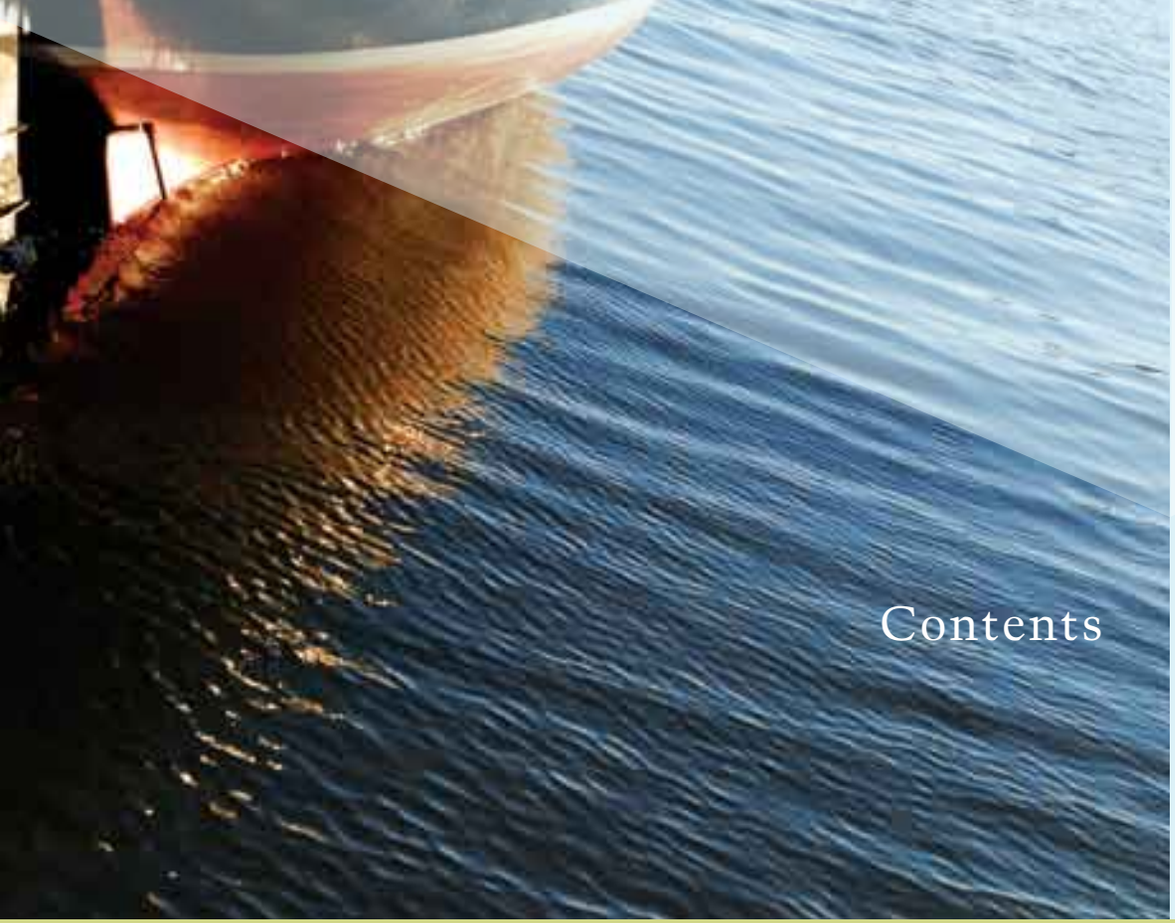
Momentum...

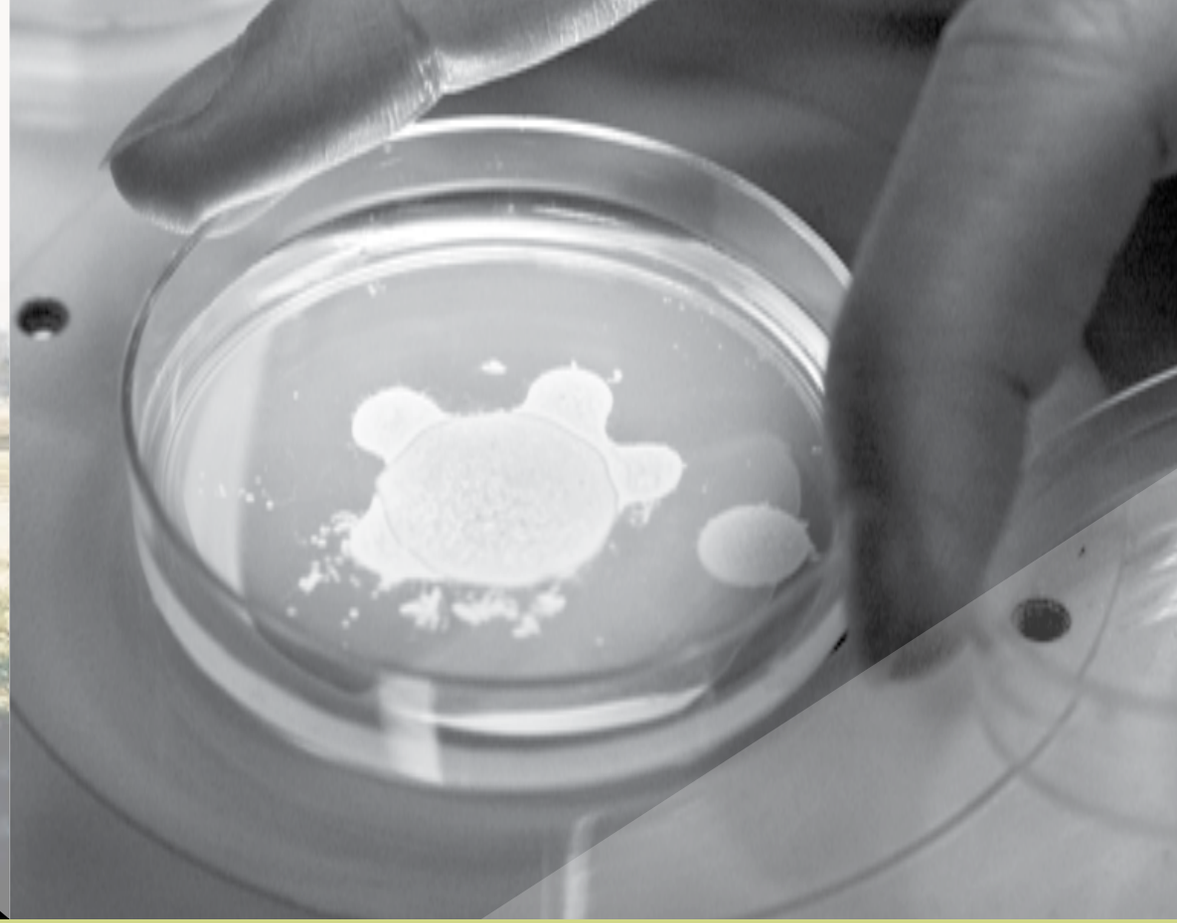
HARVARD STEM CELL INSTITUTE

ANNUAL REPORT 2007



Contents

Water is the basis of all human life. We evolved from water. Our cells are 70 percent water. Even the surface of our home, the Earth, is three-quarters water. When it is in motion and gains momentum, water is also powerful—able to carve canyons, create fertile fields, and power whole cities. Flowing water—major rivers like the Nile and the Mississippi, and even our own Charles River—also brings people together to live and work. What more fitting metaphor, then, for the Harvard Stem Cell Institute?



After all, HSCI is, first and foremost, about life—about better understanding its basic building blocks, our stem cells, and discovering how to harness their potential to improve the lives of people with many devastating, incurable diseases. Now in its fourth year, HSCI is also about momentum—significant momentum that, as you will read on the following pages, is moving us forward and bringing us closer to achieving our mission.

"I am so happy that Harvard Stem Cell Institute is doing research to find a cure."

—Hannah Thatcher, 12, of Minnesota, diagnosed with type 1 diabetes at age 3

HSCI is also about bringing people together—from both sides of the Charles River, across the Atlantic, and far beyond—to accomplish together what could never be achieved individually.

In this 2007 annual report, we are proud to tell you about our momentum in the diverse areas that comprise HSCI—from scientific collaborations that have led to both incremental steps and major advances alike, to educational programs that are helping shape the public discourse about stem cell research.

We are also pleased to publicly acknowledge all the many donors who have supported us through generous gifts to HSCI since its inception. Because we depend to a large extent on private philanthropy to fund our work, such support is vital to sustaining our momentum and turning the tide on diseases for which stem cell research holds such enormous promise.

Message from the CO-DIRECTORS

Justin Ide/Harvard News Office

The theme of this year's annual report—momentum—could hardly be more appropriate. The past year has been one of significant momentum in virtually all areas of the Harvard Stem Cell Institute, from notable scientific advances to new initiatives and program enhancements.

One was the formation of our Scientific Advisory Board (SAB), a group of six prominent scientists from the United States and abroad who provide a valuable, external perspective on HSCI's strategies and priorities. Last spring, the SAB met for the first time, spending an entire day with members of the HSCI leadership and Harvard University Provost Dr. Steven E. Hyman. We are, indeed, fortunate to have access to the expertise of these illustrious board members and look forward to their continued involvement.

Harvard University's commitment to attracting the world's leading scientists was strengthened by the recent creation of the new Department of Stem Cell and Regenerative Biology, which will be aggressively recruiting new faculty. As a joint Harvard Medical School and Faculty of Arts and Sciences department, this will reinforce HSCI's emphasis on cross-institutional collaboration.

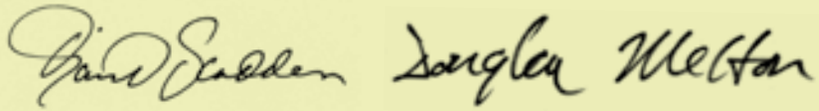
In early summer, through HSCI's Seed Grant Program, we awarded $1.8 million to support HSCI investigators conducting early-stage research. In fact, some of these seeds are already bearing fruit. We are pleased to report, for example, that a Seed Grant awarded in 2005 to one of our principal faculty members has already led to an important scientific advance, which is described in this report.

Another significant achievement in the past year was the opening of two new, large-scale core facilities—the Therapeutic Screening Center and the Genome Modification Facility, which are now fully operational. Representing a major investment by HSCI, these state-of-the-art facilities provide our entire research community with prompt access to a range of highly specialized services and expertise that enable them to keep their research moving along quickly. Even in the short time since its doors opened, the Therapeutic Screening Center has made progress toward identifying compounds that could potentially be used to treat, and perhaps even cure, a particularly devastating childhood motor neuron disease.

We have achieved momentum in many other areas, as well, often as a result of our collaborations, both new and existing. For instance, several of our disease-focused programs held daylong think tanks in which the leading minds in their respective disciplines came together to share knowledge and ideas, and define future priorities. These think tanks have been so productive that several others are being planned for the coming year.

Another measure of our momentum is the number of scientific papers published in leading peer-reviewed scientific journals. During the previous fiscal year, HSCI principal faculty members had more than 280 papers published across a broad range of disciplines.

The progress mentioned above and throughout this annual report would not have been imaginable, let alone possible, without the philanthropic support of so many generous individuals and organizations across the nation who believe in and are committed to helping us achieve our mission. To all of our supporters, we give our heartfelt thanks and our promise to keep this momentum going in the coming year.



David T. Scadden, MD, and Douglas A. Melton, PhD
Co-Directors, Harvard Stem Cell Institute

Message from the EXECUTIVE DIRECTOR

Since its creation in early 2004, Harvard Stem Cell Institute has rapidly evolved from an innovative concept into a major, international force in the rapidly expanding field of stem cell science. I had the privilege of joining HSCI as Executive Director about a year and a-half ago, and even in this relatively short period I have been astonished by the momentum this young, dynamic organization has achieved.

In this, our second, annual report, we are proud to showcase the momentum underway in all areas of HSCI—from our disease-focused research programs to activities that, while perhaps less well-known, are also a key part of our mission, such as our educational initiatives.

You will read about our new, quarterly Public Forums, through which we inform the public about the many dimensions of stem cell research, and our pilot teacher-education program, which gives educators the tools to teach their students about stem cell science. You will also learn about our ongoing participation in many local community-based educational events, like this summer's Cambridge Science Festival, and our efforts to inform the national community about stem cell research through the mass media.

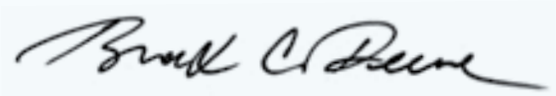
Perhaps the most tangible sign of HSCI's momentum will be the groundbreaking this fall of Harvard's 550,000-square-foot science complex in Allston, about half of which will become HSCI's new home. When this stunning new complex is completed in 2011, HSCI will be transformed from what is now a virtual community into a physical community, where many of our faculty members will work side-by-side, collaborating in a way that only physical proximity allows.

The new science complex will also house the Department of Stem Cell and Regenerative Biology, the recently established, University-wide department that brings together scientists with shared research interests from Harvard's Faculty of Arts and Sciences and Harvard Medical School under one academic "umbrella." This new department—the University's first cross-school department—will work synergistically with HSCI, and be chaired by HSCI's Co-Directors.

The momentum you will read about in this annual report is due not only to the vision and dedication of HSCI's world-class faculty members, but also to the commitment and passion of our many supporters. Many individuals and organizations have stepped up to the plate to ensure that we have the financial resources we need to keep moving forward with our important work.

Occasionally, I'm asked whether private funding will be as important to HSCI under a new administration in Washington. The answer is, unequivocally, yes. Even if the restrictions on federal funding for embryonic stem cell research are lifted during the next administration—as we, Congress, and, indeed, most of the American people desire—we will still rely heavily on private philanthropy because of the de facto decline in federal research dollars and the intense competition for limited state funds.

As we enter our fourth year, we have achieved and are sustaining a level of momentum that, even in the high-energy environment of Harvard University, is truly phenomenal—momentum that will undoubtedly transform the understanding and treatment of many terrible diseases. On behalf of the entire HSCI community, thank you for helping make it happen.



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

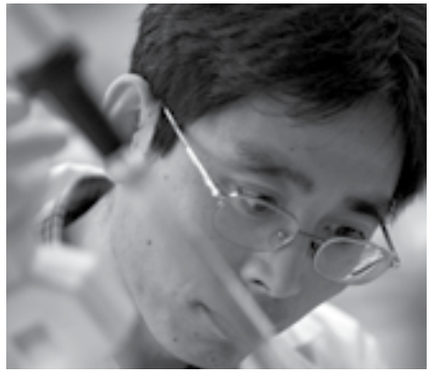
DISCOVERING the potential of stem cells

"It is fair to say that embryonic stem cells have already saved lives—not directly through cell replacement therapies—but indirectly through key insights into human disease and the development of new drugs."

—George Q. Daley, MD, PhD,
HSCI Executive Committee member

One of Harvard Stem Cell Institute's major strengths is its ability to convene leading biomedical researchers and physician-scientists from multiple disciplines and institutions to focus collectively on a specific clinical challenge.

Through a number of disease-specific programs, HSCI channels its world-class resources—both intellectual and technological—toward some of the most prevalent, devastating diseases for which stem cell research hold promise: cancer, diabetes, cardiovascular disease, nervous system diseases, blood diseases, and kidney disease.



The following section provides an overview of seven of our major disease programs, as well as our recently established Cell Development Program, which has relevance to all of these diseases. As you will learn, these programs are making progress toward their goal of discovering the potential of both embryonic and adult stem cells as powerful new tools with which to understand and, ultimately, treat many prevalent diseases.

Because stem cell research is in its infancy, much more work remains to be done. Achieving our mission—"to fulfill the promise of stem cell biology as the basis for cure and treatments for a wide range of chronic medical conditions"—will take years. But as we embark on our fourth year we can state, unequivocally, that we are well on our way.

What is described in the following section is, by necessity, incomplete. It would require many more pages to describe all of the innovative research taking place by the hundreds of scientists within the 120 HSCI-affiliated laboratories.

Therefore, we encourage you to refer to the list of selected scientific publications beginning on page 30 and to visit our website (**www.hsci.harvard.edu**) on a regular basis, where you can read about scientific advances, events, and news regarding stem cell research. From our website, you can also read or sign up to receive our free newsletter, *Stem Cell Lines*, which will keep you abreast of our research and activities throughout the year.

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DECIPHERING SELF-RENEWAL

The Blood Program

Despite vast differences in appearance and function, every tissue and organ in the human body—from doughnut-shaped red blood cells that shuttle oxygen throughout the body to star-shaped astrocytes in the brain that provide structural support—share a common ancestry: an embryonic stem cell.

A signature characteristic of embryonic stem cells and their more specialized descendants—adult stem cells—is their ability to renew themselves. Donate blood, for example, and your hematopoietic (blood-forming) stem cells rapidly replenish your supply. In a perversion of this tissue-regenerating function, cancer stem cells also renew themselves.

Currently, the molecular regulators of stem cell self-renewal in embryonic, adult, and cancer stem cells are not well understood. What are they, and how do they interact to coordinate this complex process?

If the molecular regulators of stem cell self-renewal can be identified, researchers might eventually be able to turn on these molecules (or, alternatively, release the molecular "brakes" that keep them turned off) to create abundant supplies of stem cells with which to replace diseased or damaged tissues. And in the case of cancer, they might be able to switch them off.

This is the goal of HSCI's Blood Program—to use the blood system to unravel the mysteries of stem cell self-renewal. Led by Daniel G. Tenen, MD, of Beth Israel Deaconess Medical Center, this program includes four other principal investigators whose labs are located at Massachusetts General Hospital and Children's Hospital Boston.

Using different, but complementary, research tools—from zebrafish and mouse models to powerful new genomic and proteomic approaches—this collaborative group is sharing data, information, computational tools, and the resources of HSCI's Therapeutic Screening Center to understand the mechanisms of stem cell self-renewal.

These scientists are using hematopoietic stem cells, the adult stem cells from which all the cell types of blood arise (red blood cells, platelets, and white blood cells) for several reasons. These are the optimal cells for this work because they are the best characterized of adult stem cells, are easily accessible in organisms from zebrafish to humans, and provide models for studying both normal and malignant stem cell self-renewal.

From Tank to Trial: Common Drug Boosts Blood Stem Cells

The creature may be tiny but the news is potentially big. Using the diminutive, transparent zebrafish embryo to screen for compounds that affect blood stem cell production, Blood Program investigators at Children's Hospital Boston recently discovered that a derivative of the drug prostaglandin increases the production of blood stem cells.

This discovery, made by HSCI Blood Program principal investigator Leonard I. Zon, MD, and his team and later validated in mouse models by other HSCI investigators, will soon be evaluated in a clinical trial. If results from fish and mice translate to humans, this finding may be good news, indeed, for many cancer patients undergoing stem cell transplantation.

Not surprisingly, discoveries arising from this research have the potential to benefit patients with many forms of blood diseases, such as leukemia and aplastic anemia, as well as cancer patients whose blood system must be replenished following high-dose chemotherapy. In fact, collaborations within the Blood Program have already led to the identification of a compound that may help boost the numbers of blood cells in patients undergoing treatment for cancer (*see sidebar, page 6*). Blood Program investigators have also found that a drug used to treat osteoporosis increases stem cell numbers and survival following transplantation; this drug is now being evaluated in a clinical trial involving stem cell transplantation for cancer patients.

Lessons learned from work underway in the Blood Program will not be limited to the blood system. Indeed, work completed this year indicated that a gene responsible for aging of blood stem cells was also important for age-related changes in the brain and pancreas (*see sidebar, right*). Investigators plan to determine whether the principles governing blood stem cell self-renewal are shared and, if so, whether some of the same strategies can be used to induce or interrupt stem cell self-renewal in other tissues. Through the interdisciplinary, inter-institutional collaboration that is a hallmark of HSCI, knowledge gleaned in one area of stem cell research will inform the work of many others.

TARGETING CANCER'S ACHILLES HEEL

The Cancer Program

Despite significant advances in the diagnosis and treatment of cancer, this disease—which actually is more than 100 different diseases that share in common the uncontrolled proliferation and spread of malignant cells—still claims the lives of more than half a million Americans each year.

Headed by D. Gary Gilliland, MD, PhD, Harvard Stem Cell Institute's Cancer Program marshals the broad expertise and vast technological resources of HSCI's world-class hospitals and biomedical research institutions to develop more effective, and less toxic, therapies for cancer. More than 40 Harvard faculty across HSCI are involved in this important effort.

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Stem Cells and Aging

It is well known that older people do not heal as well as younger people following injury. HSCI investigators discovered that stem cells are largely responsible. The laboratory of HSCI Co-Director and Blood Program principal investigator David T. Scadden, MD, demonstrated in mice that expression of the gene $p16^{INK4a}$ increases in blood stem cells as they age. When that gene was made deficient, stem cells from old animals functioned like stem cells from young animals, and were capable of regenerating injured bone marrow. In collaboration with laboratories at other universities, researchers also found that older animals deficient in $p16^{INK4a}$ had improved repair of brain injury and insulin-producing cell injury. These studies are important for understanding the aging process and how stem cells participate in it; they also point to possible interventions.

Conventional cancer therapies, such as surgery, chemotherapy, and radiation therapy, focus on eradicating as many malignant cells as possible. Many of these treatments are effective in reducing tumor size, but in most cases some cancer cells elude destruction, resulting in a relapse and, often, the patient's death.

There is now a growing recognition among scientists that not all cancer cells are alike—that lurking within many tumors are cells with stem-cell like properties. Though relatively small in number, these self-renewing, so-called "cancer stem cells" are resistant to conventional therapies, and may be responsible for the majority of cancer recurrences.

Believing that cancer stem cells are likely the true enemy, investigators within HSCI's Cancer Program have set their sights on developing novel, targeted therapeutics aimed specifically at these aberrant cells. Essential to achieving this goal is being able to identify these cancer stem cells in all tumor types, and to understand how they function. This work, which is well underway, will take time, but it has enormous potential for saving patients' lives.

With this goal front and center, HSCI's Cancer Program recently launched its Cancer Stem Cell Discovery Project. This multi-faceted initiative is focusing on several key areas: identifying cancer stem cells from a broad range of tumors and learning more about their unique biology; discovering what role the local cellular "neighborhood," or microenvironment, plays in maintaining malignant cells; and searching for chemicals that will specifically target cancer stem cells. The program also recently established a core facility that is available to the entire HSCI research community. Among other services, this facility procures patient tissue samples from HSCI's broad network of hospitals, and identifies cancer stem cells.

Because of the collaboration among scientists, the availability of the latest technologies, and access to a broad range of tumor tissue samples, HSCI is uniquely positioned to carry out research that may, finally, home in on cancer's Achilles heel.

REGENERATING BROKEN HEARTS

The Cardiovascular Disease Program

The numbers are simply staggering: one in every three Americans has some form of cardiovascular disease, the leading cause of death in the United States.

Five million Americans suffer from heart failure, and this year alone, a half million more will be diagnosed with this chronic degenerative disease. Coronary heart disease, the single largest killer of both women and men in this country, is an even greater scourge. In fact, each and every minute a coronary event claims the life of yet one more American, many of whom are in the prime of their lives.

These unacceptable numbers are what is driving a multidisciplinary team of more than 100 investigators in HSCI's Cardiovascular Disease Program. Their goals? To search for ways to harness the potential of stem cells to better understand the molecular causes of cardiovascular disease, and to find novel treatments, including regenerating blood vessels and heart muscle that have been irreversibly damaged by many forms of the disease. Led by Kenneth R. Chien, MD, PhD, director of Massachusetts General Hospital's Cardiovascular Research Center, over the last year HSCI's Cardiovascular Disease Program has achieved significant momentum toward this long-term goal.

International Stem Cell Expert Joins HSCI as Fellow

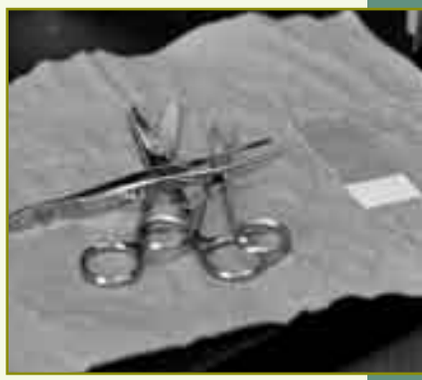
In June, Christine L. Mummery, PhD, a professor of developmental biology at the Hubrecht Institute at the University of Utrecht in the Netherlands, was named the first HSCI Radcliffe Fellow. Through a new collaboration, HSCI and the Radcliffe Institute for Advanced Study are offering sponsorship for one HSCI Radcliffe Fellow a year through Radcliffe Institute's world-renowned fellowship program. Working with investigators within HSCI's Cardiovascular Disease Program and other Harvard colleagues in the School of Engineering and Applied Sciences, Mummery is examining the role that the physical environment plays in regulating the differentiation of stem cells into the various cardiac cell types of the heart.

Last fall, for example, Chien and his team reported that they had discovered in mouse studies that a single cardiac progenitor cell—an early descendant of a stem cell with the ability to differentiate—gives rise to all three major types of cells that make up a mammalian heart. Prior to this discovery, which was also made independently by HSCI scientists Stuart H. Orkin, MD, and Sean M. Wu, MD, PhD, it was assumed that these cells had distinct origins. Both teams had coaxed these cardiac progenitor cells from embryonic stem cells.

This finding is significant on several fronts. Cardiac progenitor cells make it possible to create in vitro models with which to better understand the molecular pathways that drive cardiovascular disease. This, in turn, will allow researchers to identify novel targets for therapies, including potential patient-specific therapies through somatic cell nuclear transfer.

It is also expected that these in vitro models could provide a better way to study the potentially toxic effects of drugs on the heart. And—although this application may not be realized for many years—this discovery brings scientists one step closer to the ambitious, but worthy, goal of being able to regenerate cardiovascular tissue such as heart muscle or coronary arteries.

Since this announcement, scientists in the Cardiovascular Program are already moving from mouse to man—beginning to isolate, from human embryonic stem cells, cardiac progenitor cells that maintain their ability to become the different cardiac cell types. They have also identified the optimal cell line for cardiogenesis, and reported ways to expand these master cardiac progenitor cells from human heart tissue.



Still, much work remains to be done. This includes figuring out how to stimulate the body's cardiac progenitor cells to replicate. And devising the most effective method for delivering cardiac progenitor cells to their intended destination and, once they are there, ensuring that they engraft and become fully functional. Other work is focused on engineering specific components of the heart, such as blood vessels and muscle strips, for transplantation. But in as little as one year, HSCI's Cardiovascular Program has made significant strides toward the ultimate goal of regenerating cardiovascular tissue.

To keep this momentum going, last spring the Cardiovascular Program sponsored its first think tank. Through a variety of scientific sessions, think tank participants identified critical knowledge gaps, fostered new collaborations, and established priorities for the future. The event was so fruitful that a second think tank is planned for the coming year.

REPROGRAMMING CELLS

The Cell Development Program

It's considered a given that you can't turn back time. While this is undeniably true of human events, when it comes to our cells, it now appears that this maxim does not apply.

Switch on just four genes in an adult mouse cell, for instance, and it takes on all the properties of an earlier, far more potent, embryonic stem cell. Chemically fuse a human adult skin cell with a human embryonic stem cell and the resulting cell is converted into an embryonic state. In these examples, both of which are notable achievements of HSCI investigators, the developmental clock has, in essence, been turned back.

These and other innovative approaches, including somatic cell nuclear transfer (SCNT, or therapeutic cloning), are among strategies being pursued by HSCI investigators in the rapidly advancing, promising area of stem cell research known as cell reprogramming. A key goal of regenerative medicine, cell reprogramming is the process of directing a somatic (body) cell to a different fate—either to an earlier, embryonic or pluripotent state as in the preceding examples, or, alternatively, to a different type of somatic cell.

Cell reprogramming is the primary focus of HSCI's recently established Cell Development Program. Led by HSCI Faculty Executive Committee member Amy Wagers, PhD, of Joslin Diabetes Center, this dynamic program consists of seven up-and-coming, newly recruited faculty members across five HSCI-affiliated research institutions.

While these principal investigators are taking a different approach to the reprogramming question, their work is highly collaborative and is integrated into the overall program. Additionally, these investigators work with other scientists within HSCI and beyond to move their work forward quickly. Indeed, the Cell Development Program was recently cited by HSCI's Scientific Advisory Board as a model of scientific collaboration.

The enormous potential of cell reprogramming has made it an especially hot area of stem cell research. Work done by HSCI investigators in this field has already given scientists the means to create limitless quantities of disease-specific cells. These are valuable tools with which to study what goes awry in many degenerative diseases from an early stage, and to screen for new drug treatments.

In addition, if results in animal models translate to humans, HSCI scientists hope to ultimately be able to use cell reprogramming to generate patient-specific cells with which to regenerate tissue lost because of disease or injury. This would make it possible to replace insulin-producing beta cells in diabetics, for example, or muscle cells in patients weakened by muscular dystrophy. And because reprogramming could create replacement cells genetically matched to the recipient, immune-system rejection would be a non-issue.

Finally, this research will give scientists tools with which to identify the mechanisms that direct normal cell differentiation and repair—mechanisms that could be manipulated to steer cells toward a different, desired fate or to stimulate or replace the body's natural repair processes.

In addition to conducting pioneering research, some of which made international headlines this year, faculty of the Cell Development Program are also very involved in many initiatives aimed at sharing and disseminating knowledge and spurring productive collaborations.

Specifically, all seven faculty actively participate in a scientific exchange program that fosters ongoing collaborations among stem cell scientists at HSCI and the United Kingdom. This coming year, they will initiate a similar program with colleagues from California. In addition, faculty members briefed members of Congress last year on stem cell research, participated in the National Academy of Sciences (NAS) meeting

to update NAS guidelines on human embryonic stem cell research, and served on several states' stem cell research advisory committees.

These energetic, young scientists are equally involved at the local level—teaching undergraduate students, fellow HSCI investigators, and members of the public; participating in numerous HSCI programs and events; and serving on HSCI's Faculty Executive Committee.

GENERATING BETA CELLS
The Diabetes Program

The discovery of insulin in the early 1920s transformed diabetes from a certain death sentence to a chronic condition that, with constant vigilance and care, can usually be managed, albeit with the ever-present risk of serious complications. Still, nearly a century later, this disease—which affects nearly 21 million Americans, or an astonishing seven percent of the nation's population—still eludes a cure.

Through HSCI's Diabetes Program, an interdisciplinary group of scientists from throughout Harvard's research hospitals and institutions have joined forces to achieve what many in the scientific community believe is possible—to find a cell-based cure for diabetes, particularly type 1 (formerly called insulin-dependent) diabetes.

A cell-based cure for type 1 diabetes appears tantalizingly within reach because this disease is caused by the absence of a single type of cell—insulin-producing pancreatic beta cells—that the body's immune system, in a case of friendly fire, mistakes for a foreign invader and destroys.

In simple terms, the focus of HSCI's Diabetes Program is to generate sufficient numbers of beta cells for transplantation into patients who need them. This is not to suggest that this endeavor is simple. Indeed, scientists must first understand the interaction between beta cells and the immune system, why the immune system attacks, and why the beta cells respond as they do, among other questions. Despite these challenges, HSCI scientists are achieving significant momentum in this rapidly evolving field of research.

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HSCI Co-Director Honored in Time 100

In May, HSCI Co-Director, Douglas A. Melton, PhD, was cited by *Time* magazine as one of the 100 most influential people in the world in the past year. In his essay supporting Melton's selection for this special honor, actor and stem cell research advocate Michael J. Fox, wrote, "[Doug] has the vision and compassion to know that true humanity lies in relieving human suffering, not acquiescing to politics or ideology."

Led by Gordon C. Weir, MD, of Joslin Diabetes Center, HSCI's Diabetes Program draws on the expertise of more than 60 investigators working in laboratories throughout HSCI's affiliated research institutions. The program is divided into two sub-groups—one headed by HSCI Co-Director Douglas A. Melton, PhD (*see sidebar*, *page 11*), of Harvard's Faculty of Arts and Sciences, and the other by Richard Maas, MD, PhD, of Brigham and Women's Hospital. Although each group is taking a different tack, both are focused on pursuing promising strategies to generate large quantities of pancreatic beta cells to replace those that are missing in patients with diabetes.

Melton's group is looking at ways to convert human embryonic stem cells—the undifferentiated cells from which all tissues develop—into pancreatic beta cells in vitro. Currently, this research is focused on directing both human and mouse embryonic stem cells to become beta cells through a series of differentiation steps that recapitulate those that occur during normal development. Melton and his team are working in close collaboration with HSCI's new Therapeutic Screening Center to identify the factors that promote each step along the pathway from an undifferentiated embryonic stem cell to a fully functioning beta cell.

The Diabetes Program sub-group, led by Maas, is pursuing another potentially rich source of replacement beta cells—pre-existing beta cells. In a typical HSCI collaboration, Maas and fellow scientists at several HSCI-affiliated institutions are using advanced technologies, such as high-throughout screening and the specialized expertise available at HSCI's Therapeutic Screening Center, to identify—and ultimately use to their advantage—the intrinsic factors that control the proliferation and survival of beta cells.

SEARCHING FOR KIDNEY STEM CELLS

The Kidney Program

The kidneys are marvels of engineering, a vast network of one million filtering units, called nephrons, that remove waste products and excess water from the blood while simultaneously maintaining a delicate balance of the proper levels of vital chemicals in the bloodstream.

Alarmingly, an estimated eight million Americans have less than half the kidney function of a healthy young adult, and another 12 million have earlier stages of kidney disease. By all measures, including a steadily growing number of patients requiring kidney dialysis (now more than 400,000 in the United States), kidney disease is a growing public health problem. Because there is no cure and replacement organs are in very short supply, this problem is only expected to get worse.

Most kidney disease develops slowly, often as a consequence of diabetes or high blood pressure. An insidious condition, chronic kidney disease can ultimately lead

to kidney failure and death. A less common but often lethal form of kidney disease is acute kidney failure, in which the kidneys fail suddenly due to the sudden decrease in blood flow caused by trauma, surgery, or heart attack, or by medications or toxins in the blood.

The Harvard Stem Cell Institute Kidney Program, led by Joseph V. Bonventre, MD, PhD, of Brigham and Women's Hospital, is searching for kidney stem cells or progenitor cells (early descendants of stem cells) that could be studied to learn how kidney disease develops and, in time, harnessed to improve the care and outcomes of the millions of people with kidney disease.

For a number of years, members of HSCI's Kidney Program have studied the normal processes of kidney development and the kidney's rapid and robust ability to repair itself following injury. This remarkable capability is often not seen in many patients with acute injury, and is frequently subverted by maladaptive influences in those with chronic disease.

Members of the HSCI Kidney Program are using the latest research tools to identify and characterize embryonic and adult kidney stem/progenitor cells with the goal of enhancing normal kidney repair, as well as understanding and, ultimately, preventing and treating processes resulting in abnormal repair. The pace of this work is expedited by the availability of novel, and critically important, mouse models developed in HSCI's Genome Modification Facility, and state-of-the-art technologies within HSCI's Therapeutic Screening Center.

In collaboration with HSCI investigators who are studying other organs, members of the Kidney Program are looking closely at a specific area of the kidney—the renal papilla—as a potential niche, or residence, of stem/progenitor cells. Other Kidney Program investigators are studying the factors that regulate the differentiation of stem/progenitor cells into kidney cells.

If isolated, kidney stem/progenitor cells could potentially be marshaled to further enhance the body's intrinsic, powerful response to kidney injury among patients with acute kidney failure, as well as those with chronic and congenital kidney diseases.

In addition, kidney stem/precursor cells could be used to create disease-specific stem cell lines with which to better understand the early stages of kidney disease and to screen drugs for their therapeutic potential.

Another exciting, potential application of kidney stem/progenitor cells on HSCI researchers' radar screens is to use them in kidney dialysis devices, where it is anticipated they could provide a more effective replacement for failed kidney function than devices that are currently in use.

TACKLING COMPLEX DISORDERS

The Nervous System Diseases Program

The sheer complexity of the nervous system—which by most estimates includes thousands of distinct sub-types of neurons (nerve cells), as well as supporting non-neuronal glial cells—might make it seem an unlikely focus of stem cell research and potential cell-based therapies.

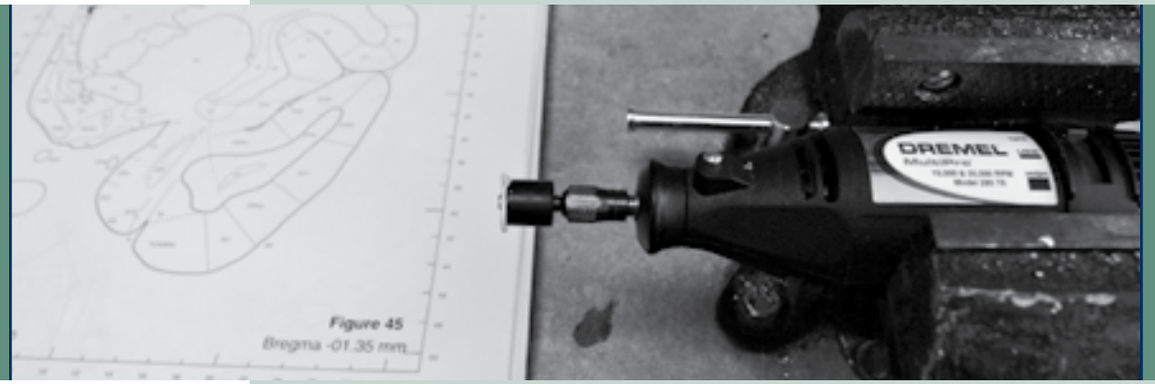
Yet diseases of the nervous system—amyotrophic lateral sclerosis (ALS), Parkinson's disease, multiple sclerosis, and deafness, to list just a few—are, in many cases, terrible, intractable diseases. Consequently, carrying out this research, while undeniably challenging, is well worth the potential payoff in terms of improving and saving millions of lives. Indeed, that is the ultimate goal of HSCI's Nervous System Diseases Program, led by Massachusetts General Hospital neuroscientist Jeffrey D. Macklis, MD, DHST.

Like the nervous system itself, HSCI's program is complex and functions with a high degree of connectivity. Comprising approximately 45 Harvard faculty throughout HSCI-affiliated institutions, the program is organized into five disease-focused working groups: motor systems (which includes diseases such as ALS, Huntington's disease, and cerebral palsy), Parkinson's disease, retinal disorders, hearing disorders, and glial-based disorders (diseases such as multiple sclerosis and some aspects of cerebral palsy).

Through regular strategic planning sessions, monthly inter-lab meetings, symposia, and many other inter-institutional, interdisciplinary initiatives, investigators within these five groups frequently collaborate with one another and with members of the entire program, as well as with scientists throughout the broader HSCI research community and well beyond. For example, in 2006 and again in 2007, the Nervous System Diseases Program convened two think tanks that brought together international experts on Parkinson's disease. The program is planning a third think tank for 2008 on diseases linked to forebrain neurons, such as ALS and Huntington's disease.

Largely as a result of these collaborations, over the past year the Nervous System Diseases Program has achieved significant momentum in a number of different areas. The major focus has been on neurodegenerative diseases in which either a single neuron, a dual neuron population, or glial populations, are predominantly involved. These types of diseases were strategically selected because they are the ones most likely to proceed expeditiously to novel treatments and, perhaps, even cures. That said, neurodegenerative diseases share much of the same biology, so a lesson learned about one disease is, in many cases, a lesson learned about all.

The motor systems group is making significant progress on a number of fronts. Through the HSCI ALS Brain Circuitry Program grant, Macklis and five other HSCI faculty are leading a multi-focused effort using precursor/stem cells to study the molecular development and survival of corticospinal motor neurons, the neurons of the brain that degenerate in ALS. Already, Macklis and his colleagues have identified the first molecular-genetic control programs yet discovered for any type of brain neuron. The knowledge arising from this research—which will apply to many other



complex neuronal sub-types, as well—is expected to reveal targets for the prevention, treatment, or perhaps even the eventual cure of ALS and other motor neuron diseases. This work is enhanced by the recent development of an ALS mouse stem cell line by faculty of HSCI's Cell Development Program (*see sidebar, right*).

Another major, ongoing focus on the Nervous System Diseases program is studying the molecular development of the dopaminergic (dopamine-producing) neurons that die or cease functioning in Parkinson's disease. Because this is such a high priority, it was the topic of the Nervous System Diseases Program 2007 think tank.

Working in close collaboration with HSCI's Therapeutic Screening Center, investigators in the motor systems group are also screening for compounds in disease-specific cells that could potentially help patients with spinal muscular atrophy (SMA), an incurable disease that strikes infants and young children. Parallel efforts are now underway toward the neuron populations in both the striatum and cerebral cortex that degenerate in Huntington's disease.

In addition to these initiatives, the hearing group has expanded over the past year, with investigators throughout HSCI-affiliated institutions forming groups of shared interest. And in the glial-disorders group, a new, collaborative project between investigators at Dana-Farber Cancer Institute and HSCI's Therapeutic Screening Center is taking place to screen for compounds that might be potential therapeutics for multiple sclerosis.

In Vitro ALS Model Provides Unlimited Cells for Study and Screening

With funding from a 2005 HSCI Seed Grant, HSCI Principal Faculty member Kevin C. Eggan, PhD, and Tom Maniatis, PhD, of Harvard's Faculty of Arts and Sciences, used embryonic stem cells derived from mice to create an in vitro model—a "disease in a dish" so to speak—of a form of the neurodegenerative disease, amyotrophic lateral sclerosis (ALS). This achievement gives scientists an unlimited quantity of ALS-specific cells with which to study this fatal disease from its earliest stages and to screen for potential treatments. This in vitro model also revealed the effect that neighboring glial cells had on the neurons, raising potential implications for studying novel therapeutic approaches. The techniques used by this team could also be applied to many other diseases.

"HSCI is ideally situated to demonstrate both the clinical and financial value of stem cell-derived therapeutics." —*Lee L. Rubin, PhD, Director, Therapeutic Screening Center*

ACCELERATING the pace of research

For stem cell research to realize its full potential as rapidly as possible, scientists engaged in this work must have prompt, affordable access to cutting-edge technologies and highly specialized expertise and services that, in some cases, are unique to this burgeoning field.

One of HSCI's key strengths is its ability to offer a wide spectrum of state-of-the-art resources—many of which are beyond the reach of any individual institution or laboratory—to its entire research community both efficiently and cost-effectively.

By funding essential "core" facilities that can be shared by all of its investigators, HSCI is actually achieving two important goals: accelerating the pace of stem cell research and, at the same time, fostering interdisciplinary, inter-institutional collaborations that could lead to future breakthroughs.

Since HSCI's inception, its scientists have had prompt access to flow cytometry core facilities at three HSCI-affiliated medical institutions, thereby avoiding long delays for these essential research services. They have also taken advantage of the Human Embryonic Stem Cell Core Facility at Children's Hospital Boston, a unique program that offers expertise, hands-on training, and seminars in the highly specialized field of mouse and human embryonic stem cell research.

In addition, HSCI's researchers have tapped the resources of the Center for Human Cell Therapy/HSCI Translational Research Program, which assists with the complex process of ushering potential cell-based therapies from the laboratory into the clinic (*see sidebar*, *page 19*).

Last year, HSCI made significant investments in two new, large-scale core programs that are further accelerating the pace of research—the Therapeutic Screening Center and the Genome Modification Facility—both of which are now fully operational. Like the other HSCI cores, these state-of-the-art facilities are providing valuable services to and, just as importantly, forming productive collaborations with scientists throughout HSCI.

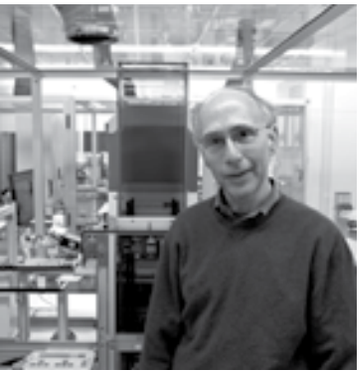
Led by Lee L. Rubin, PhD, the Therapeutic Screening Center (TSC) is a unique program within a university-hospital setting, bridging the gap between basic research and traditional pharmaceutical approaches with the goal of rapidly moving HSCI's discoveries from the laboratory into the clinic. Among the services provided by the TSC are sophisticated, high-throughput technologies rarely available in an academic

"Because stem cell research is considered too new or risky by many venture capital investors, HSCI's Therapeutic Screening Center represents a new, but increasingly vital, step along the pathway from basic discoveries made in the academic-hospital setting to the development of new therapies for the benefit of patients."

—Lee L. Rubin, PhD, Director, Therapeutic Screening Center

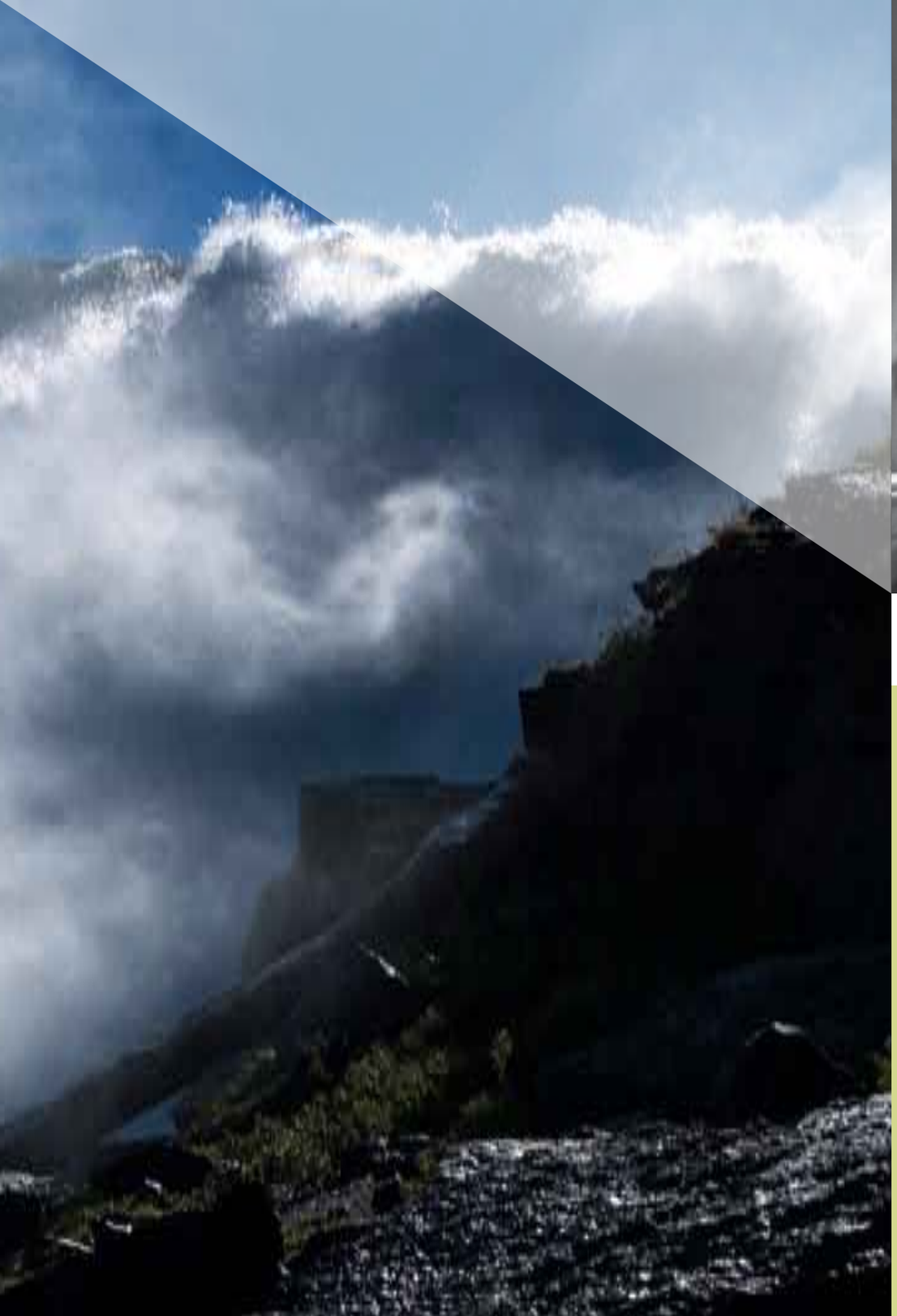
environment, highly specialized scientific expertise from the biotech sector, and a diverse library of compounds with which to search for potential therapeutic agents.

Working in close collaboration with investigators throughout HSCI's disease-focused programs, the TSC identifies the factors that direct adult and embryonic stem cells to proliferate and differentiate—information that could lead to the discovery and development of novel drugs for use in patients or to produce cells for transplantation.



Although the TSC's scheduled projects span multiple disease areas, from diabetes to lung cancer, one major focus is motor neuron diseases. The TSC now has the unprecedented ability to generate billions of motor neurons a week from embryonic stem cells, including disease-specific embryonic stem cells derived from mouse models, making it possible to screen for potential therapeutics in the specific neuronal cell type affected by these diseases.

The Genome Modification Facility (GMF), directed by Manfred Baetscher, PhD, and overseen by Andrew McMahon, PhD, uses ultra-sophisticated techniques and specialized equipment to create novel strains of mice (transgenic mice) and mouse models of specific diseases, which are essential research tools to many stem cell scientists. The often-delicate procedures used to create these mice require technical skills, expensive micromanipulation equipment, and special procedures beyond the capability of most laboratories.



Stem Cell-Based Treatment Being Developed for Clinical Trials

Every year, one in every 2,500 children born in the United States has a condition in which the diaphragm does not close completely during fetal development (congenital diaphragmatic hernia), allowing some organs to migrate into the chest cavity. Typically, the opening is closed with a Teflon patch shortly after birth.

Stem cell research may lead to a more enduring solution—a “stem cell patch” grown from stem cells isolated from the mother’s amniotic fluid prior to the child’s birth that, unlike the Teflon version, can grow with the child.

This novel approach, led by Children’s Hospital Boston pediatric surgeon Dario O. Fauza, MD, is in the process of development for clinical trials within the Center for Human Cell Therapy/HSCI Translational Research Program, headed by Leslie E. Silberstein, MD. HSCI has provided support for the necessary validation studies to obtain approval from the Food and Drug Administration for these trials.

SUPPORTING innovative investigations

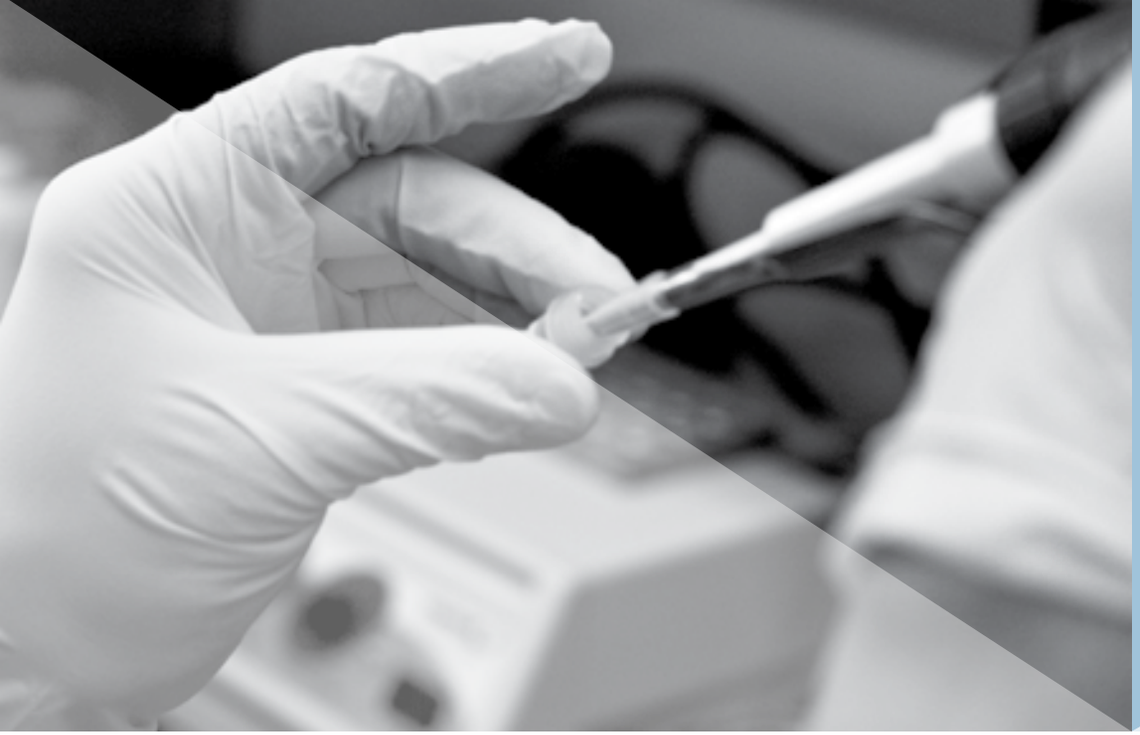
Federal limitations on human embryonic stem cell research and the de facto decline in federal dollars for all biomedical research—coupled with the fact that stem cell research is in its relative infancy and, thus, considered too high risk by some private investors—can make it difficult for stem cell scientists to obtain adequate funding for their work.

To help address this challenge and create momentum in stem cell research, in 2005 HSCI established its Seed Grant Program, which provides early-stage funding for investigations in diverse areas of stem cell research that are aligned with HSCI's mission.

In the short time since the program's inception, HSCI has awarded 35 grants totaling $6.3 million to dozens of investigators throughout the HSCI research community. These scientists are conducting investigations spanning a broad range of areas, from basic stem cell biology to stem cell-based therapies for a host of prevalent diseases, including cancer, diabetes, and neurodegenerative conditions such as Parkinson's disease and amyotrophic lateral sclerosis (ALS). Research supported by HSCI seed grants has already contributed to significant scientific advances.

HSCI seed grant recipients are selected in a rigorous review process conducted by a multi-institutional panel of HSCI-affiliated experts. While the awards are based on scientific merit, the highest priority is given to projects that would be difficult to fund from other sources—either because they involve human embryonic stem cells or are considered too high risk by conventional funding sources. The grants are also intended to support junior faculty conducting collaborative research.

Each seed grant is generally awarded for a two-year period, with recipients receiving a total of $180,000.



"The research we carried out with our HSCI Seed Grant funding was a huge success. We were able to show that embryonic stem cells can be used to create limitless quantities of cells for the study of ALS (amyotrophic lateral sclerosis). In addition to enabling a new approach for the study of human disease, these results have made it possible for us to secure subsequent funding from other sources."

—Kevin C. Eggan, PhD, 2005 Seed Grant recipient

2007 HSCI seed grant recipients

Li Chai, MD / *Brigham and Women's Hospital*
Zheng-Yi Chen, PhD / *Massachusetts General Hospital*
Dieter Egli, PhD* / *Harvard University Faculty of Arts and Sciences*
Richard Gregory, PhD* / *Children's Hospital Boston*
Benjamin Humphreys, MD, PhD / *Brigham and Women's Hospital*
Carla Kim, PhD / *Children's Hospital Boston*
Kameran Lashkari, MD / *Schepens Eye Research Institute*
Stuart Orkin, MD / *Children's Hospital Boston*
Sridhar Rao, MD, PhD / *Dana-Farber Cancer Institute*
and Ibrahim Domian, MD, PhD / *Massachusetts General Hospital*
Sabina Signoretti, MD / *Brigham and Women's Hospital*

** The Paul Singer Family Foundation supported the work of these two investigators, who are conducting human embryonic stem cell research. HSCI gratefully acknowledges this generous gift.*

2006 HSCI seed grant recipients

Raymond Anchan, MD, PhD / *Brigham and Women's Hospital*
Scott Armstrong, MD, PhD / *Children's Hospital Boston*
Bradley Bernstein, MD, PhD / *Massachusetts General Hospital*
Keith Blackwell, MD, PhD / *Joslin Diabetes Center*
David Breault, MD, PhD / *Children's Hospital Boston*
Rona Carroll, PhD / *Massachusetts General Hospital*
Konrad Hochedlinger, PhD / *Massachusetts General Hospital*
Hanno Hock, MD, PhD / *Massachusetts General Hospital*
Charles Lin, PhD / *Massachusetts General Hospital*
Anjana Rao, PhD / *Immune Disease Institute (formerly CBR Institute for Biomedical Research)*
Rosalind Segal, MD, PhD / *Dana-Farber Cancer Institute*
Yaming Wang, MD / *Brigham and Women's Hospital*
Jing-Wei Xiong, PhD / *Massachusetts General Hospital*

A gift from an anonymous donor supported four 2005 HSCI Seed Grants for work focused on human embryonic stem cells.

INFORMING the public

Few areas of science are as passionately debated, yet as frequently misunderstood, as stem cell research. As the leader in this emerging field, HSCI is committed to providing the public with an accurate, unbiased understanding of stem cell research and the many scientific, legal, ethical, and political issues that surround it.

During the past year, HSCI has actively sought out opportunities to inform the public about stem cell research at the regional and national level. For instance, the Institute launched the HSCI Public Forum, a series of free, quarterly educational sessions geared to a lay audience. Each Public Forum draws 100 or more people from all walks of life to listen to experts representing diverse disciplines and points of view discuss and debate many facets of stem cell research.

The inaugural Public Forum featured the authors of three books on stem cell science, who addressed the current state of stem cell research. Representatives of the world's major religions came together at Harvard Divinity School to discuss religious perspectives on stem cell research at the second Public Forum. The season's final forum, "Stem Cell Science 101," covered the basics of stem cell research—from the definition of a stem cell to the concept of reprogramming and more. This popular, informative series will continue on a quarterly basis throughout 2007-2008.

HSCI scientists and research advances were also regularly and prominently featured in local and national media throughout the year as part of a concerted effort to educate the public about the many dimensions of stem cell research.

For example, HSCI faculty appeared on National Public Radio's "Science Friday" and Public Broadcasting System's Charlie Rose Science Series. They were also interviewed by and profiled in influential newspapers and magazines throughout the nation, including the *New York Times*, the *Washington Post*, the *Wall Street Journal*, the *Boston Globe*, and *Time* magazine, among many others.

In June, HSCI held a joint press conference with Massachusetts Institute of Technology to announce progress toward one of the major milestones of regenerative medicine—cellular reprogramming—which was covered extensively by media around the world.

HSCI also played an active role in community events, including the first Cambridge Science Festival, a nine-day public event that showcased the city's many contributions to science and technology. During the festival, HSCI partnered with the Radcliffe Institute for Advanced Study to hold a town meeting on stem cell science that focused on several topical issues, including the significance of stem cell science and the ethical and social implications of this research.

HSCI's newsletter, *Stem Cell Lines*, was launched last fall, bringing news about the Institute's research, faculty, events, and programs to friends and supporters of HSCI three times a year. The newsletter augments several other regular HSCI communication vehicles, including a new weekly electronic update and a monthly research e-newsletter.

Throughout the coming year, HSCI will continue to reach out to members of the public in myriad ways—giving them unbiased information with which to make well-informed, thoughtful decisions about stem cell research.

FOSTERING collaborations

HSCI is a powerful convening mechanism with the unique ability to foster collaborations not only in biomedical research, but also in all other fields that intersect with stem cell research, such as law, business, education, religion, and government.

For researchers to make headway against the complex, challenging diseases for which stem cell research holds promise, it is imperative that they collaborate frequently and openly—to share ideas, insights, discoveries, knowledge, successes and, as is inevitable in any scientific endeavor, setbacks.

With its extensive network of faculty throughout all of Harvard University, HSCI is a remarkably powerful convening mechanism with the unique ability to foster such collaborations—not only in biomedical research, but also in all other fields that intersect with stem cell research, such as law, business, education, religion, and government.

During the past year, HSCI developed many productive collaborations through a range of internal and external initiatives, some of which were enhancements of previous efforts and several of which are new. Several collaborative projects involving HSCI scientists and their colleagues around the globe—in New York, the United Kingdom, and Sweden, to name just a few—have come out of various think tanks, colloquia, and mutual laboratory visits during the year.

One high-profile new event, held last October in Cambridge, was HSCI's first Stem Cell Leadership Summit. This stimulating daylong program brought together several hundred prominent stem cell scientists, ethicists, venture capitalists, biotech leaders, and supporters of stem cell research from around the nation for talks and discussions on how to ensure that stem cell science fulfills its promise.

Building on the momentum from the first summit, HSCI's second Stem Cell Summit, in October 2007, will be expanded to a two-day event in Boston that focuses on the entire breadth of stem cell research, from scientific advances and political issues to business opportunities. Among the highlights of this year's Stem Cell Summit will be a panel discussion among a group of U.S. governors, moderated by former New Hampshire Governor Jeanne Shaheen, who now directs the Institute of Politics at Harvard's Kennedy School of Government.

In October 2006, the Third Annual Tony & Shelly Malkin Symposium drew nearly 500 participants, who interacted with colleagues and heard presentations about promising new research involving cellular reprogramming by leaders in the field. The Fourth Annual Malkin Symposium, which will focus on cancer stem cells, will take place in November 2007.

Worldwide Collaborations

This past year, HSCI hosted members of the parliaments of both Norway and Great Britain, who were eager to learn about and collaborate on social policy issues related to stem cell research. HSCI faculty also traveled extensively throughout the United States and abroad—from Argentina to Australia—to conduct classes, give lectures, and collaborate with their peers in the international scientific community.

In addition to scientific interactions, this past year HSCI hosted members of the parliaments of both Norway and Great Britain, who were eager to learn about and collaborate on social policy issues related to stem cell research. HSCI faculty also traveled extensively throughout the United States and abroad—from Argentina to Australia—to conduct classes, give lectures, and collaborate with their peers in the international scientific community.

As in years past, HSCI's popular inter-lab meetings, held five times a year at Harvard Medical School, continued to draw 200-plus attendees to share their work and collaborate with others within HSCI research community. HSCI also continued its monthly Seminar Series at the Massachusetts General Hospital Center for Regenerative Medicine, which features presentations on a broad range of topics by leading international scientists, enabling HSCI to stay engaged with the broader stem cell research community.

This spring, the governor of Massachusetts announced a new funding initiative for the life sciences. HSCI and related institutions within the state were frequently consulted in the development of that plan. A significant part of the announcement was the establishment of a stem cell bank at the University of Massachusetts, to which HSCI will contribute its stem cell lines—the most created within any single institution in the world. HSCI will also help provide training and other related services.

Collaboration within HSCI was further strengthened by HSCI's Second Annual Retreat, held in June. More than 300 members of the HSCI research community attended the daylong event, which featured updates on HSCI's progress and future plans, presentations by the leaders of HSCI disease programs and core facilities, and scientific poster presentations.

Because HSCI is such a large, diverse, and geographically dispersed community, internal communication is absolutely essential to fostering and maintaining ongoing collaborations. One of the most exciting internal initiatives launched last year was HSCI's new intranet service, "iStem." Although in its early stages, iStem gives the entire HSCI research community a versatile and powerful new tool for collaboration.

EDUCATING future generations

As an integral part of Harvard University, HSCI shares the university's commitment to education at all levels. Because stem cell research extends well beyond the traditional boundaries of science, HSCI is actively involved in educating not only future generations of scientists, but also current and aspiring teachers, journalists, ethicists, business executives, and policymakers.

Drawing on the wealth of expertise of faculty across the University's many medical and research institutions and schools, last year HSCI continued and enhanced its existing education programs, while launching several exciting new initiatives. The 2006 calendar year ended with HSCI Co-Director Douglas A. Melton, PhD, giving the annual Howard Hughes Medical Institute holiday lecture series to a national audience of high school students on the topic of stem cell science.

Building on this momentum, HSCI developed a pilot course for grades 9–12 science teachers and curriculum-development specialists. This weeklong, credit-eligible course covered a broad range of topics, from the current state of stem cell research to the ethical and legal implications of this work, and included visits to HSCI laboratories and facilities. In future years, this course will be open to all educators interested in integrating stem cell science into their curriculum.

In March, HSCI faculty presented workshops at the Annual Symposium on Biotechnology Education at Boston's Museum of Science, giving middle school, high school, and community college educators the information, resources, and tools they need to teach their students the basics of stem cell science.

Another important, ongoing initiative is the HSCI Medical Scientist Training Fellowship, which provides a two-year stipend to support the training of qualified physician-scientists (combined MD/PhD students) whose thesis project or long-term research goals involve stem cells. With the decrease in federal funding for physician training, this program helps talented, bright young men and women fulfill their promise as clinicians and scientists.

Now in its third year, HSCI's Summer Undergraduate Research Internship Program continues to be a powerful learning experience for students who are considering a career in some aspect of stem cell science, whether research, science journalism, or a related field.

"I was very lucky to have had two months to be absorbed in stem cells—working in the lab with them, attending seminars about them, discussing them with my fellow interns and HSCI faculty, and even teaching local high school students about them. This internship made me more certain about my passion to pursue a career in research."

—Ahmad Mahran, a student at Ain Shams University, Egypt, and a 2007 HSCI summer research intern

Last year, thanks to a grant from the Howard Hughes Medical Institute, the program broadened its reach to include students from universities and colleges well beyond Harvard; this year's group comprised students from across the United States, as well as the United Kingdom and Egypt. Thus far, 91 students have participated in this unique educational experience, during which students work in HSCI labs under the guidance of mentors, give talks, and write papers.

Exposing undergraduates to the possibilities and excitement of stem cell research also led to the creation of the Harvard College Stem Cell Society, a student-run club that recently launched an initiative to engage local high school students in science writing as a possible career opportunity.

As in previous years, HSCI faculty from many HSCI-affiliated schools and medical institutions continued to teach undergraduate and graduate-level courses and seminars on topics ranging from basic stem cell biology to the ethical and societal issues that are unique to stem cell research.

Teaching is not confined to Cambridge and environs; in June, four HSCI faculty members traveled to Argentina to teach young Latin American graduate and postdoctoral students about stem cell biology through the Program for the Advancement of Biomedical Sciences Education (PABSELA), a Harvard Medical International program.

SHAPING the ethical debate and public policy

Many areas of science and medicine touch on issues of morality, from euthanasia to genetic engineering. But perhaps no other realm of contemporary science is viewed more frequently through an ethical lens than stem cell research, which focuses on such fundamental—and, to some, unanswerable—questions as to when life begins.

Rather than shying away from these provocative questions, since its inception HSCI has taken a leadership role in guiding the ethical debate about stem cell research as well as shaping public policy through its Program in Ethics and Public Policy. It has done so not to espouse a particular agenda. Rather, the goal is to stimulate thought and discussion, and to educate the Harvard biomedical research community, local and national policymakers and opinion leaders, and the public alike about the ethical and public policy implications of this research.

As an integral part of HSCI, this program is actively involved in teaching, domestic and foreign policy discussions, educational conferences and symposia, public-education programs, media events, and many other activities. A number of these are conducted in collaboration with existing programs in ethics and health care policy at schools throughout Harvard, including its schools of law, medicine, and government.

Last spring, for example, HSCI's Program in Ethics and Public Policy teamed with Harvard Law School's Petrie-Flom Center for Health Law Policy, Biotechnology, and Bioethics and Harvard University's Program in Ethics and Health to sponsor "Re-engineering Human Biology," an interdisciplinary conference that explored many of the legal and ethical implications of today's biotechnology, including stem cell research.

"The distinction between a potential person and an actual one makes a moral difference. Sentient creatures make claims on us that nonsentient ones do not; beings capable of experience and consciousness make higher claims still. Human life develops by degrees." *—Michael J. Sandel, DPhil, Director, Program in Ethics and Public Policy*

For the second consecutive year, HSCI also continued to generate plenty of lively debate among Harvard undergraduates enrolled in "Ethics, Biotechnology, and the Future of Human Nature." This enormously popular course is taught by Michael J. Sandel, DPhil, director of the Program in Ethics and Public Policy, and HSCI Co-Director Douglas A. Melton, PhD. Sandel, a Professor of Government at Harvard, also teaches a Harvard graduate-level seminar, "Ethics and Biotechnology," that explores the moral and political implications of recent advances in biotechnology, and speaks and writes frequently about these topics.

HSCI also encourages regular discussions and debate about ethical issues related to stem cell research among its research community by supporting the popular Bioethics Brown Bag Discussions—a bi-monthly series of informal lunchtime forums at Children's Hospital Boston. These get-togethers have been so well-received that in the coming months HSCI will support similar groups at Massachusetts General Hospital and Brigham and Women's Hospital.

HSCI faculty also play an active role in shaping state and national public policy on stem cell research. Last year, for instance, HSCI faculty briefed members of Congress on embryonic stem cell research, as well as legislators and policymakers in the states of Connecticut, Maryland, and California. HSCI faculty also spoke at a National Academy of Sciences (NAS) public symposium in Washington, D.C. on national guidelines for human embryonic stem cell research. Other HSCI faculty serve on an advisory committee for the NAS guidelines, which were established in 2005 to encourage responsible practices for privately funded human embryonic stem cell research.

SELECTED scientific publications

In biomedical research, the "coin of the realm" is publication in leading peer-reviewed scientific publications, which disseminate information to scientists throughout the world.

By this measure, HSCI is wealthy indeed. From June of 2006 through June of 2007, more than 280 papers—an average of more than 20 a month—by HSCI faculty were published in influential journals like *Nature*, *Nature Neuroscience*, *Cell*, *Science*, *Cell Stem Cell*, and many, many others.

What makes HSCI's list of recent scientific papers noteworthy is not just the high number, although that is certainly impressive. What distinguishes this list is the breadth of disciplines it represents: blood (62 papers), cancer (30), cardiovascular disease (34), diabetes (14), development (46), nervous system diseases (22), technology (13), imaging (18), and so on. Indicative of the highly interdisciplinary nature of HSCI's research, HSCI's 2006–2007 papers span 14 different areas of investigation.

Following is a partial list of scientific papers by HSCI principal faculty members published in the previous year. For the complete list, please visit our website at **www.hsci.harvard.edu.**

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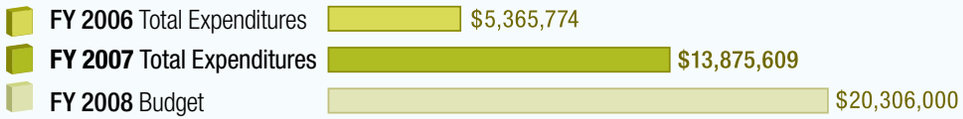
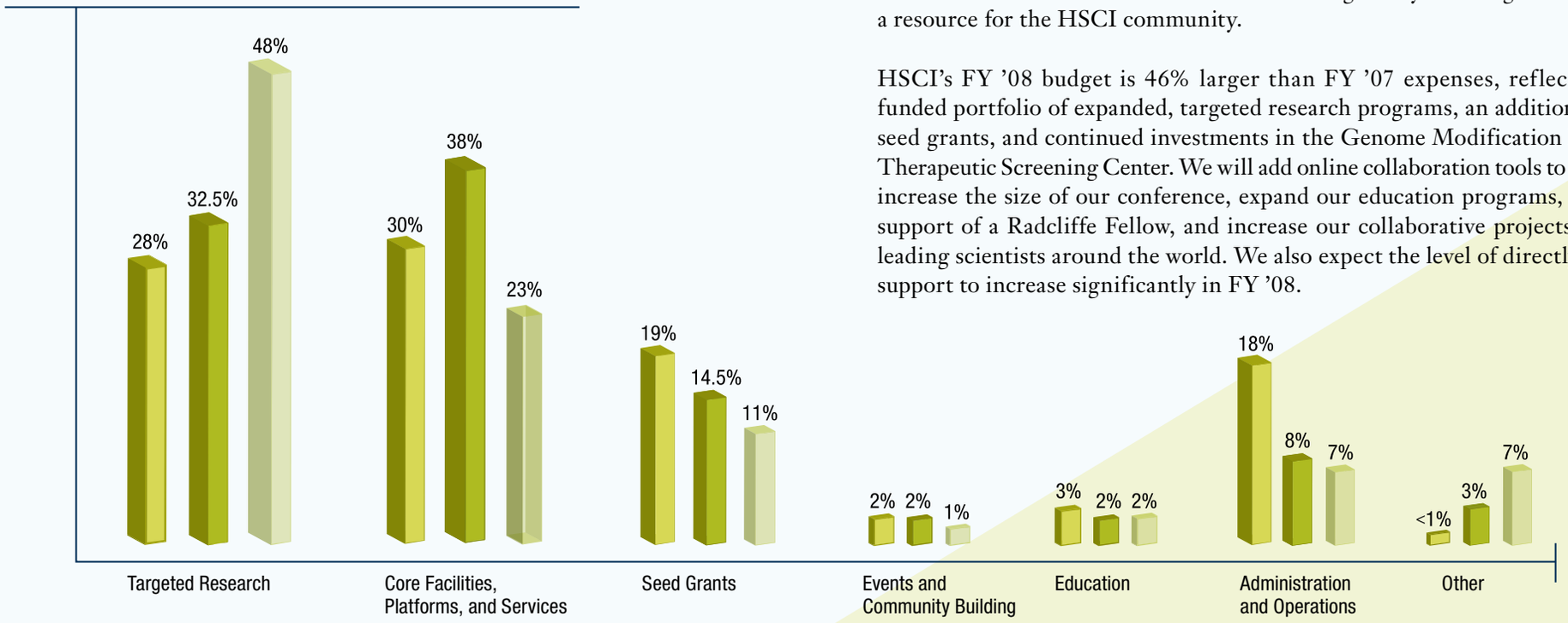
FINANCIAL REPORT

Fiscal year 2007 (July 1, 2006–June 30, 2007) was a year of continued growth in all programmatic areas for Harvard Stem Cell Institute. In total, HSCI spent $13.9 million in FY ’07, an increase of almost three-fold from FY ’06 ($5.3 million).

Our investment in research—seed grants; core facilities, platforms, and services; and targeted research programs—represented 85% of total expenses. This compares to 77% in FY ’06. In addition to the ramp-up of our major disease programs, specific research investments of note this past year included the launch of the Therapeutic Screening Center and the Genome Modification Facility.





Events and community-building activities consumed only 2% of expenses but continued to be a key component of our work. New in FY ’07 was our first external conference, the Stem Cell Leadership Summit. HSCI also participated in talks and an exhibition at the biotechnology industry’s annual convention in Boston, BIO International 2007.

Ongoing HSCI educational endeavors include the Summer Undergraduate Research Internship Program, the Medical Scientist Training Fellowship, and support of the Harvard undergraduate Stem Cell Society. The HSCI Program in Ethics and Public Policy co-sponsored its first conference with the Harvard Law School. Also new in FY ’07 was the quarterly Public Forum series.

In the administration area, we rebuilt our website on a new technical platform that allows for easier and more frequent updating. We also added content so that the HSCI website can serve as an information gateway for the general public and a resource for the HSCI community.

HSCI’s FY ’08 budget is 46% larger than FY ’07 expenses, reflecting a fully funded portfolio of expanded, targeted research programs, an additional round of seed grants, and continued investments in the Genome Modification Facility and Therapeutic Screening Center. We will add online collaboration tools to our website, increase the size of our conference, expand our education programs, incorporate support of a Radcliffe Fellow, and increase our collaborative projects with other leading scientists around the world. We also expect the level of directly sponsored support to increase significantly in FY ’08.

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FACULTY
47 Principal Faculty
84 Affiliated Faculty

SCIENTISTS
750+

SCIENTIFIC PUBLICATIONS
(June 2006–June 2007)
280+

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