fellowships, and four Instructor Development Awards.

NIH TRAINING PROGRAM

Now in its second year, HSCI's Training Program supports eight graduate and postdoctoral students engaged in stem cell research in the laboratory of an HSCI principal faculty member. The program is funded by a five-year, $2 million National Institutes of Health (NIH) Training Grant awarded to HSCI in 2008. More typically awarded to individual university departments, the NIH Training Grant is an acknowledgement of the strengths of HSCI's cross-institutional model.

Trainees in the HSCI Training Program, which is under the direction of HSCI Co-Director David Scadden, MD, are selected through a competitive application process. Most appointments last for two years and provide partial tuition (for graduate students); a stipend; and training-related expenses, such as travel to a major conference. Trainees work in the lab of a principal investigator who is their primary mentor, but also have a team of mentors to guide and inform their research.

This training is especially valuable because it is expressly designed to provide a well-rounded early research experience. For example, all trainees must develop a research plan with their mentors, give an annual oral presentation to a review committee, present a poster at the HSCI Annual Retreat, attend a stem cell conference, and participate in educational research activities like the HSCI Seminar Series. Graduate student trainees are required to complete required course work through the Harvard Department of Stem Cell and Regenerative Biology, and postdoctoral trainees must supervise and mentor an intern, graduate student, or research technician.

"We offer the undergraduates selected to be in the HSCI Internship Program a unique, intensive, hands-on research experience that, in some cases, has completely altered the course of their careers."

—M. William Lensch, PhD, HSCI Faculty Advisor for Education and HIP Faculty Director

GRADUATE FELLOWSHIPS

Much of the future progress in stem cell research will be achieved by today's graduate students. HSCI is fortunate to be able to support graduate training through two fellowships funded by generous philanthropists: The HSCI Sternlicht Awards for Graduate Students and the Mignone Fellows Program.

Established in 2007 by Harvard Business School alumnus Barry S. Sternlicht and Mimi Reichert Sternlicht, the Sternlicht Director's Fund for Graduate Students in Diabetes Research provides one to two years of support to Harvard graduate students working in diabetes-related stem cell research. The 2009 Sternlicht Fellows, Sinisa Hrvatin and Adriana Tajonar, are conducting research under the direction of HSCI Co-Director Douglas Melton, PhD, in Harvard's Department of Stem Cell and Regenerative Biology.

Inaugurated last year, the HSCI Mignone Fellows Program is funded by the Roberto and Allison Mignone Fund for Stem Cell Research. The fund was established with a generous gift from Roberto A. Mignone and Allison H. Mignone, both graduates of Harvard and Harvard Business School, to support graduate student research in stem cell and regenerative biology within HSCI-sponsored research projects. The first Mignone Fellows, Tim Ahfeldt and Elena Piskounova, are conducting research within HSCI's Stem Cell Regulation Project. Ahfeldt is working in the laboratory of HSCI principal faculty member Chad Cowan, PhD, at Massachusetts General Hospital; Piskounova is working at Children's Hospital Boston in the laboratory of HSCI principal faculty member Richard Gregory, PhD.

ACCELERATING RESEARCH THROUGH *Community Building*

RENEWAL EVENT

In February, more than 100 friends of HSCI gathered at Harvard Business School to hear four of HSCI's leading scientists discuss where the field of stem cell biology is heading over the next five years.

Introduced by Harvard President Drew Faust, PhD, and hosted by Harvard Business School Professor William Sahlman, PhD, the HSCI "Renewal" event featured an on-stage panel discussion among HSCI Co-Director Douglas Melton, PhD, Therapeutic Screening Center Director Lee Rubin, PhD, and principal faculty member Konrad Hochedlinger, PhD, as moderated by HSCI Co-Director David Scadden, MD.

"This critical emerging field [of stem cell biology] promises to bring us toward cures that only a few years ago would have been...unimaginable."

—Harvard University President Drew Faust, PhD, at the HSCI Renewal Event

The researchers explained that over the next five years there will be a growing emphasis on the use of stem cells as tools for the study of diseases and drug development, with much of this work emanating from HSCI. The group also talked about how important cross-lab, inter-institutional, interdisciplinary collaboration has been to HSCI's success, which Harvard President Drew Faust, PhD, described as "a model for modern science."

HSCI faculty in the audience also participated in the conversation, offering examples of how their research benefited from such collaboration and sharing their perspectives on several new areas of research.

STEM CELL SALONS

During its first five years, HSCI fostered a sense of community and collaboration through its popular inter-lab meetings, which were held every other month during the academic year. Moderated by senior HSCI faculty, each inter-lab provided a forum for junior or newly appointed faculty, postdoctoral fellows, and graduate students from three different labs to discuss their work on a common theme.

Last fall, HSCI introduced a new format—the Stem Cell Salon—which evolved from the inter-lab meetings. Held in the fall and winter at various HSCI-affiliated institutions, the thematically consistent salons were designed as informal gatherings to engage in discussion on a particular topic and facilitate networking.

Moderated by senior HSCI faculty, each salon featured a topic of broad interest to the stem cell research community, with expert guest discussants representing various perspectives. The first salon addressed the challenges of working with iPS (induced pluripotent stem) cell technology and how these cells can be integrated into research studies. The second focused on mesenchymal stem cells and their potential therapeutic applications. Advances in regulating cell differentiation was the topic of the third, and final, salon of the year.

SEMINAR SERIES

Since 2005, HSCI has sponsored a twice-monthly Seminar Series, which brings leading stem cell scientists from throughout the United States and abroad to HSCI to present their work, visit HSCI laboratories, and interact with HSCI researchers.

The popular lunchtime series, which was sponsored by Stemgent during the 2009-2010 academic year, gives HSCI scientists an opportunity to learn first-hand about the research in which their peers from around the globe are engaged, while giving presenters the chance to discover what is underway at HSCI. In addition to the group lecture, the one-on-one meetings throughout the day help form the basis for subsequent collaborations that cross the boundaries of disciplines, institutions, and countries.

To appeal to a broad audience, Seminar Series topics address virtually all aspects of stem cell biology. Last year, for example, topics included the discovery of drugs for cardiomyocyte regeneration and protection, stem cells in cancer, and how mesenchymal stem cells repair tissue.

ANNUAL RETREAT

HSCI's Annual Retreat is a much-anticipated event that gives the entire HSCI research community the opportunity to come together for a whole day with HSCI leadership and their colleagues to learn about the institute's initiatives and research, connect with peers and meet new colleagues, and "talk shop." Each year, approximately 300 members of the HSCI community take time from their busy schedules to attend the retreat.

Held on the Harvard campus, this year's retreat featured talks by Patrick Vallance, Senior Vice President, Medicines Discovery and Development, at GlaxoSmithKline, who addressed the process of developing medicines, and Robert Langer, ScD, David H. Koch Institute Professor at Massachusetts Institute of Technology, who discussed the applications of biomaterials and controlled-release systems in regenerative medicine. Highlighting this year's translational theme was a talk by HSCI Executive Committee Chair Leonard Zon, MD, about his experience of taking a discovery from the laboratory to a clinical trial (see sidebar, page 7). One of the most popular events of every retreat is the scientific poster session, which this year featured 47 posters.

STEM CELL SYMPOSIUM

Every fall for the past six years HSCI has hosted a full-day symposium on a specific stem cell topic presented by a panel of

preeminent stem cell scientists from institutions throughout the United States and abroad. Past topics have addressed areas of great interest to the stem cell research community, including cancer stem cells, cell reprogramming and pluripotency, and stem cells and their microenvironment in development and disease.

Held at the Harvard Club of Boston, this year's symposium focused on "Stem Cell Research in Diabetes and Metabolism," covering topics such as creating stem cell-generated islets, using stem cells to understand the autoimmune response in type 1 diabetes, and stem cell-based approaches to treating obesity and diabetes. The symposium was chaired by HSCI faculty Gordon Weir, MD, and Amy Wagers, PhD, with a panel of speakers from the United States and abroad led by HSCI Co-Director Douglas Melton, PhD.

INTERDISCIPLINARY CONFERENCES

Because collaborations across disciplines will accelerate progress in stem cell research, HSCI sponsors and participates in interdisciplinary conferences that bring stem cell biologists together with experts in other fields.

In May, for example, HSCI was one of the sponsors of the Society for Biological Engineering's second International Conference on Stem Cell Engineering, which was held in Boston. In addition to being a sponsor, HSCI played a major role in the conference, which covered a wide range of topics at the intersection of stem cell biology and bioengineering. HSCI executive committee member George Daley, MD, PhD, co-chaired the event, HSCI Co-Director Douglas Melton, PhD, gave a closing keynote address, and several other principal faculty members presented their research.

INTERNATIONAL PRESENCE

As the world leader in stem cell research, HSCI maintains a strong presence on the international stage for the purpose of sharing scientific advances, exchanging knowledge, and fostering new research collaborations.

For instance, this year as in years past, a number of HSCI principal faculty members were invited speakers at the annual meeting of the International Society for Stem Cell Research (ISSCR), a rapidly growing organization founded in 2003 by HSCI Executive Committee Chair Leonard Zon, MD. This year HSCI principal faculty member Amy Wagers, PhD, joined HSCI faculty David Scadden, MD, George Daley, MD, PhD, and Leonard Zon, MD, on the ISSCR's Board of Directors.

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Financials

Total expenditures for Harvard Stem Cell Institute in fiscal year 2010 were $18.6 million. Despite the overall economic conditions and budget challenges facing the university as a whole, we were able to maintain spending at a level consistent with the previous fiscal year as a result of obtaining increased sponsored research and directed funding. We were also able to take advantage of enhanced federal support for stem cell research as the result of new National Institutes of Health (NIH) policies which, however, is now in question as we start our new fiscal year.

FY10 research program expenditures totaled $15.9 million, up from $15.6 million in FY09. Of this total research support, $6.3 million comprised sponsored research dollars, a 43% increase from the previous year. Among the notable new and continuing sponsored awards were:

- GlaxoSmithKline, in multiple disease areas (see page 10)
- the Leona M. and Harry B. Helmsley Charitable Trust Type 1 Diabetes Program (HSCI is leading a multi-organization consortium)
- NIH Grand Opportunities grant in cancer (see page 14)

Additional components of HSCI's $15.9 million total research program support included:

- $5.7 million for research targeted to major disease programs
- $1.8 million for seed grant funding
- $2.1 million for core facilities

An important development in FY10 was a reduction of HSCI subsidies to existing core facilities, thereby enabling HSCI to launch the new iPS Core Facility on Harvard's Cambridge campus.

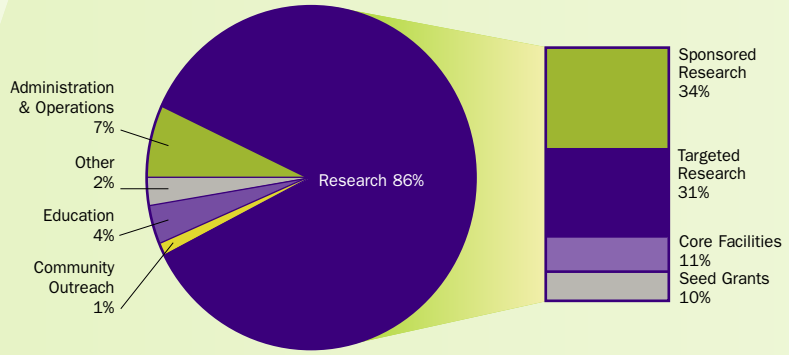
HSCI's spending outside its research program was as follows:

- administration and operations costs in FY10 were stable at $1.3 million, dropping to 7% of annual expenditures
- education costs of $673,000, including the Clinician-Scientist Program and the HSCI Internship Program, rose from 2% to 4% of HSCI's expenditures
- community outreach and events held steady at $221,000, which is 1% of total HSCI annual expenditures

In FY10, HSCI demonstrated its commitment to continued support for stem cell science despite ongoing uncertainty in the funding climate. At the same time, HSCI successfully managed its expanding programs while constraining the costs to administer these projects.

The significant increase of sponsored research funding demonstrates our success in leveraging donor investment to secure additional research dollars. We expect the level of sponsored research from the commercial sector to continue in drug discovery applications and begin to develop in areas of cellular therapy. We will continue our funding of basic science but can expect that as we accelerate progress toward the clinic and expand our portfolio of later-stage projects, such as pre-clinical and clinical trials, this will require a relatively greater investment.

HSCI FY10 Expenditures by Category as a % of Total Budget



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Since its inception, HSCI has benefited enormously from the input and support of a group of committed individuals who saw the promise of this unique organization and have given generously of their time, talents, and resources.

As HSCI has evolved from a bold concept to a complex organization, this varied group of leaders in industry, finance, venture capital, disease foundations, academia, and philanthropy has—largely behind the scenes—continued to play an active, essential role in HSCI's continuing success.

In early 2010, HSCI established an Advisory Board that formally brings together some of the members of the group to collectively focus on the challenges and opportunities that lie ahead.

"We felt it was important for these people to meet each other, and that the benefit of their combined expertise would be even greater than their significant individual contributions," says Advisory Board Chairman William Sahlman, PhD, a professor of Business Administration at Harvard Business School and expert in entrepreneurship, who has been actively involved with HSCI for years.

The 12-member Advisory Board, which met for the first time in early 2010 and will convene twice a year, has many roles, some of which are evolving. One of the most important is for members to counsel HSCI leadership about their directly relevant areas of expertise—be it raising capital, forming corporate partnerships, or leveraging resources—to help HSCI achieve its mission. Another is to serve as ambassadors for HSCI around the world—to share their knowledge of and excitement about the institute's work and, in so doing, help increase the understanding of and support for HSCI.

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Memorial gifts help the Harvard Stem Cell Institute sustain programs that are central to its mission. Thank you to those supporters who chose to remember a loved one through a memorial gift. Those who were memorialized with gifts to the Harvard Stem Cell Institute in the fiscal year that ended June 30, 2010 are listed below.

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We have done our best to ensure that these lists are accurate. If we omitted or misspelled any names, please accept our apologies and let us know by calling 617.496.4050 or sending an e-mail to scott_balderson@harvard.edu.

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The Harvard Stem Cell Institute is a scientific collaborative established to fulfill the promise of stem cell biology as the basis for cure and treatments for a wide range of chronic medical conditions.

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2004

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400+ (July 2009–June 2010)

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