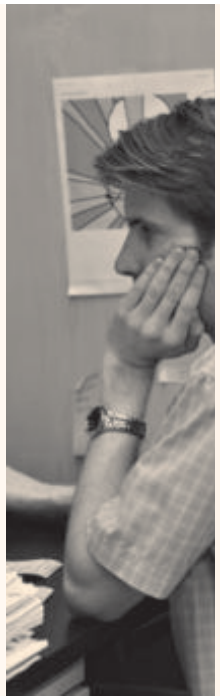
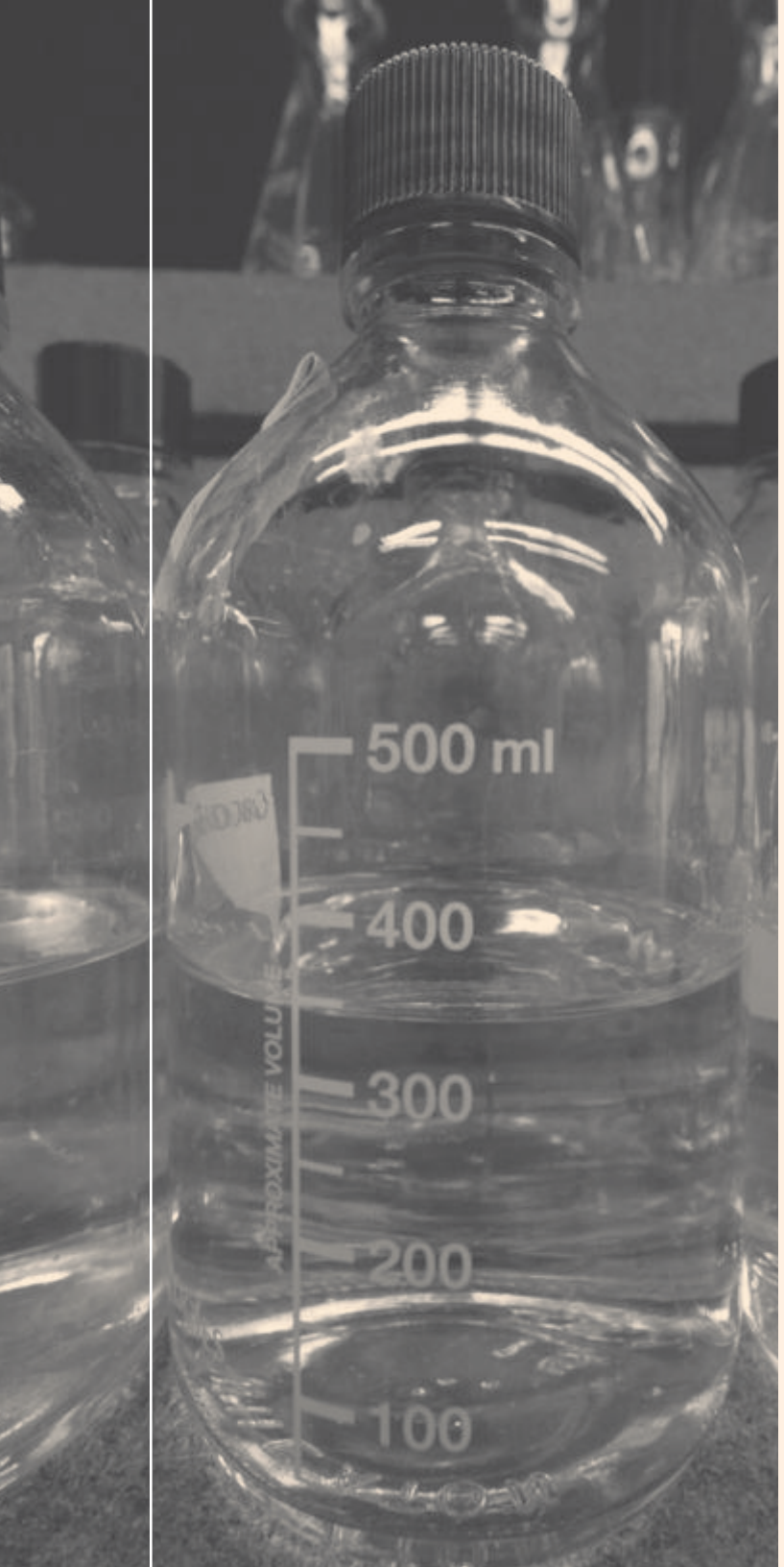


PROGRESS



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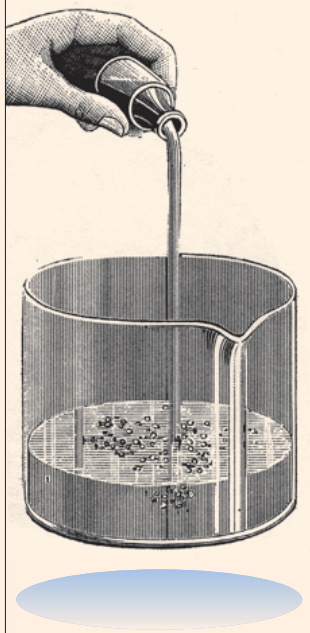


PROGRESS

In his book *The Structure of Scientific Revolutions*, philosopher Thomas Kuhn describes science as progressing in two separate but complementary phases. During "normal science," researchers are building on previous discoveries, asking the next logical questions, and filling in the gaps to support well-established theories. "Revolutionary science" occurs when evidence for a new theory is established, thus raising unexplored questions to be answered by "normal science." These paradigm shifts, as Kuhn calls them, are critical in opening up new avenues of research, but are unable to move a scientific field forward without the work that occurs during the "normal" phase. Paradigm shifts are much like the discovery of a new continent—an achievement that marks the potential for exploration rather than an end in itself.

This past year has been an exciting one for stem cell research, which in many ways has been the product of both normal and revolutionary phases. Step-wise progress has been made across all regions of the field, as holes in our understanding of stem cell biology have been filled and paths toward clinical applications uncovered. More dramatically, the paradigm shift of cellular reprogramming took place, creating new opportunities for scientists working across different diseases, tissue types, and animal models.

On both of these fronts, it has been a particularly exciting year for the Harvard Stem Cell Institute. After four years of research, collaboration, and momentum, HSCI has demonstrated its ability to push the field forward and make substantial progress toward the ultimate goal of truly understanding disease processes and the development of treatments. There is a long journey ahead, but today there is land where there was once only water and sea monsters. And for that we celebrate our progress and carefully plan for the days of exploration to come.

FROM THE SCIENTIFIC DIRECTORS

Progress. There's a word with a myriad of different meanings, depending upon who is using it or reading it. And never are the understandings of what constitutes progress so different as when scientists and non-scientists are discussing developments in science and medicine. For those without training in the biological sciences—especially for those suffering from a serious chronic illness, or those whose families members are suffering—advances in stem cell science seem to be coming at a frustratingly slow pace. But those of us whose lives are anchored in the laboratory and clinic are constantly astounded at how fast the field is moving. In fact, we can both safely say that at no point in our careers have we seen so much progress in so little time in any other field.

Progress? Just in the past year Harvard Stem Cell Institute researchers have created a stem cell line from the skin cells of patients with Lou Gehrig's Disease—ALS—and coaxed those stem cells to develop into those very brain cells that die in patients with ALS. Progress? This is the first time that it has ever been possible to produce the cells needed to study a disease in a lab dish.

Progress? Just in the past year HSCI scientists for the first time demonstrated that transplanted muscle stem cells can both improve muscle function in mice with a form of muscular dystrophy and replenish the stem cell population for use in the repair of future muscle injuries. Progress? A year ago, we didn't know if this kind of cell therapy would ever be possible.

Progress? Just in the past year HSCI scientists have not only improved on the methodology for producing stem cells using the recently discovered iPS technique, they have also been at the forefront of advancing our understanding of how that reprogramming works. Progress? Without that understanding we cannot take the steps that will be necessary before we can safely use iPS cells to treat diseases in people.

Progress? HSCI scientists have actually discovered in mice a way to directly reprogram one form of adult cell to turn it into another—a finding that may turn on its head current concepts of regenerative medicine. Progress? Just imagine what it would mean to be able to turn common pancreatic cells into the precious insulin-producing beta cells destroyed in diabetes, or turn support cells in the brain into the motor neurons killed in ALS.

To those whose lives depend upon multiple, daily injections of insulin, or those who are watching their mother's Parkinson-afflicted hands shake more uncontrollably every day, or those who have watched a beloved father disappear into the fog of Alzheimer's disease, progress must seem a cheap word.

But to those of us struggling to solve some of the most basic, difficult questions ever asked of scientists, this has been a year of truly astounding progress. And we believe that, by the time you finish reading this, the Harvard Stem Cell Institute's third Annual Report, you will agree with us and will share our optimism and excitement for the year to come.

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

FROM THE EXECUTIVE DIRECTOR

Having read the Scientific Directors' letter, you already know why we decided on "Progress" as the title and overarching theme of this, the third Harvard Stem Cell Institute Annual Report. I have little doubt that as you read the summaries of what our scientists have accomplished this year, you will indeed agree that progress is the word that best describes what has been achieved in the past 12 months.

But before you turn the page, I'd like to take just a moment to briefly describe a different kind of progress we at HSCI have made this year, the kind of progress that rarely makes it onto front pages or into evening newscasts—and that is the progress we've made in establishing the *institution* of HSCI, and all that that entails. Consider, for example, the work that has been expended on establishing and expanding relationships with and among Harvard's affiliated hospitals, where the laboratories of most of our scientists are located. Those relationships include not only the scientific collaborations among our researchers—the very collaborations that make HSCI so unique—but also the collaborations that have led to the establishment of core facilities, and have also led to successful, groundbreaking agreements on the usually thorny issue of intellectual property rights. It is the progress we've made on these issues, and the strength of our science, that this past year has led to our first collaborations with the commercial sector, including a $25 million collaborative agreement with international pharmaceutical giant GlaxoSmithKline.

Two other major developments provide examples of the institutional progress at HSCI this past year—the establishment of the Department of Stem Cell and Regenerative Biology, the first cross-school department in Harvard's history, and the beginning of construction on the cutting-edge science complex that will house HSCI, the new department, and two other interdisciplinary science initiatives.

The new department will work side by side with the Harvard Stem Cell Institute. HSCI will continue to foster collaboration among all Harvard scientists doing stem cell-related research, will raise funds for that research, will underwrite research, and will continue to engage in activities that extend beyond the purview of a department including exploration of the multiple social, political, religious, ethical, and financial issues that surround stem cell research and active engagement in public policy issues and public education.

At the same time, the Department of Stem Cell and Regenerative Biology will hire faculty, teach undergraduate and graduate courses, and provide an academic home for some of our leading scientists. While the formation of the new department that has responsibility for undergraduate and graduate education and a dedicated faculty strengthens HSCI, the larger network and broader focus of HSCI in turn support the department in its mission. These missions are complementary but distinct. The reach and the resources of Harvard's undergraduate, graduate, and medical schools, together with the affiliated hospitals, will help each group enable the other's mission.

And the new First Science complex, the first building to rise on Harvard's expanded campus across the river in Allston, will provide HSCI with its first real home, a place where some of our scientists will do all their work, and a number of others will have laboratories in addition to those they now have in the hospitals. It will provide a place where researchers can come to share ideas and findings, and work literally side by side in state-of-the-art facilities with neighbors from other disciplines and domains.

In short, we are building a new business model for early stage R&D and believe that we are making good progress. But it is a journey, and our continued progress very much depends upon your ongoing involvement and support.

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

Disease Programs

The greatest strength of the Harvard Stem Cell Institute is the ability to bring together leading researchers and physicians from across multiple disciplines and institutions to work collectively on a specific challenge. Through its disease-specific programs, HSCI supports these focused collaborations by holding think tanks, seminars, and other events; providing access to world-class core facilities; supporting the new ideas of both junior and senior faculty through seed grant awards; and funding basic science and clinical translation research in specific disease areas.

The following section provides an overview of our major disease programs, as well as two technology programs—the Cell Development Program and the new Stem Cell Regulation Program—which have relevance to all of our disease programs.

BLOOD DISEASES PROGRAM

The HSCI Blood Diseases Program was formed to maximize the local scientific expertise in the blood diseases field. The program has two main projects—one, on using the blood system to understand cellular renewal mechanisms; the other, on how to create blood cells from embryonic and other pluripotent stem cells.

The first project's research agenda is focused on identifying the molecular and cellular characteristics and pathways involved in self-renewal of hematopoietic (blood) stem cells. "Turning on" self-renewal is critical for stem cells to expand as needed for regenerating damaged tissues. Similarly "turning off" self-renewal is critical for stopping cell growth and interrupting out-of-control processes such as occur in the perpetuation of malignancy in cancer. Understanding the basis for self-renewal and these controls is central to creating stem cell therapies.

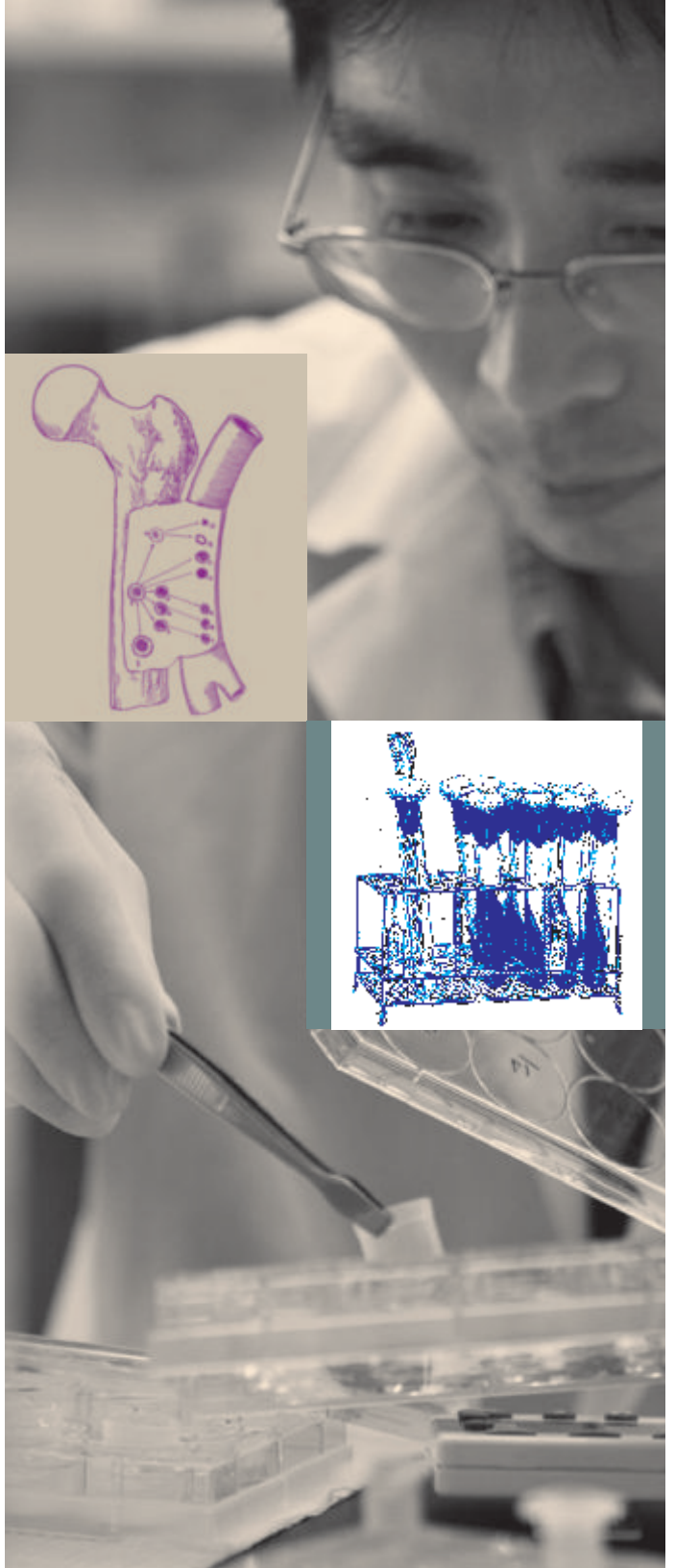
A second, complementary project is focused on creating hematopoietic stem cells from pluripotent stem cells using multiple techniques—parthenogenetic derivation, somatic cell nuclear transfer (SCNT), and direct gene-based reprogramming to produce induced pluripotent stem (iPS) cell lines. A large number of new cell lines have been created, including 12 new human embryonic stem cell (hESC) lines and dozens of iPS lines from patients with hematologic diseases and other conditions. These lines are contributing to studies of immune deficiency and several inherited bone marrow failure conditions. This work in disease-specific cell lines is now being integrated into the new iPS core facility.

Greater Than the Sum of Our Parts In the first project, six sub-projects are under way to study mechanisms of differentiation, epigenetic traits, and niche characteristics of hematopoietic stem cells in several models, including embryonic stem cells, adult hematopoietic stem cells, and leukemia stem cells. 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, and computational tools.

All six of the sub-projects have produced multiple data sets from their experiments, and though each lab has conducted its own analysis, the data's full potential in analyzing the data sets from across labs and experiments is limited by the time and resource restrictions of each lab. Seeking to capitalize on this opportunity, the program is creating a common system to support these data sets and enable broad analysis in collaboration with bioinformatics professionals from the Harvard Initiative in Innovative Computing. The first step of collecting and aligning all existing data from the labs is under way.

The program's near-term goal is to complete and test the database using the combined data from these core labs. Once stabilized, the system will be made accessible to the larger blood diseases research community, both for contributing their own data sets to the project and for using the system to enhance their own research.

Forming the basis for a new iPS core facility at HSCI, the disease-specific iPS lines have been derived by reprogramming cells from patients with a variety of genetic conditions that impair bone marrow function, including immunodeficiency, Down Syndrome, Gaucher's disease, and Shwachman-Diamond Syndrome. Researchers are using these lines to study how gene defects influence abnormal hematopoietic development. Investigators in the Blood Program are also comparing the potential of the ESC lines to generate blood following *in vitro* differentiation to that of the cohort of newly derived iPS lines.



A Model for Other Systems Blood is arguably the best-understood mammalian organ system and has become a model for other systems in terms of the study approach, the methods employed, and the tools developed. Consequently, HSCI scientists expect that the regulators of stem cell self-renewal that are discovered in the blood system will also help researchers in other disease areas by determining if stem cells in different tissues share regulatory mechanisms. Similarly, the increased understanding of reprogramming techniques and differences among cell types will apply broadly. The disease-specific cell lines created by this project will jump-start the iPS core facility and accelerate the use of *in vitro* disease-specific models. In addition to providing a deeper understanding of biological processes, this combination of tools, techniques, and model systems will help inform the design of tests and screens for compounds that control the self-renewal process in disease, representing potential therapeutics and a potential market application prior to developing cell-based therapies.

CANCER PROGRAM

Most existing cancer therapies are designed to shrink a tumor mass, but do not eradicate the tumor. Following tumor mass reduction therapy, in 80% of cases the tumor will return and either the cancer or the toxicity of the treatment will be fatal. The HSCI Cancer Program's research is aimed at developing new cancer-eradicating, rather than tumor-shrinking, therapies designed to destroy cancer stem cells, which are believed to be responsible for the growth and propagation of tumors.

There is evidence that cancer stem cells exist in central nervous system, colon, pancreatic, and ovarian cancers, however these stem cells cannot yet be positively identified nor can they be purified for therapeutic research. Thus, the program's first goal is to meet this challenge by identifying and purifying colon and ovarian cancer stem cells. The team chose to focus on these two cancers first because the experiments require large tumor tissue samples, which exist in these cancers. HSCI's clinical presence is critical because obtaining the tissue samples for researchers requires access to specialized surgical facilities that treat patients with these diseases.

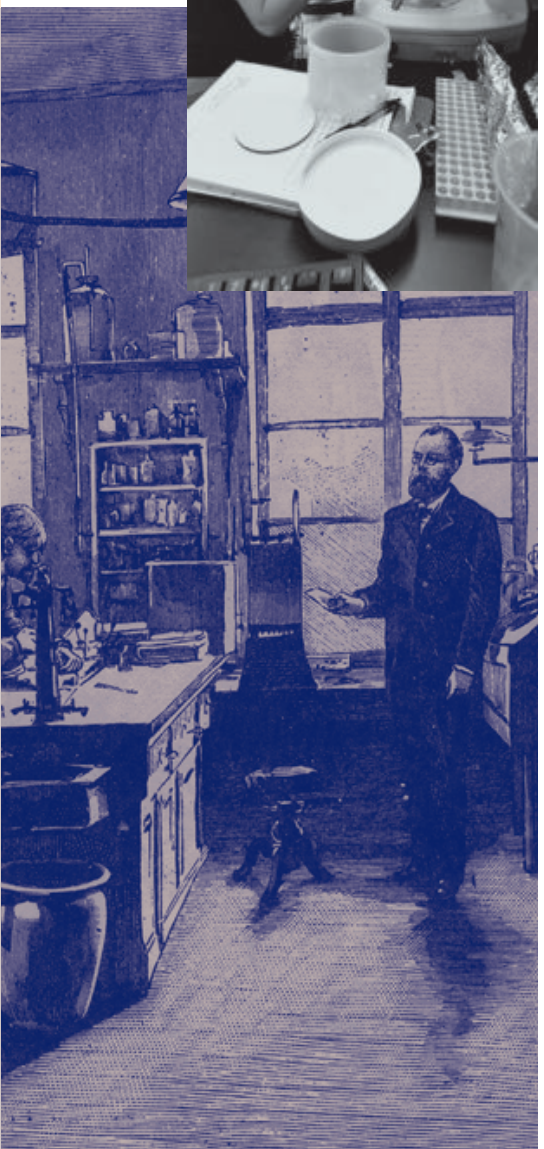
Collaborating with World-Class Hospitals Working in collaboration with HSCI-affiliated surgical oncology hospitals—the Massachusetts General Hospital for ovarian cancer and the Brigham and Women's Hospital for colon cancer—has made the complicated and multi-step process of sample acquisition feasible and has allowed HSCI researchers to identify primary tumor cells in human colon and ovarian cancer. From these primary cells the team has narrowed down the possible cancer stem cell populations to a few candidates in each case.

Screening for Cures The program is also working with purified leukemia cells and has designed a method for efficiently and effectively purifying the stem cells and screening for drugs that could target and destroy leukemia cells without affecting normal cells. There are approximately 200 types of leukemia (the complexity of solid tumors is even greater), and each may have a unique stem cell. However, this technique specifically targets the stem cell properties shared by all leukemia cells, thus avoiding the need to uniquely identify individual stem cell types.

Once the team has successfully identified colon and ovarian cancer stem cells, they will use the method developed for purifying and screening leukemia stem cells to search for treatments for colon and ovarian cancer. This year, HSCI also funded a seed grant that will focus on developing screens for the genes that regulate breast cancer stem cells.

Initiating a Broad Discussion Moderating this year's Malkin Symposium, which focused on cancer stem cells, were Gary Gilliland, Director of HSCI's Cancer Program, and Jerome Ritz, an HSCI Faculty Executive Committee member. Speakers at the event included Owen N. Witte, MD, of the University of California at Los Angeles; John Dick, PhD, of the University of Toronto; Scott Armstrong, MD, PhD, an HSCI Principal Faculty member at Children's Hospital Boston; Kornelia Polyak, MD, PhD, of the Dana Farber Cancer Institute; and Peter Dirks, MD, PhD, of the University of Toronto, Hospital for Sick Children.

CARDIOVASCULAR PROGRAM



The HSCI Cardiovascular Program has three primary aims: create a human model of cardiac disease by studying and working with human heart tissue; advance regenerative and interdisciplinary medicine in human cardiac cell therapy; and, develop the next generation of clinician-scientists.

Progress and Breakthroughs A new opportunity exists to create induced multi-potent cardiac cells using the reprogramming technique developed and refined by HSCI investigators. With this technology, the availability of human muscle tissue is potentially limitless, allowing researchers conduct experiments that were previously not possible. In parallel, the program is moving forward in its hESC research, specifically in the areas of transplant rejection prevention and heart muscle formation—two of the biggest hurdles in heart disease treatment.

In a recent breakthrough, HSCI Cardiovascular Program researchers purified a master heart stem cell. In collaboration with Kit Parker, PhD, of Harvard's School of Engineering and Applied Sciences, and investigators from the Broad Institute and Children's Hospital Boston, exciting follow-up work is being done to apply these master cells to an engineered thin film cardiac strip. The resulting strips of functional heart muscle have already been successfully transplanted in mice.

The development of the cardiac strip is moving the Cardiovascular Program in two critical directions. One research aim is ultimately to translate the cardiac strip technology to human transplantation. The other is to use the strips as new *in vitro* model to screen potential drugs and chemicals for toxicity and effectiveness—an application that has already attracted a high level of private sector interest.

The scientific progress and growing excitement in the cardiac community can be seen by:

- our funding of several new seed grants in the cardiac field
- plans to create disease-specific cell lines with iPS cells from patients with different cardiac conditions to study the diseases and search for new treatments
- comparison of cardiomyocytes derived from iPS cells and ESCs to understand their functional differences at the organ level

Strengthening the Next Generation of Stem Cell Scientists The HSCI Cardiovascular Program has taken a lead role in the training and fostering of the clinician-scientists—MD and MD/PhD investigators—in the HSCI community. Cardiovascular research is just one of the many areas of stem cell biology in which successful research requires not only current stem cell biology knowledge but also a clinical, surgical, and diagnostic understanding of disease in patients. Clinician-scientists will be essential to the translation of research into treatments and cures.

This year, with a gift from GlaxoSmithKline Research & Development Limited (GSK) and in cooperation with the Massachusetts General Hospital, HSCI launched a new Clinician Scientist Program to support these investigators at several stages in their careers and will provide funding for students enrolled in MD/PhD programs, fellowships for junior investigators, and laboratory start-up funds for clinician-scientists, all in the field of stem cell biology. Kenneth Chien MD, PhD, head of the HSCI Cardiovascular Program, will lead the new program.

DIABETES PROGRAM

The HSCI Diabetes Program is composed of clinician-scientists and basic researchers across several institutions and foundations, both HSCI-affiliated and external, who are focused on the central challenge of how to make more beta cells that could be used to treat diabetes.

Research Progress and Scientific Breakthroughs One key research finding established by HSCI faculty is that an adult pancreatic stem cell does not exist. This knowledge has been fundamental in directing the program's focus toward two research goals: turning hESCs into beta cells that could be transplanted into patients and stimulating the existing beta cells in diabetics to replicate.

Making progress toward the first of these goals, HSCI researchers have identified chemicals that can induce hESCs to take the initial two steps in becoming functional beta cells. The Diabetes Program's unique approach in determining the steps that direct the differentiation of beta cells—nicknamed the "molecular biography of the cell"—is now being followed by HSCI's Cardiovascular Program and Nervous System Diseases Program.

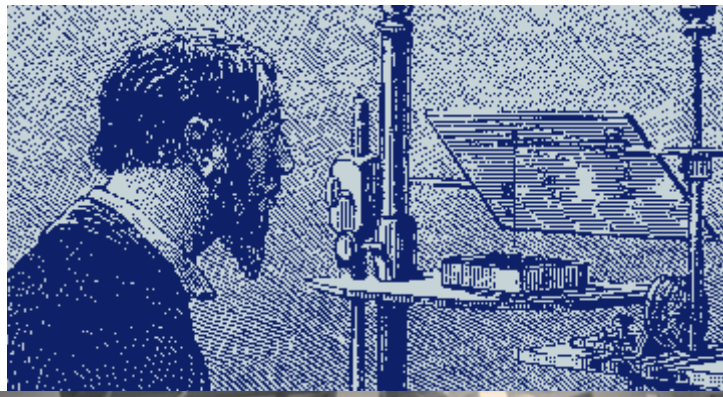
This year, Douglas Melton, PhD, announced a major breakthrough in directly reprogramming pancreatic cells into insulin-producing beta cells. Rather than first reprogramming a cell into an embryonic-like cell and then directing it to become a beta cell, Melton has shown it is possible to directly reprogram one type of pancreatic cell into another. This is a fundamental finding that will drive a new understanding of cellular behavior that is applicable to diabetes and other diseases.

Technology Advancements The program has also moved the field of diabetes research forward through the creation and refinement of new technologies. HSCI researchers are the world leaders in creating hESCs for the purpose of deriving beta cells. These valuable stem cell lines have been sent to hundreds of labs across the globe, at no charge, to speed research. HSCI has created over 40 hESC lines and has distributed more of them than any other institution.

The Diabetes Program's scientists have also created a widely used mouse model to study beta cell regeneration. In this model, a drug that kills the mouse's beta cells is first put into its drinking water. After its beta cells die, the mouse regenerates these cells by the division of the residual beta cells. Experiments are under way to find the signals responsible for this cell regeneration.

Fostering Future Research and Researchers The Diabetes Program's success is due in part to funding of innovative early-stage research. Since 2005, four HSCI seed grants have been awarded to diabetes-related projects that have resulted in several scientific papers and established foundational data that has led to larger research projects. Success also hinges on asking the right questions, and the program aimed to identify these questions at this year's HSCI Diabetes Think Tank. The event provided an opportunity to discuss possible new research avenues, assess current activities, and identify opportunities for additional projects and collaborations.

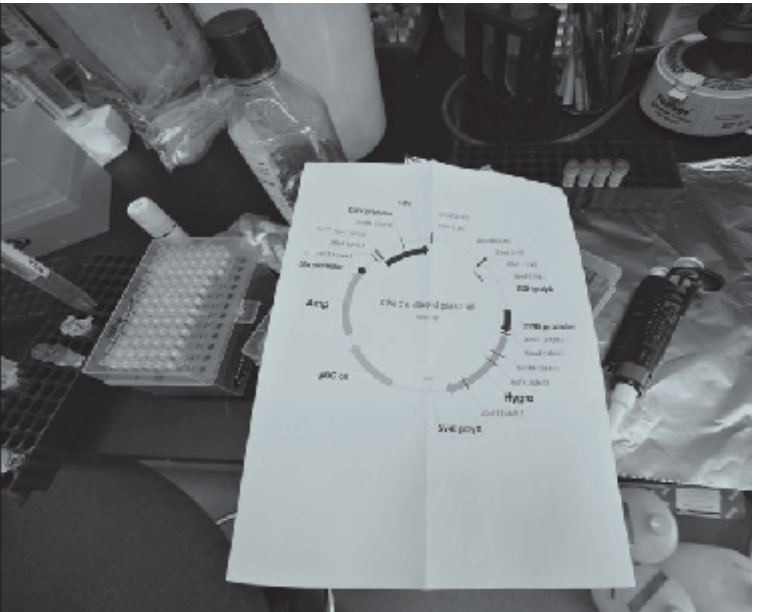
Training the next generation of scientists is also fundamental to the future of the field as a whole. Initiated by a generous donor gift, this year was the first in which HSCI awarded graduate student fellowships to promising students conducting diabetes-related stem cell research.



KIDNEY PROGRAM

The HSCI Kidney Program's central goal is to advance therapies for kidney disease by combining principles of stem cell and developmental biology with an understanding of injury and repair mechanisms. Nephrons, which are the key functional units of the kidney, consist of a filtering unit, the glomerulus, and a complex tubule responsible for filtering the blood. The small tubules collect the filtrate and process it before passing it on to ducts leading to the bladder. If tubules are damaged they can be repaired, but if the damage is severe enough the nephron may be destroyed and the ability of the kidney to function is impaired. Consequently, the team has identified the tubule cells in the kidney nephron as its focus, with a special emphasis on the "proximal tubule cells," which comprise a large part of the nephron.

Understanding Repair Mechanisms Many theories exist on kidney repair. However, a recent study by HSCI Affiliated Faculty member Benjamin Humphreys, MD, PhD, HSCI Executive Committee member Andrew McMahon, PhD, and Joseph Bonventre, MD, PhD, head of the HSCI Kidney Disease Program, and their team went a long way toward elucidating how the tubules repair themselves. By tagging the mature epithelial cells that form the tubule walls with a fluorescent protein, the team was able to demonstrate that the replacement cells after injury are coming from the epithelium itself rather than from circulating stem cells that enter the kidney or from local tissue-specific stem cells in the tissue between the tubules. Cells that derive from the bone marrow and enter the kidney after injury might not be sitting on the sidelines, however. Other evidence suggests that they may be offering some assistance in stimulating the epithelial cells to multiply.



Multiple Skill Sets Applied to Multiple Animal Models This past year, one of the most striking advances in the HSCI Kidney Program has been the solidification of interactions between investigators in traditionally separate specialties, including high-level cell and molecular biology of the kidney, pathophysiology of kidney disease, and developmental biology. The program's researchers have approached fundamental problems with a clinical perspective and both short-term and long-term goals of therapeutic applicability in patients.

Collaboration among HSCI researchers has led to sharing expertise and findings from different model organisms and technologies. In zebrafish, new advances have been made in identifying the various segments of the tubular structure. Because Polycystic Kidney Disease (PKD) is the most common genetic kidney disease and accounts for 10% of all people on dialysis, the team is in the process of creating a PKD-specific iPS cell line. Development of this and additional disease-specific cell lines will enable superior modeling of the disease *in vitro*, leading to a better understanding of disease and ultimately screens for the identification of new treatments.

***In Vitro* Kidney Cells** Another important use of kidney cells grown in the laboratory is to screen drugs for potential toxicity before they are introduced into animals or humans. There is no good model for *in vitro* kidney toxicity screening today because the cells tend to lose their differentiated state and become less "kidney-like" or less "epithelial-like" outside the body. Understanding how to drive an epithelial cell back toward the differentiated state it normally possesses inside the body will enable the development of more accurate preclinical toxicity testing systems. The group's strategy builds on the work of other HSCI researchers that have found that a cell's identity may be governed by only two or three master transcription factors. By "reprogramming" cells using these key proteins, a cell's identity can be changed fundamentally.

"We will also be working with Lee Rubin's group at the HSCI Therapeutic Screening Center to help us screen for molecules that modulate the differentiation state of cultured epithelial cells. If we can do that, we can use them for toxicology and for more sophisticated kidney assist devices," Bonventre said. Taking this technology back inside the body, one might even use the differentiated cells to create artificial tubules and nephrons with the help of bioengineered materials—completing the regeneration that the kidney is unable to do on its own.

NERVOUS SYSTEM DISEASES PROGRAM

The HSCI Nervous System Diseases Program's mission is to develop new and effective therapies for diseases of the nervous system, especially those involving the degeneration of or injury to specific cell types. Because the nervous system includes so many distinct types of neurons, glia, and functional circuitries, the program is organized into the following five research groups: motor system disorders (including ALS, spinal cord injury, Huntington's disease, forms of cerebral palsy, and stroke); Parkinson's disease; retinal disease; hearing disorders; and glial-based disorders (including multiple sclerosis and forms of cerebral palsy).

Each of these groups is trying to answer three key questions:

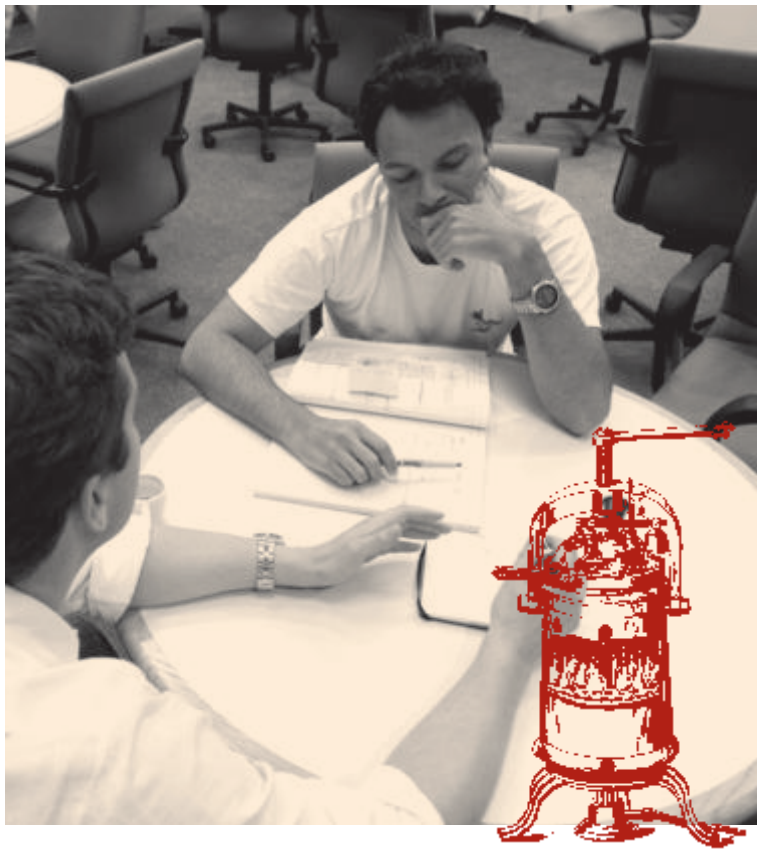
- Do adult stem cells that have the ability to differentiate into the key types of neurons or glia exist within the nervous system?
- What key molecules and genes control the extremely precise differentiation of these cells?
- Can such adult progenitors and/or embryonic stem cells be directed to differentiate into cells that can be used to replace diseased or injured cells—either by local progenitors in the tissue or by cells grown in the laboratory?

Key research findings in the past year include:

- New control genes have been identified that may be critical for nervous system stem cells to define themselves and differentiate into the specific neurons that die in ALS and are injured in spinal cord injury
- Key candidate control molecules in "corticospinal motor neurons" were investigated, and it was discovered that these neurons, central to the diagnosis and morbidity of classic human ALS, degenerate quite early in the most commonly studied transgenic mouse model of familial ALS
- Chemical screening has begun for agents that activate oligodendrocyte progenitors to a remyelinating state, potentially beneficial in both MS and demyelinating forms of cerebral palsy

Technology Advancements New genetically engineered mouse lines are being produced to aid the investigation of specific adult progenitors in the brains of young and adult mice that appear to have the ability to produce replacement neurons for ALS and spinal cord injury.

In another important technological advancement, the ability to create specific nervous system cell types from hESCs has made it possible to achieve both the quality and quantity of cells needed to conduct therapeutic screening in search of small molecules, compounds, gene products, and proteins that could be turned into diverse therapeutics for diseases. At HSCI's Therapeutic Screening Center, headed by Lee Rubin, PhD, Director of Translational Medicine at HSCI, researchers are using this technology to search for treatments for orphan nervous system diseases.



Sparking Collaborations Annual think tanks have been an incredible success and benefit not only the Nervous System Diseases Program but also the international research community. Each year, HSCI assembles world leaders in nervous system disease research to combine their expertise on a specific topic with the objective of identifying key areas of focus for the field and developing collaborative research projects. Throughout the year, monthly program inter-lab meetings, where faculty, postdocs, and students from across different labs present work-in-progress for critical evaluation and advice, have also proven highly valuable to the community as a whole.

OTHER SCIENTIFIC PROGRAMS

Muscle Program

HSCI's support of stem cell research in muscle began with a single seed grant award in 2005 to Amy Wagers, PhD, an HSCI Executive Committee member. In just three years, the HSCI muscle research community has blossomed and notable progress has been made. Journal clubs, reagent sharing, research collaborations, and sponsored grants, including additional HSCI awards, are just some of the results of this enthusiastic and growing concentration.

The program's research focus is on satellite muscle stem cells as they relate to muscle disease and injury and how to make muscle cell transplantation possible. This year, Wagers and colleagues made exciting progress toward this goal by identifying stem cells in adult skeletal muscle that are transplantable and, when transplanted, repair damaged muscle immediately, and regenerate, creating a pool of self-renewing cells that can be activated at a later time in the case of injury. Transplantation of these stem cells in mice with the Duchenne form of muscular dystrophy has shown clear muscle function improvement as well as replenishment of the stem cell population. Experiments were also done with healthy mice in which injury was induced and the same repair and replenishment is seen. In addition to working on other forms of muscular dystrophy and other muscle diseases, the program now plans to apply its learnings from the mouse model to human cells.

Skeletal Program

The HSCI Skeletal Program is focused on research relevant to the engineering of organ parts, such as the tooth germ, from stem cells. In the long term, these studies may lead to the development, either *in vivo* or *in vitro*, of biological or bio-mimetic tooth replacement components suitable for clinical application.

In one set of experiments, the goal has been the construction of tooth germs *in vitro* that could be then grafted into the adult mouse jaw. Concurrent *in vivo* work, funded by the NIH, demonstrated that activation of one particular signaling pathway is sufficient to activate the generation of new teeth. With the support of HSCI, the team has now tested and confirmed this same ability in embryonic stem cells. The aim for the coming year is to conduct similar studies using human embryonic stem cells. The HSCI hESC Training Facility at Children's Hospital Boston provided critical training for the team's investigators who are now planning this transition.

Germ Cell Program

The HSCI Germ Cell (Reproductive System) Program is focused on addressing key questions in ovarian cancer. Because the ovary is regenerative and cyclical, it is hypothesized that a somatic stem cell exists, which regenerates the surface epithelial cells of the ovary, and is responsible for hormone production and ovulation. The team's three goals are to identify and characterize these somatic stem cells of the ovary, understand their relationship to surrounding tissue and their role in ovulation, and characterize the steps that occur if these somatic cells give rise to ovarian cancer. Once the normal somatic cell is characterized, comparisons can be made with malignancies and carcinoma, allowing insight into the steps and genetic switches that occur in the development of cancer.

Using two mouse models previously constructed by Douglas Melton's lab, the team developed a new transgenic mouse that has been used to identify cells that divide very slowly, or very little, in comparison to surrounding cells. This has allowed the team to focus in on a specific population of cells and their specific functional capacities. The single population of cells that was found to divide in response to the ovulatory cycle in mice is believed to be a somatic stem cell population in the ovaries. The next step is to move toward studying human samples, by applying the key findings from the mouse model and identifying a correlated cell population in human tissue.

CELL DEVELOPMENT PROGRAM

"Being an HSCI-funded investigator has held a lot more value than just the dollars and cents of the grant. The faculty interactions at the monthly meetings, inter-lab, and at the poster sessions have been very positive."

– Laurie Jackson-Grusby, PhD, member of the Cell Development Program

Two years ago, the Cell Development Program emerged from the common interest of six HSCI junior faculty members in elucidating the biochemical pathways that control nuclear reprogramming and mechanisms of cellular differentiation. This dynamic program brings together a group of like-minded and collaborative young investigators from five HSCI-affiliated research institutions who are committed to supporting each other's research projects as well as fostering the careers of other junior investigators.

It has been an exciting year for the Cell Development Program. The team's research efforts have established new model systems for testing nuclear reprogramming in cell culture and in whole organisms, and have opened the door to answering fundamental questions in stem cell biology and cell fate determination. Their success has resulted in multiple high-profile publications and provides a compelling example of the advantages gained through collaborative science.

Multiple Breakthroughs One breakthrough publication came from program member Konrad Hochedlinger, PhD, and colleagues, in which his team defined molecularly and temporally the sequence of events that occurs during conversion of adult cells into an embryonic-like state following exposure to virally-introduced "reprogramming genes." This important work on adult mouse skin cells will help researchers narrow the field of candidate chemicals and proteins that might be used to safely turn these processes on and off. Developing such a chemically-based strategy will be essential for many therapeutic uses of

reprogrammed cells because currently researchers must use cancer-causing genes to initiate the reprogramming process, and retroviruses, which could activate additional cancer genes, to insert these genes into the target cells.

Another major breakthrough came from Amy Wagers, PhD, whose lab demonstrated that transplanted skeletal muscle stem cells can engraft to both improve muscle function in mice with a form of muscular dystrophy and to replenish a functional stem cell pool that can be used in the repair of future muscle injuries. This study supports the concept that skeletal muscle contains functional adult stem cells and that transplantation of these cells can support therapeutic muscle regeneration.

Kevin Eggan, PhD, also published a landmark paper that represents the first time scientists are known to have produced human pluripotent stem cell lines from the cells of adult patients suffering from a genetically-based disease. The newly derived stem cells, which were generated from patients with ALS, will be to use to uncover the root cause of this disease and to screen for new drugs that may help treat the disease.

Supporting the HSCI's Mission The Cell Development Program's faculty are some of the most active members of the HSCI community and frequently contribute to the institute's mission beyond the scope of their research projects. By participating in HSCI Inter-lab Meetings, symposiums, retreats, public forums, internship programs, and other internal events and initiatives, these faculty members both encourage scientific exchange and support HSCI's public outreach missions. The faculty also support the research infrastructure of the HSCI, with five members serving as directors of HSCI core facilities, including the newly established iPS core, which is the first effort of its kind and aimed at generating and distributing human disease-specific stem cell lines for research.

Members have also helped foster both inter-state and international collaboration by hosting a Junior Faculty Symposium with colleagues from the California Institute for Regenerative Medicine and working on joint projects with researchers from the United Kingdom Centres of Excellence at Cambridge and Edinburgh. These efforts help accelerate progress by identifying and capitalizing on new opportunities for collaboration by leveraging the unique expertise of the different labs.

A Growing Community Encouraged by both the Cell Development Program's members and its success, a new group of five junior faculty members has come together to establish the new Stem Cell Regulation Program. This exciting collaboration, which was inspired by discussions at events organized by HSCI, will focus on the molecular regulation of stem cell identity, maintenance, and differentiation in normal development and disease.

TRANSLATIONAL PROJECTS

HSCI's mission of "taking out" key diseases would be impossible to achieve without mechanisms to reach the clinic. One of these is The Center for Human Cell Therapy (CHCT). Located at the Immune Disease Institute (IDI) and led by Leslie Silberstein, MD, of Children's Hospital, CHCT was established to provide an infrastructure to rapidly translate novel cell therapy protocols from the laboratory to the clinic and facilitate bench-to-bedside development of cellular therapies. HSCI scientists work with the CHCT to understand what needs to be done to meet regulatory requirements, develop pre-clinical and clinical trial protocols, and work with the FDA and other regulatory bodies to bring therapies to the clinic.

The Stem Cell Patch Every year, one in every 2,500 children in the United States is born with a condition called congenital diaphragmatic hernia, in which the diaphragm does not close completely during fetal development, allowing some organs to migrate into the chest cavity. Typically, the opening is closed with a Teflon patch shortly after birth, and often must be replaced as the child grows. However, stem cell research may lead to a more enduring solution—a "stem cell patch" grown from mesenchymal stem cells (AMSCs) 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 pediatric surgeon Dario O. Fauza, MD, is quickly being moved toward the clinic with the help and guidance of the CHCT. Currently, HSCI is funding a study in large animals with the goal of conducting a study in people within a year. So far results have been positive, showing that the AMSC-based graft can repair the damage and continue to grow with the animal, making further operations unnecessary.

As this project approaches the milestone of first-in-human clinical trials, Fauza has a vision of what might lie beyond. "I believe that transplants' days are numbered ... The fact that you would need a patient to die or to donate part of his or her body to save somebody else is a wonderful gift, but that will never cover the needs of the population. What we've seen so far allows us to have realistic expectations that tissue engineering in our lifetime will eventually be a substitute for transplantation techniques."

Fauza is working on addressing additional types of neonatal defects testing the right combination of cell type, material, structure, and growth environment for the specific applications. In addition to solving critical clinical needs, this work shows how multiple scientific disciplines need to interact and collaborate, how resources and know-how need to be leveraged, and how the clinic and the laboratory need to inform each other if stem cell therapies are to move forward effectively and efficiently.

Other Projects Recent work by HSCI Executive Committee chair Leonard Zon, MD, of Children's Hospital, has led to a Phase I clinical trial with the CHCT to test a drug that has been shown to expand the number of hematopoietic stem cells in cord blood. If successful, this might mean that only one unit of cord blood would be necessary for reconstituting an adult immune system. This drug was first identified as a result of a screening project in zebrafish, demonstrating how the use of relevant animal models can accelerate the process of moving to the clinic.

Another project now in the CHCT lab is the result of an HSCI seed grant that focused on the use of mesenchymal stem cells as drug delivery vehicles to address human brain tumors.

In another step in moving fundamental technology toward clinical application, researchers at the Whitehead Institute and HSCI reported successfully reducing symptoms in a Parkinson's disease rat model by using dopamine-producing neurons derived from reprogrammed adult skin cells. This significant experiment demonstrated for the first time that reprogrammed cells have the ability to integrate into the neural system and positively affect neurodegenerative disease. In the coming year, we expect many more such experiments as we apply the multiple disease-specific cell lines and types that we can now create to *in vitro* and *in vivo* models, hastening the time that we can bring such therapies to people.

Seed Grants

HSCI seed grants provide early funding for innovative projects in important areas of stem cell research. These focused, two-year grants allow scientists to pursue "high-risk/high-reward" avenues of research that might be difficult to fund from other sources. The grants are also intended to support junior faculty in the early stages of their independent careers, and to support senior faculty entering brand-new, otherwise unfunded, areas of science.

The majority of the 45 seed grants awarded since 2005 have generated results that were published in scientific journals and have led to larger projects funded by the NIH or foundations.

In 2007, the Millipore Foundation made a gift of $500,000 to the HSCI Seed Grant Program to support one recipient per year for the next five years. The 2008 Seed Grant recipient Sangeeta Bhatia, MD, PhD, of Brigham and Women's Hospital has been named HSCI's first Millipore Foundation Seed Grant Fellow.

"The HSCI seed grant has given me a tremendous research opportunity for clinical translational research. Furthermore, this grant has generated a significant amount of enthusiasm for embryonic stem cell research within Brigham and Women's Hospital, especially among the clinical faculty in the department of Obstetrics and Gynecology. Since starting my project, one clinical embryologist and two OB/GYNs have voluntarily joined me to help with the project and two more have expressed an interest. I believe what HSCI is doing is helping bridge the gap between basic science investigation and clinical applications so that promising results can be safely and expeditiously brought into clinical application for patient use."

—Raymond Anchan, MD, PhD (2006 HSCI Seed Grant Recipient)

In May, 10 new seed grants were awarded to investigators selected from a pool of 64 applicants from HSCI-affiliated institutions.

2008 HSCI Seed Grant Recipients

Paola Arlotta, PhD
Massachusetts General Hospital
Sangeeta Bhatia, MD, PhD*
Brigham and Women's Hospital
Caroline Burns, PhD
Massachusetts General Hospital
Stephen Haggerty, PhD
Massachusetts General Hospital
Xue Li, PhD
Children's Hospital Boston
Judy Lieberman, PhD
Immune Disease Institute
William Pu, MD
Children's Hospital Boston
Zhong Wang, PhD
Massachusetts General Hospital
Rebecca Wingert, PhD
Massachusetts General Hospital
Sean Wu, MD, PhD
Massachusetts General Hospital

* HSCI gratefully acknowledges the generous gift from the Millipore Foundation supporting this project.

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
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.

CORE FACILITIES

"We greatly appreciate the support of HSCI for this core facility. I think it has provided a much-needed, essential resource that has been transformative in the work of many HSCI investigators."

– Amy Wagers, PhD, Co-Director of the HSCI Flow Cytometry Core Facility at the Joslin Diabetes Center

One of the ways that HSCI is able to accelerate research progress is by funding core facilities that provide its entire research community with shared access to critical state-of-the-art technologies, expertise, and services that are beyond the means of any individual laboratory or institution.

Therapeutic Screening Center At HSCI's Therapeutic Screening Center, headed by Lee Rubin, PhD, Director of Translational Medicine at HSCI, researchers perform screening assays against stem cells or cells grown from stem cells in order to identify small molecules, compounds, gene products, and proteins that could be turned into diverse therapeutics to cure diseases.

One way that screening assays use disease-specific cell lines is to look for drugs that could help treat a given disease. The stem cell-based screens pursue this goal by addressing questions on two levels. The first asks mechanistic questions about a specific disease's biology and the second explores how these mechanistic insights can be translated into the search for therapeutic targets.

Screens can also be used to search for drugs or biologics that direct stem cells into becoming a specific type of cell—a process known as targeted differentiation. Knowing how to generate a certain type of cell from stem cells is critical for treating conditions where cells have been injured or died, such as in diabetes.

The Therapeutic Screening Center is an important hub of collaboration at HSCI, as the state-of-the-art technology is an invaluable resource across different disease areas and model organisms. Due to enormous demand by HSCI researchers, the center has rapidly expanded over the past year, resulting in many new projects, including new relationships with pharmaceutical and biotechnology companies.

Genome Modification Facility 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 a critical tool to help scientists readily identify, isolate, manipulate, and genetically modify stem cells for their research. The often delicate procedures used to create these mice require technical skills, expensive micromanipulation equipment, and special procedures beyond the capability of most laboratories.

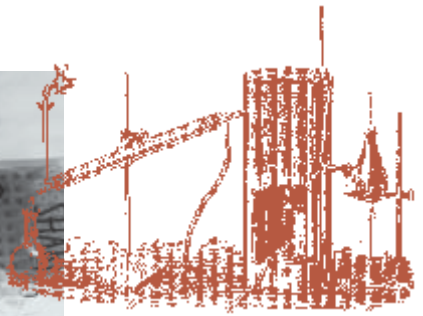
New services the GMF initiated over the past year include ES Cell Gene Targeting, Sperm Cryopreservation, and SpeedCryo, a service that includes the cryopreservation of both mouse sperm and embryos. These services have already become very popular, and demand continues to grow. In 2007, the GMF completed a total of 99 services and has since logged 109 service projects during the first half 2008. The GMF is also planning to introduce additional services in the next year.

Flow Cytometry Core Facilities In the three years since the HSCI flow cytometry cores were established at Beth Israel Deaconess Medical Center, Joslin Diabetes Center, Brigham and Women's Hospital, and Massachusetts General Hospital, HSCI scientists have been provided with state-of-the-art cell sorting capabilities that have both advanced research and fostered innovation and collaboration among HSCI

investigators. For example, work performed in the Joslin core has supported at least 40 peer-reviewed publications and 34 funded grant applications by HSCI Principal and Affiliated Faculty. In addition, the Joslin core has trained more than 50 researchers in HSCI-affiliated labs in the principles and applications of flow cytometry, and informal interactions in the core have helped to spur new collaborations and new research directions in a number of HSCI labs.

Human Embryonic Stem Cell Core Facility HSCI's Human Embryonic Stem Cell Core Facility at Children's Hospital Boston has provided a unique program that offers expertise, hands-on training, and seminars in the highly specialized field of mouse and human embryonic stem cell research. Since the core was established, more than 70 scientists representing over 50 laboratories have received training in basic hESC culture techniques. In addition to classes and training, the core has also held over 100 scientific journal and bioethics discussions and more than 10 seminars on hESC technologies, patents, funding restrictions, and stem cell guidelines.

New iPS Core Facility In August 2008, HSCI Executive Committee member George Daley, MD, PhD, together with HSCI faculty Chad Cowan, PhD, and Konrad Hochedlinger, PhD, and other colleagues, published that he had produced a robust collection of 20 disease-specific stem cell lines using the new iPS technique. Coupled with this achievement was the announcement of a new HSCI iPS Core laboratory located at Massachusetts General Hospital that will serve as a repository for iPS cells produced by HSCI scientists. The core will also function as a technical laboratory to produce these disease-specific lines and make them available to scientists worldwide.



BUILDING COMMUNITY

Because HSCI is a distributed community, events play an important role in enabling researchers to connect, sparking new collaborations, and creating a supportive environment where ideas are shared and feedback is provided.

Held on a bimonthly basis at the Harvard Medical School, **HSCI Inter-lab Meetings** are typically attended by up to 200 members of our community and consist of presentations from three different labs on a common theme. This year's topics were "Stem Cells and Developmental Biology," "Cellular and Molecular Signals That Affect Self-Renewal and Differentiation," "Regulatory Mechanisms in Development and Disease," "Embryonic Stem Cell Derivation and Biology," and "Translational Approaches to Stem Cell Therapies." The Inter-labs are moderated by HSCI senior faculty and are specifically designed to provide junior investigators, postdoctoral fellows, graduate students, and newly appointed faculty the opportunity to share their most recent work with the wider HSCI community.

This June, more than 300 members of HSCI's research community gathered at the Harvard Business School to attend the **Third Annual Retreat**. The day featured updates on HSCI's progress and future plans, presentations by the leaders of HSCI disease programs and core facilities, and scientific poster presentations.

Engaging and Collaborating with the Global Stem Cell Community HSCI's faculty is made up of many of the world's most accomplished stem cell scientists, yet it is important to remain engaged with the global stem cell research community. Each year HSCI hosts renowned scientists from around the world to discuss pivotal areas of stem cell research.

The **Fourth Annual Tony & Shelly Malkin Stem Cell Symposium**, attended by approximately 400 members of the HSCI community, brought together an experienced panel of scientists to discuss research developments related to the cancer stem cell. The scientific talks, along with a well-attended poster session, represented the wide range of research being conducted in this field. The theme of the day was also addressed in an evening dinner keynoted by Jeffrey Flier, MD, Dean of the Harvard Medical School. Dean Flier discussed how institutional heterogeneity both challenges and enriches scientific and clinical pursuits.

HSCI also continued its twice-monthly **Seminar Series** at the Massachusetts General Hospital Center for Regenerative Medicine, which featured presentations on a broad range of topics by leading international scientists. In 2007-2008, this Series was generously sponsored by BD Biosciences.

Building on the success of the previous two Parkinson's Disease Think Tanks, this year Jeffrey Macklis, MD, DHST, head of HSCI's Nervous System Diseases Program, hosted the **HSCI Nervous System Diseases Think Tank**, bringing together international experts for two days to discuss diseases linked to corticospinal motor and forebrain projection neurons, such as ALS and Huntington's disease. The event began with a public seminar at the Harvard Medical School and was followed by intimate small group discussions at the Harvard Humanities Center.

Think tanks have proven to be an effective way for the attending experts to hone in on the next steps needed to move the field forward in a specific area, and HSCI has awarded grants to turn these ideas into action. Based on the success of these programs, HSCI also held a **Diabetes Think Tank**, a **Cardiovascular Think Tank**, and is planning to expand its think tank sessions to include programs on ALS and other disease areas.

In September, members of HSCI also convened a **Junior Faculty Symposium** with colleagues from the California Institute for Regenerative Medicine in an effort to identify areas of significant collaborative potential. Thirty-six investigators shared their science during this two-day program that was partially funded by Millipore and Cell Press.

Beyond the Bench
There are many ethical, political, and commercial implications to the advancing field of stem cell research, and HSCI continued to sponsor events that encourage open and productive discussion of these issues.

Educating the Public Each quarter HSCI hosts a panel discussion on stem cell-related topics for the general public. These **Public Forums** provide the community at large the opportunity to hear directly from people whose work interfaces with the field of stem cell research—scientists, physicians, lawyers, journalists, and others. The events are taped and can be viewed on the HSCI website.

Topics addressed this year were:

- Policy and Funding Considerations for Stem Cell Research
- Stem Cells and Key Diseases
- Tissue Engineering
- Stem Cells and the Media

HSCI also collaborated with Harvard Law School's Petrie-Flow Center for Health Law Policy, Biotechnology, and Bioethics for a **book discussion** of "Stem Cell Century: Law and Policy for a Breakthrough Technology" by Russell Korobkin, Professor of Law at UCLA and Visiting Professor at Harvard Law School. This was broadcast to a wider audience by C-Span Book TV.

HSCI continued its partnership with Harvard's Humanities Center to co-sponsor another year of **"Between Two Cultures,"** an experiment in intellectual exchange across the sciences, humanities, and social sciences. This university-wide faculty seminar explores the ethical, social, scientific, political, and philosophical implications of new developments in biotechnology. Guests this year included Eric Kandel, Raymond Kurzweil, K. Anthony Appiah, Marc David Hauser, and Sherry Turkle.

The October 2007 two-day **Stem Cell Summit**, co-sponsored by HSCI, the Genetics Policy Institute, and the Burrill Life Sciences Media Group, presented a broad view by advocates, industry, foundations, scientists, clinicians, and hospitals of how stem cell biology is perceived, funded, and advanced. Almost 100 speakers, many of them HSCI-affiliated investigators as well as experts from around the world, presented on topics such as the future of stem cell research, philanthropic giving, and collaboration from the vantage point of research hospitals. The third Stem Cell Summit, with HSCI as host, will be held in September 2008 and will focus on "Moving Stem Cell Research from Bench to Bedside."

EDUCATION AND TRAINING

Education and training are central to HSCI's mission because stem cell research extends well beyond the lab bench or the classroom as we seek to educate future generations of scientists at all levels.

Reaching Out to High School Teachers Building on the success of last year's **Teacher Professional Development Course**, HSCI again offered a summer course designed for high school teachers who want to learn about stem cell science and approaches for developing effective curriculum in this area. The weeklong program covered a broad range of topics, from the current state of stem cell research to the ethical and legal implications of the science, and included visits to HSCI laboratories and facilities. HSCI also provided classroom materials, including educational DVDs, slide-sets, and white papers, in order to help the teachers develop academic offerings and classroom sections on stem cell science.

Encouraging Undergraduates' Interests in Stem Cells There are very few places in the U.S. where undergraduate students can have direct access to cutting-edge stem cell science, let alone participate in it. Three years ago, the **HSCI Internship Program** was launched with the aim of providing undergraduates from all over the world an internship that includes hands-on laboratory experience, direct mentorship from a stem cell researcher, a seminar series, and a focused educational program.

The 2008 HSCI Internship Program was the largest program to date, representing an exciting opportunity for the 37 undergraduate students (selected from over 300 applications) to gain experience in stem cell research while working in an HSCI laboratory under the supervision of an experienced researcher. Extending Harvard's impact beyond its own walls, the 2008 summer program included 15 Harvard College students and 22 non-Harvard students, including three international students.

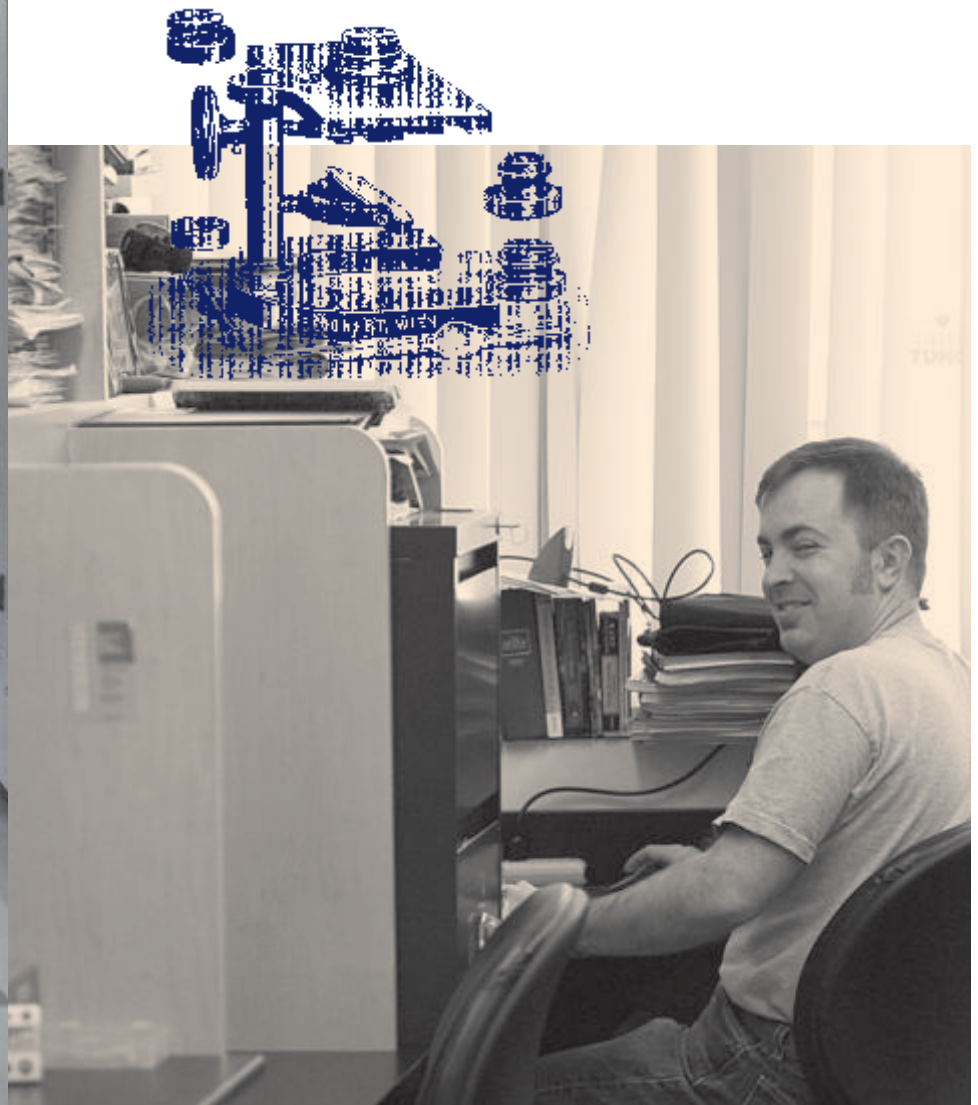
Supporting Graduate Students, Post Docs, and Young Investigators Initiated by a generous donor gift, this year was the first in which HSCI awarded **graduate student fellowships** to promising students conducting diabetes-related stem cell research. The program provides grants of up to $85,000 each year toward the recipients' graduate school costs.

HSCI is also actively involved in the training and fostering of the next generation of MD and MD/PhD investigators in the HSCI community. This year, with a gift from GlaxoSmithKline Research & Development Limited (GSK) and in cooperation with the Massachusetts General Hospital, HSCI launched a new **Clinician Scientist Program** to support these investigators at several stages in their careers and will provide funding for students enrolled in MD/PhD programs, fellowships for junior investigators, and laboratory start-up funds for clinician-scientists, all in the field of stem cell biology.

Providing Leadership in a Burgeoning Field This year HSCI launched an online review of topics related to stem cell biology called **StemBook**. It consists of original, peer-reviewed chapters written by top researchers in the field from around the world and is overseen by an international editorial board of notable stem cell scientists. By providing a freely available, open-access resource of high-quality information about stem cell science, HSCI has built a useful, encyclopedic but current, tool for researchers at HSCI and the entire global stem cell community.

Through a collaboration between HSCI and the Radcliffe Institute for Advanced Study, 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**. Mummery, a highly regarded stem cell scientist, spent her research sabbatical in the fall of 2007 collaborating with investigators from HSCI's Cardiovascular

Disease Program and other Harvard colleagues from the School of Engineering and Applied Sciences in examining the role that the physical environment plays in regulating the differentiation of stem cells into the various cardiac cell types of the heart. In addition to pursuing collaborative projects, Mummery also shared her expertise as a keynote speaker at several HSCI events. Future fellows may come from other science or non-science disciplines, but their work must involve or relate to stem cell science and be interdisciplinary, showing integration of stem cell science into one or more other disciplines.



ALLSTON UPDATE

Construction for HSCI's new home in the First Science building in Allston is well under way. The new building will house the Harvard Stem Cell Institute and the newly formed Department of Stem Cell and Regenerative Biology, as well as other multi-disciplinary programs in systems biology and bioengineering. The four-building complex now known simply as First Science is the first new complex being constructed on Harvard's extended campus in Allston. First Science has been designed specifically to facilitate interdisciplinary and collaborative research and will contain faculty laboratories, shared core facilities, administrative offices, a conference center, and dedicated seminar and teaching space. Building on the success of the HSCI, the anticipated move to Allston in the summer of 2011 presents an opportunity for the institute to expand and strengthen the already vibrant community of stem cell scientists involved in its research and education programs.

The co-location of HSCI and the new department in First Science will facilitate better connections across the University, including the numerous schools and hospitals that are involved in interdisciplinary education and research. Bringing together many members of the HSCI community to work in one location will enable them to intensify their collaborations and will provide new opportunities for undergraduates, graduate students, and medical students to receive training in stem cell biology and regenerative medicine. Close links and direct interactions with scientists in the systems biology and bioengineering fields are expected to spark new innovative, cross-disciplinary collaborative projects.

The HSCI will continue to extend well beyond the First Science complex. Some HSCI scientists will transfer their full research programs to Allston, while others will split their labs between Allston and their current locations, and still others will continue to be integral members of the HSCI community but will maintain their labs where they are. Moving from a virtual network to more of a hub-and-spoke model will allow HSCI to maintain its connections to the hospital labs, clinics, and core facilities across Harvard and affiliates while providing a center of gravity to its efforts.

SELECTED SCIENTIFIC PUBLICATIONS

The 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.

Blood

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Min IM, Pietramaggiori G, Kim FS, Passegue E, Stevenson KE, Wagers AJ. The transcription factor EGR1 controls both the proliferation and localization of hematopoietic stem cells. *Cell Stem Cell*. 2008 Apr 10;2(4):380-91.

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Diabetes

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FINANCIALS

The Harvard Stem Cell Institute's total expenditure in the Fiscal Year 2008 reached $16.2 million, representing a 17% increase over Fiscal Year 2007.

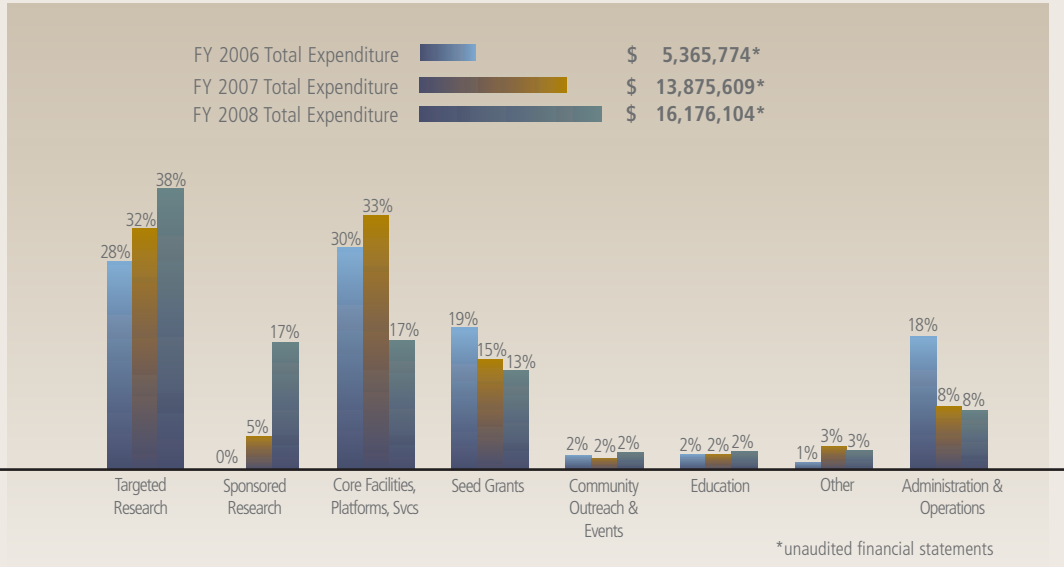
Spending in the combined research programs grew to $13.7 million, holding at 85% of the total expenditure. Within these programs, spending in Sponsored Projects more than tripled in FY 2008 compared to the prior year, while spending in Targeted Research grew by 36%. The Seed Grant program stayed at approximately the same level of $2.1 million.

The overall spending in Core Facilities, Platforms, and Services declined in FY 2008 due to the one-time infusion of start-up capital in the Therapeutic Screening Center in the prior year. HSCI is continuing its commitment in this critical area. In fact, we expect an increase in FYs 2009 and 2010 as the Screening Center will be facing capacity constraints, and we are investing in a new iPS Core Facility.

Programs in Education and Community Outreach kept pace with the overall growth, continuing the range of highly successful initiatives that began in prior years. Programs such as the Stem Cell Leadership Summit, the Public Forum series, and the undergraduate summer internship program have reached their respective target audiences in bringing issues to public discourse and have continued to grow. Applications for the summer intern program nearly doubled this year. Positive response to our 2007 pilot training program for high school teachers led to our continuing the program in 2008. StemBook, an online publication managed by HSCI with contributions from experts from around the world, is a new resource to be launched this fall. In addition, HSCI is committed to its continuing support for the training of graduate students, clinician-scientists, and their research projects through new gifts both to the HSCI and the new Department of Stem Cell and Regenerative Biology.

Expenses in Administration and Operations held steady compared to the prior year as a percentage of overall spending, reflecting success in supporting the growing organization despite overall inflationary factors and an expanding volume and range of services for events, symposiums, and workshops.

Breakthroughs by HSCI principal faculty this past year have generated excitement in the scientific and clinical research communities and sparked new interest from the commercial sector. As we move into Fiscal Year 2009, we expect to see an increase in the leveraging effects of private gifts on sponsored collaborative projects with companies and foundations.



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