HOWARD HUGHES MEDICAL INSTITUTE

2007 ANNUAL REPORT

WHAT'S NEXT

The primary purpose and objective of the Howard Hughes Medical Institute shall be the promotion of human knowledge within the field of the basic sciences (principally the field of medical research and education) and the effective application thereof for the benefit of mankind.

LETTER FROM THE PRESIDENT

What's next? That's a question that scientists associated with the Howard Hughes Medical Institute ask themselves every day. What are the next questions? What experiments might generate answers? How will we get there? With whom can we collaborate? What's just over the horizon?

The drive toward "next" is an essential part of the scientific endeavor and of HHMI's culture—a culture that prizes bold thinking and scientific risk taking, a culture that rewards innovation and discovery. Success rarely occurs at predictable intervals, making patience a paradoxical feature of HHMI's approach to discovery research. HHMI is a patient, long-term investor in people.

Teaching students to think like scientists—to pose questions and then take incremental, challenging steps toward answering them—is also fundamental to HHMI's approach to education. For two decades, HHMI has sought to hook students on the power of discovery by engaging them

Thomas R. Cech

in hands-on research at all age levels, particularly as undergraduates at the nation's colleges and universities. HHMI helps train the "next" generation of scientists and scientifically knowledgeable citizens.

This annual report highlights the work of HHMI scientists—investigators, researchers at the Janelia Farm Research Campus, and international research scholars—who have tackled big problems that took many years to solve. For example, Joanne Chory and her colleagues at California's Salk Institute spent 10 years developing the tools they needed to understand which tissues drive growth in plants. A similar long-term focus yielded new insights into the evolution of color vision at the Johns Hopkins University School of Medicine, where HHMI investigator Jeremy Nathans and his colleagues created genetically engineered mice that can literally see red.

This year we also celebrate the contributions of Craig C. Mello at the University of Massachusetts Medical School in Worcester. Mello shared

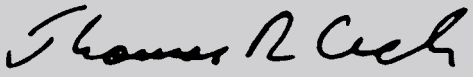
the 2006 Nobel Prize in Physiology or Medicine with Andrew Z. Fire, then of the Carnegie Institution of Washington in Baltimore and now at the Stanford University School of Medicine, for their discovery of RNA interference. The two collaborators picked their way through a maze of unusual experimental results and became intrigued by the possibility that double-stranded RNA played a role in silencing gene activity. Undeterred by the apparent absurdity of the idea, they discovered a regulatory system that controls gene expression in both plants and animals, including humans.

Evidence of scientific achievement notwithstanding, Mello recalls that he was an indifferent student and far more interested in playing outdoors near his family's Virginia home until he encountered academic science courses during seventh grade. Inspired by wonderful teachers, Mello says in an autobiographical essay for the Nobel Foundation that he became "an avid reader of science fiction, an amateur astronomer, and a serious student." We hope that HHMI's science education effort—now 20 years old—will continue to nurture both sides of that student-teacher equation, creating communities of learning at different educational stages and in different environments.

This annual report calls attention to a variety of initiatives, from a boot camp for graduate students to a $22.5 million program that over the next five years will link biomedical research institutions with local schools around the nation. We're even undertaking an educational experiment of our own by taking a direct role in the development of a genomics research course for undergraduates. HHMI has created the Science Education Alliance within the Office of Grants and Special

Programs, and the SEA staff will spend the next year working with leading scientists and grantees to develop the course, including a syllabus and resource kits. The goal is to roll out the course to successive groups of colleges and universities beginning in fall 2008 and, over time, evaluate the impact of the experience for both students and teachers.

No person or organization can focus solely on the future. Indeed, the search for "what's next" is built on an appreciation of the past and of history. This year we pause to recognize the singular contributions of William Rice Lummis in establishing HHMI as a world leader in biomedical research. For the past 23 years—beginning with his appointment as a charter Trustee by the Delaware Court of Chancery and continuing until his retirement in March 2007—Will Lummis served the Institute with consummate grace, steadfast dedication, and judicious intelligence. His leadership ensured the Institute's reorganization and set the stage for the success we now enjoy. We'll give him the next word.



Thomas R. Cech, Ph.D.
President

CONVERSATION

WILLIAM R. LUMMIS

William R. Lummis was nine years old when his dashing cousin Howard Hughes arrived in Houston in July 1938 for a celebration hailing his record-setting plane flight around the world. Hughes stayed at the family home, an encounter that Lummis recalls made him a "big shot" among his friends.

Flash forward to 1976. Lummis, by then a distinguished Houston attorney and father of four, was called upon to claim Hughes's body at the Texas Medical Center following his death. Almost immediately, Lummis assumed responsibility for unwinding the Hughes estate—a sprawling empire that ranged from thousands of acres of Las Vegas real estate to the Howard Hughes Medical Institute, which controlled the Hughes Aircraft Company.

After spending three decades in the "Hughes vineyard," Lummis retired in spring 2007 as one of HHMI's charter Trustees. Long admired for his leadership in securing the Institute's future, Lummis reflected on his tenure.

How would you describe Howard Hughes's greatest legacy?

A

Hughes's career was unbelievable. His investments were in the right places and he focused on matters that were of interest to him. Aviation was very important to him—he flew all the time—and so was moviemaking. But at a very early age—in his early 20s—he let it be known that he wanted his estate to be left for the good of mankind, and that's what he did. His real legacy is the Institute and his foresight in founding it with that brief charter—namely, "the promotion of human knowledge within the field of the basic sciences...." He never altered it.

What were your hopes for the Institute when you sought its reorganization in the Delaware Chancery Court?

A

Because Hughes died without a will, the estate was in chaos and besieged by litigation. I thought the attorney general of Delaware could be of assistance in calming down the distractions and permitting an orderly administration of the Hughes estate. This tactic was successful in reaching the desired result. We were also able to set the Institute on a course of fulfilling the promise and charitable purposes for which it was originally organized.

Did you expect to serve as a Trustee for more than 20 years?

A

My experience as a Trustee has been thoroughly exciting, and the long-term association with the other Trustees and staff has been extremely satisfying, particularly under the very capable board leadership of George Thorn, Irving Shapiro, and Hanna Gray. The original group was appointed for life, and none of us had any idea of how long our services would be required. We all worked together and we all worked hard.

What challenges did you and the other Trustees face?

A

The Trustees started with a clean sheet of paper in designing a new organization. We had very little to go on except in those areas we felt reflected the desires of Hughes himself, and we were fortunate in being able to attract tremendously talented people. It was clear to the Trustees that we had to focus on Hughes's desires for the Institute, and the only way to get the financial resources to do that was to sell the Hughes Aircraft Company. The sale was the linchpin of our success because that $5 billion allowed us to do some serious planning.

What are some of the significant milestones?

A

There have been so many in the evolution of the reorganized Institute that they are difficult to rate in terms of importance. The Institute has been extremely fortunate in being able to acquire two important properties—for the headquarters in Chevy Chase [Maryland] and for the Janelia Farm Research Campus [in Loudoun County, Virginia]. I was very concerned about Janelia Farm in the beginning, but with the help of some of the financial people, satisfied myself that we had the resources to do it even though we were biting off a big chew. My hat's off to [HHMI president] Tom Cech and the scientific staff for their vision.

What do you hope the Institute will accomplish in the future?

A

I have no idea, but I am assured that its endeavors will be extremely exciting and successful considering the quality of management and scientific personnel. The nice thing is that we have control of our own destiny in terms of financial resources. I think we have something to be proud of at the Institute.

THINKING LIKE A SCIENTIST

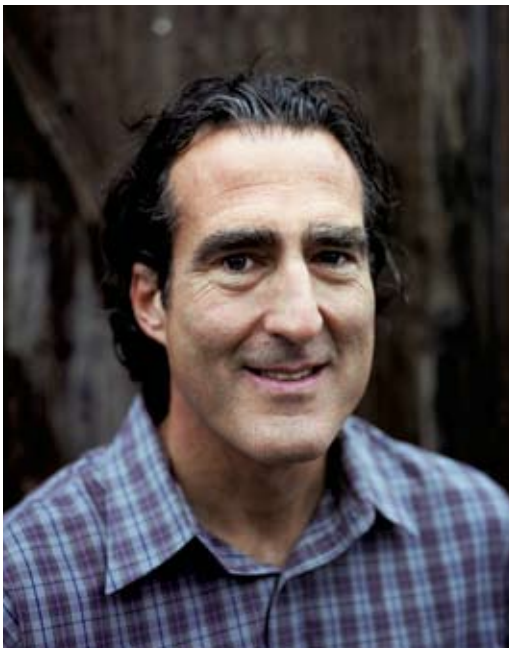
SCIENTIFIC RESEARCH might be described as the relentless pursuit of what's next. That insatiable curiosity drives HHMI investigators to delve more deeply when confronted with perplexing problems. In the quest for knowledge, they draw on their creativity and have the courage to question their assumptions. From identifying previously unknown cellular mechanisms to finding an unexpected pathway for an important tumor-suppressing protein, HHMI investigators have pushed the bounds of scientific understanding. As scientific disciplines continue to converge, communicating and collaborating with the best minds in research becomes an essential part of thinking like a scientist.

DRIVEN TO EXPLORE

Craig C. Mello, an HHMI investigator at the University of Massachusetts Medical School, has spent his life applying his analytic and creative gifts to exploring the world around him. His curiosity and willingness to entertain new ideas drove the research that led to the 2006 Nobel Prize in Physiology or Medicine, shared with Andrew Z. Fire of the Stanford School of Medicine. The prize recognized their work in discovering RNA interference—gene silencing by double-stranded bits of RNA.

Mello and Fire received the ultimate honor for scientific achievement by overturning scientific dogma: rather than being simple cellular debris, short snippets of double-stranded RNA could regulate gene expression. Still, the creative thinking that led them to propose their radical idea doesn't seem particularly noteworthy to Mello.

"I think everybody thinks like a scientist. It's just a matter of getting better at it. Your average kid is doing it all the time," Mello argues. "Scientists are just creative in a way that is constrained by reality."



HALTING CANCER

Gregory J. Hannon

Scott W. Lowe

Cells have numerous mechanisms to keep cancer at bay. None plays as crucial a role in shutting it down as the tumor-suppressing protein p53, which is mutated in half of all cancers. In the 25 years since p53 was discovered, the mechanism by which it encourages damaged cells to die or become dormant has only been partially described. Shutting down proteins known to interact with p53 failed to block its ability to control tumors. Faced with genetic evidence that p53 did something more, HHMI investigators Gregory J. Hannon and Scott W. Lowe of Cold Spring Harbor Laboratory explored a peculiar fact about cancer cells—the relative lack of mysterious bits of RNA, called microRNAs. Hannon and Lowe discovered that in addition to interacting with a host of proteins and DNA, p53 activates a family of microRNAs that in turn triggers cell suicide or renders a cell dormant. Hannon says that the hole in the p53 pathway "may well be filled by microRNAs." The next job is trying to understand how the cell integrates all the output of p53 activation.

"I think everybody thinks like a scientist.... Scientists are just creative in a way that is constrained by reality."

—Craig C. Mello

A seemingly impossible laboratory result compelled Mello to pursue the work that resulted in winning a Nobel Prize. In 1994, he heard about a graduate student at a Cornell University lab, Su Guo, who tried to block a gene in the tiny worm *Caenorhabditis elegans* by injecting it with antisense RNA—a strand of RNA designed to bind with single-stranded RNA molecules that have the opposite genetic sequence and prevent the cellular machinery from using the RNA as a template to make a protein. It worked just as expected. However, when the Cornell student injected "sense"—or same sequence—RNA, which shouldn't affect gene expression, the gene was similarly blocked. Most people assumed that antisense RNA had simply contaminated the sense RNA preparation.

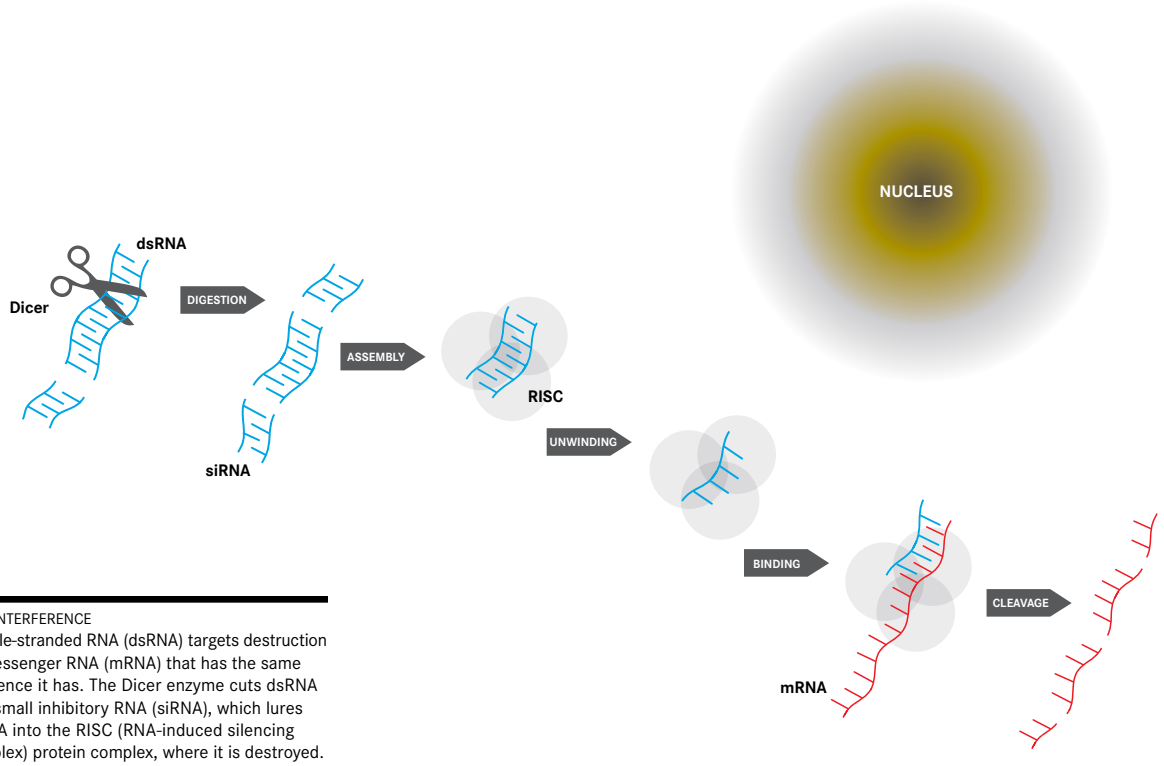
Mello, however, was fascinated and began exploring the phenomenon as a project separate from his study of how *C. elegans* embryos develop. A couple of serendipitous mishaps in his laboratory presented additional puzzling results: the gene-silencing effect spread from parent to offspring and from cell to cell. Rather than being frustrated, Mello was driven to understand the strange findings.

"I guess it's my personality. I'm not afraid of things that are weird," Mello muses. "It's important to be excited about odd and unusual results, and in this case it was clearly something interesting."

Mello discussed these findings with Fire, then at the Carnegie Institution of Washington's Department of Embryology in Baltimore. Fire posited that perhaps double-stranded RNA was responsible for the effect by somehow amplifying RNA's ability to silence genes. Because double-stranded RNA forms when single-stranded RNA loops back on itself, Fire's idea explained the unusual results first observed in 1994.

"Communication and discussing ideas are integral parts of science because those conversations generate ideas more efficiently," Mello says. "Of course, you have to do experiments, too."

When Mello and Fire did the experiments, they found that double-stranded RNA was far more efficient at silencing gene expression than antisense RNA. They published their results on RNA interference (RNAi) in the journal *Nature* in 1998, triggering an explosion of research. The mechanism they had discovered was part of a system regulating the expression



RNA INTERFERENCE
Double-stranded RNA (dsRNA) targets destruction of messenger RNA (mRNA) that has the same sequence it has. The Dicer enzyme cuts dsRNA into small inhibitory RNA (siRNA), which lures mRNA into the RISC (RNA-induced silencing complex) protein complex, where it is destroyed.

of many genes and included a protein called Dicer, which chops up double-stranded RNA into double-stranded fragments 20 to 25 base pairs long.

Mello's work is now evenly divided between projects investigating RNAi and embryonic development in *C. elegans*, and the two fields continue to converge. "It really is the most amazing feeling when you first see the connections long before you can prove they exist," Mello notes. "There is still so much to learn."

Since winning the Nobel Prize, Mello has discovered that he has joined an elite group of scientists whose ideas and opinions are highly regarded. He is invited to many meetings and workshops on topics in and outside his areas of expertise. "The Nobel Prize has given me the opportunity to educate myself and learn about some new things," he says.

One new interest is global health. As scientists begin to search for potential therapies based on RNAi, Mello believes most of them will be very expensive. If he's right, those therapies may benefit only a small part of the world's population. "Any treatments that are developed aren't going to be simple or inexpensive," he says. "You can't escape the fact that there are huge economic disparities in the world that we as a society need to address."

Mello believes solving such problems requires communication among a host of different fields, from science to politics to economics. He has found himself reaching out to other disciplines to learn as much as he can about global public health. "I just feel the need to be thinking," he says.

SYSTEMS BIOLOGY BOOT CAMP

In late August 2007, new graduate students in the systems biology program at the University of California, San Francisco (UCSF), entered a grueling two-week boot camp of 14-hour days filled with lectures, seminars, and labs. The boot camp, first conducted in August 2006, is designed to introduce the students to interdisciplinary science. Active at the nexus of physics, mathematics, and biology, systems biology explores the interactions between components of biological systems and how these interactions give rise to the function and behavior of the systems.

UCSF is one of 13 institutions chosen to participate in the first phase of an HHMI and National Institute of Biomedical Imaging and Bioengineering (NIBIB) initiative designed to foster Ph.D. scientists who are comfortable conducting interdisciplinary research. "Systems biology requires intense communication across disciplines," says HHMI investigator and program director **Joseph L. DeRisi**. "The boot camp breaks down barriers that result from different scientific backgrounds and forces the students to form a cohesive network and act together." The UCSF program is codirected by HHMI investigator **David A. Agard**, and crucial input is also provided by HHMI investigator **Jonathan S. Weissman**.

Later in the program, the students—who have backgrounds in fields such as biochemistry, physics, biology, and biotechnology—take on a team challenge. Three- to four-member groups attempt to design a new synthetic behavior for yeast, and they end up spending days and nights in the lab to meet the challenge. These intense experiences help develop communication skills and broaden thinking, preparing the students to solve the scientific problems of the future.

UCSF graduate students Brittany Belin (right) and Monica Tremont working in the boot-camp lab.

ANTIQUITY'S CONTROL SWITCH

HHMI investigator **Ronald R. Breaker** from Yale University began his work on RNA "sensors" as an intellectual exercise and discovered a legacy from a time when RNA ruled the world. Struck by how efficiently laboratory-engineered RNA sensors—dubbed riboswitches—could react to the presence of nutrient molecules, he hypothesized that such entities must exist in nature. In 2002, he found a riboswitch at work in bacteria that helped the microorganism sense the availability of a certain vitamin. Since then, dozens of riboswitches have been discovered, and Breaker has been seeking to understand the role they play in higher organisms. In May 2007, he discovered that a riboswitch in the fungus *Neurospora crassa* regulates RNA processing. He continues to investigate how these bits of antiquity exert control in higher modern organisms.

SEEING IN NEW WAYS

A LONG EVOLUTIONARY history has endowed flies with near 360-degree vision and humans with the ability to see sharp images of the world in brilliant color. HHMI scientists have discovered that in some cases the smallest of genetic changes is responsible for marked improvements in vision. Despite our visual acuity, however, our eyes fail us when we attempt to observe the routine activities of molecular biology—we simply can't see individual molecules in action. Faced with such limitations when trying to understand processes like protein folding and viral infection, HHMI researchers have found new ways to visualize what can't be seen.

Karel Svoboda

Michael D. Ehlers

ILLUMINATING NEURONS
HHMI investigator Michael Ehlers genetically engineered a light-sensitive protein into the neurons of mice. This illustration shows a beam of light activating a neuron in the olfactory bulb.

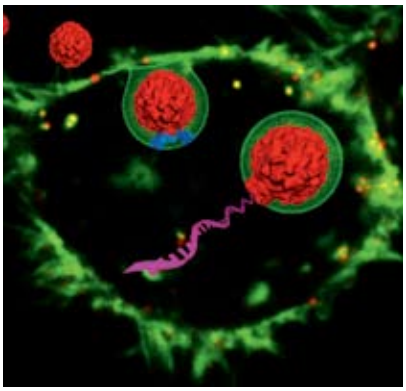
SIMPLY CHANNELING COMPLEXITY

A simple flick of a light switch is all you need to see what's inside a darkened room. Working independently, two HHMI research teams have found similarly straightforward ways to turn on a light in the brain. Using the light-sensitive protein that enables green algae to migrate toward light, both techniques offer revolutionary ways to map the function of brain activity.

HHMI investigator **Michael D. Ehlers** and his group at Duke University illuminated the brain by genetically engineering the algal protein channelrhodopsin-2 into the neurons of living mice. These mice developed and behaved normally. Ehlers triggered neuronal impulses in the live animals by shining an ultrafine fiber optic light source onto the engineered neurons. By focusing the light on the olfactory bulb, he generated impulses to the olfactory cortex. Ehlers discovered that the cortex couldn't respond to a single neuron but instead needed input from a distributed array of neurons. "We believe that this light-induced activation technique is a major technical breakthrough in the functional analysis of neural circuitry," Ehlers says.

Janelia Farm Research Campus group leader **Karel Svoboda** flipped his switch in the brain by introducing channelrhodopsin-2 into specific subsets of neurons in mice at various stages of embryonic development. Exposing brain slices from these mice to laser pulses, Svoboda's team mapped the signals generated as the channelrhodopsin-2–laden neurons proceeded to fire. Svoboda is using the technique to explore how the two brain hemispheres connect. Preliminary evidence indicates that axons in one area of the brain seek neurons of the same type in different parts of the brain in what Svoboda calls "a simplifying principle of connectivity."

Both Svoboda and Ehlers are pushing their techniques to the next level by finding more specific ways to target neurons genetically. Svoboda plans to explore the properties of synaptic connections. Ehlers intends to investigate methods for light stimulation of connected brain regions, which could be precursors to new technologies for neural activation in the brain and spinal cord.



POLIOVIRUS INFECTION
Poliovirus (red) infects a cell by first binding to multiple cell-surface receptors (blue). The cell membrane (green) folds around the virus and creates a sac inside the cell. The virus then releases its RNA genome (pink).

IMAGING INFECTION

For decades, scientists have debated how poliovirus infects human cells. **Xiaowei Zhuang**, an HHMI investigator at Harvard University, and her colleague James Hogle at the Harvard Medical School found a way to peer at the process and settled the question: unlike viruses that need hours or days to infect a cell, poliovirus needs only minutes to release its genome and initiate an infection.

Zhuang and Hogle developed a novel method of light microscopy to watch individual viruses entering a cell by tagging the protective shell of the poliovirus with a red fluorescent dye and its RNA genome with one glowing green.Through the microscope, they could "see" the tagged virus enter the cell. Once inside the cell, poliovirus wasted no time releasing its green-glowing RNA genome from the viral shell. "We settled the debate.... If the viruses don't get into the cell, they do not release their RNA," Zhuang says. Her research opens new avenues of inquiry because poliovirus enters the cell via a pathway that has yet to be illuminated.

"We settled the debate.... If the viruses don't get into the cell, they do not release their RNA."

—Xiaowei Zhuang

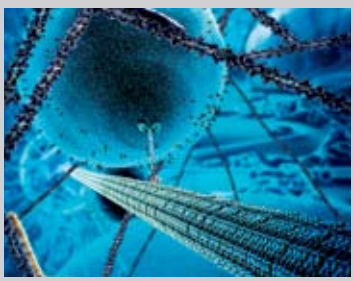
FROM PRIMITIVE TO COMPLEX

HHMI investigator **Charles S. Zuker** demonstrated the power, and beauty, of evolution when he and his colleagues at the University of California, San Diego, explored the differences between two forms of insect eyes. Compound insect eyes come in two varieties: the complex "open" eye of flies that creates 800 distinct light-gathering units and enhances peripheral vision, and the more primitive "closed" eye of a beetle that fuses those 800 light-gathering units. Zuker found the difference between these two eyes lies in a single regulatory gene called *spacemaker*. When the *spacemaker* gene is expressed in a primitive insect eye, it triggers the eye to organize into the more complex version. "It's not unusual to see alterations in regulatory proteins with a profound effect on form and function," Zuker said. "This new finding, however, is unique because it illustrates how a change in a single structural protein can lead to such a spectacular change in form and function."

Charles S. Zuker

FLUORESCENT EYES
This fruit fly's compound eyes express a fluorescent reporter protein. Analysis of fly eyes helped determine the crucial role of the *spacemaker* gene in the construction and evolution of insect eyes.

THE INNER LIFE OF THE CELL



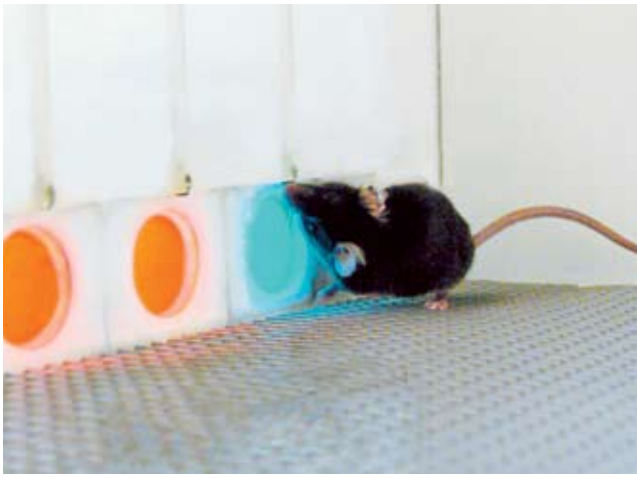
For most undergraduate biology majors, the intricate and dynamic molecular machines making up the living cell reside in static illustrations in their textbooks. To bridge the gap between science education and multimedia, **Robert Lue**, an HHMI undergraduate program director at Harvard University, initiated an integrated computer learning system called Biovisions. His research indicates that scientific animations boost student comprehension by as much as 30 percent. The program's first animation, called *The Inner Life of the Cell*, brings to life the workings of white blood cells in scenes documenting cellular activities such as motor proteins plodding along cellular scaffolding and structural proteins rapidly forming filaments and just as rapidly falling apart. Produced by XVIVO, a scientific-animation firm in Connecticut, the breathtaking eight-minute animation received a 2006 Telly Award, a premier award honoring outstanding local, regional, and cable TV commercials and programs, as well as video and film productions. *The Inner Life of the Cell* can be viewed at **http://multimedia.mcb.harvard.edu.**

SEEING RED

Humans and other primates maintain a significant advantage over other mammals—they see the world in full color. Mice, like most mammals, are red-green color blind. This discrepancy in color perception lies with the types of photoreceptors present in the eye. Full-color vision (trichromacy) occurs when an animal's eye harbors photoreceptors capable of detecting blue, green, and red wavelengths. The more limited dichromatic vision exists when the eye has only blue and green photoreceptors.

Building on work exploring the evolution of color vision that began in the early 1980s, HHMI investigator **Jeremy Nathans** at the Johns Hopkins University School of Medicine and his colleague Gerald Jacobs at the University of California, Santa Barbara, asked what happens when you mimic the crucial event in the evolution of color vision by introducing the gene for the red photoreceptor into the mouse genome. Would the mice see in full trichromatic color, or would the brain lack the ability to process information from the newly acquired photoreceptor? The researchers found that the brain seamlessly processed the information from the new red photoreceptor, permitting the animals to see red.

"What we are looking at in these mice is the same evolutionary event that happened in one of the distant ancestors of all primates and that led ultimately to the trichromatic color vision that we now enjoy," Nathans says, noting that a common way the brain may expand our experience of the world is by adding new sensory receptors.



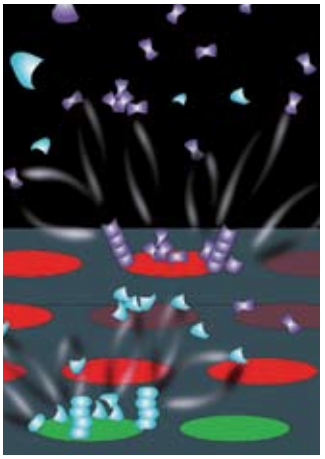
COLOR VISION
Colored lights show that the brains of genetically altered mice can process information from new photoreceptors in their eyes. Here, a mouse deciding that the third colored panel looks different from the other two is rewarded with a drop of soy milk.

"What we are looking at in these mice is the same evolutionary event that happened in one of the distant ancestors of all primates and that led ultimately to the trichromatic color vision that we now enjoy."

—Jeremy Nathans

Susan L. Lindquist

PRION ASSEMBLY
A microarray is used to probe the mechanisms of prion assembly. Two prion species (blue and purple shapes) are washed over a microarray spotted with different segments of the prion Sup35 (green and red dots). The prion species attach to specific sites and form amyloid masses.



PROBING PRIONS

Faced with a vexing scientific problem, HHMI investigator **Susan L. Lindquist** at the Whitehead Institute for Biomedical Research employed commonly used tools in an entirely new way to study the workings of the infectious proteins known as prions. Since their discovery in the early 1980s, prions have confounded scientists. Responsible for fatal brain disorders such as mad cow disease and Creutzfeldt-Jakob disease, prions exist in two differently folded configurations. One is innocuous. The other, called the "prion state," converts normal prion proteins to the prion state, forming brain-destroying protein clumps called amyloid masses. Lindquist and postdoctoral fellow Peter Tessier used protein microarrays to provide insights into how prion-state proteins convert normal prion proteins and how prions jump from species to species.

Lindquist and Tessier studied a version of the prion protein from the yeast *Saccharomyces cerevisiae*, known as Sup35, by exposing peptides bound to protein microarrays to the nonprion state of Sup35. They discovered that amyloid masses coalesced only over array segments corresponding to two regions involved with the conversion to the prion state. The team suspects that specific peptides cause the protein to adopt a prion configuration and that those peptides trigger amyloid masses to develop. They are now using the arrays to study how prions initially form.

By creating a hybrid Sup35 prion that fused an active region from *S. cerevisiae* to one from the yeast *Candida albicans*, Lindquist and Tessier established that the hybrid Sup35 could interact with both yeast species—but at different temperatures. The finding illustrates how different prion shapes can play a role in jumping the species barrier. The team's technique has the potential to be used in high-throughput drug screens and to provide generalized insights into protein folding.

Q&A

JACK E. DIXON

A VISION OF THE FUTURE

Jack E. Dixon joined HHMI as vice president and chief scientific officer in February 2007 after having served on the Institute's Scientific Review Board and Medical Advisory Board. A professor of pharmacology, cellular and molecular medicine, chemistry, and biochemistry, he maintains a bicoastal existence, keeping one foot in his lab at the University of California, San Diego, where he studies a family of enzymes called protein tyrosine phosphatases, and one foot at HHMI. His choice keeps him grounded as he pursues his vision for HHMI research.

What is HHMI's approach to funding research that fosters new approaches and innovation?

A

We identify good people—the innovators and the risk takers—and turn them loose for a sufficient period of time so that they can take a good run at the problems. Demanding short-term results is shortsighted and a sure formula for playing it safe. Scientific research takes time.

What areas of science are ripe for breakthroughs?

A

Major unsolved problems exist everywhere. Why is it we can't make a vaccine against the AIDS virus? Why have we made great progress against some forms of cancer and virtually none against others? To get talented investigators to commit to solving these difficult problems and make true breakthroughs, we have to give them the freedom—the time and the money—to explore.

Do the pace and demands of science today require special attention to new ways to tackle scientific questions?

A

The biggest difference today is that scientists must communicate and collaborate. Science today involves more people communicating with each other across several disciplines.

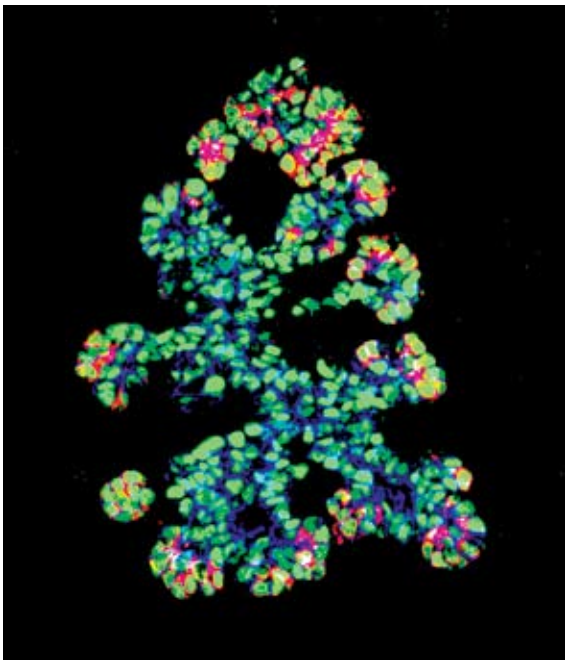
How do the HHMI–Wellcome Trust International Postdoctoral Fellowships foster communication and collaboration?

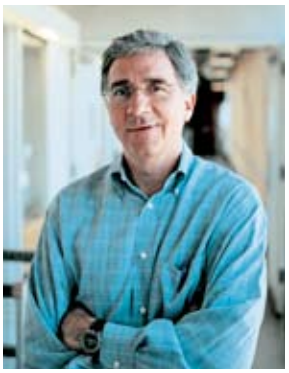
A

Today's science is conducted on an international platform, and this is one way we can help foster international collaborations. In this visiting scientist program, postdoctoral fellows working in HHMI or Wellcome Trust laboratories can spend up to a year working in an overseas lab. The program promotes collaborative science and develops what we hope are lasting ties between international research labs.

CAPACITY FOR GROWTH

PLURIPOTENT human embryonic stem cells possess the remarkable capacity to mature into all of the more than 200 kinds of cells making up the human body: skin, bone, nerve, blood, heart, muscle, and so on. By their very nature, the cells suggest possible new ways to treat devastating diseases such as Alzheimer's, Parkinson's, cancer, and diabetes. HHMI investigators are exploring the boundless potential of human, animal, and plant stem cells in order to make headway in understanding basic biology, plant behavior, and diseases like diabetes. The path from infinite possibilities to human therapies is fraught with difficult biology and sensitive questions. As HHMI researchers delve into the mechanisms by which stem cells maintain their capacity for growth, they are encountering both the limitations of the current embryonic stem cell lines and the possibility of finding new sources of these cells.





Douglas A. Melton

A DEVELOPING MOUSE PANCREAS
A confocal image of an embryonic mouse pancreas at about two weeks shows epithelial cells (blue), a key transcription factor (green), and progenitor cells (red).

NEIGHBORLY DIFFERENCES

For more than a decade, HHMI investigator **Douglas A. Melton** at Harvard University has studied how embryonic stem cells give rise to the pancreas and its insulin-producing beta cells, which are destroyed in patients with type 1 diabetes. His quest is to identify new therapies for that disease. Melton's most recent research grew in a natural direction when he decided to compare the pancreas to the liver.

Unlike the pancreas, which cannot regrow sections that have been surgically removed, the liver regenerates into a fully functioning organ just weeks after the removal of as much as two-thirds of its mass. The molecular basis for this difference may offer vital clues to help researchers eventually generate beta cells from stem cells. Melton studied how these developing organs in mouse embryos responded to the loss of progenitor cells—partially differentiated embryonic stem cells. His team discovered that the liver reaches its full size regardless of the number of liver progenitor cells, but the number of pancreatic progenitor cells dictates the size of the pancreas.

Melton posits that there are two classes of organs: one includes organs such as blood, liver, and skin that quickly and efficiently renew themselves. The other includes organs such as the pancreas, kidneys, and lungs, which don't. "It could be that organs that don't have adult stem cells [which are similar to progenitor cells] are just not very good at replenishing themselves," Melton says "Our studies were on the pancreas, but my expectation would be that organs like the kidneys and the lungs—both of which do not regenerate themselves—may fall into this same class."

It's possible that these organs have a counting mechanism or respond to external signals, limiting their ability to grow and regenerate. Melton is now teasing out the mechanisms that regulate an organ's capacity to grow.

BOUNDLESS POTENTIAL—LIMITED

Thomas C. Südhof

Pluripotent embryonic stem cells hold seemingly boundless potential. HHMI investigator **Thomas C. Südhof** at the University of Texas Southwestern Medical Center and stem cell biologist **Yi Sun** at the University of California, Los Angeles, demonstrated that certain existing stem cell lines may have more limited potential.

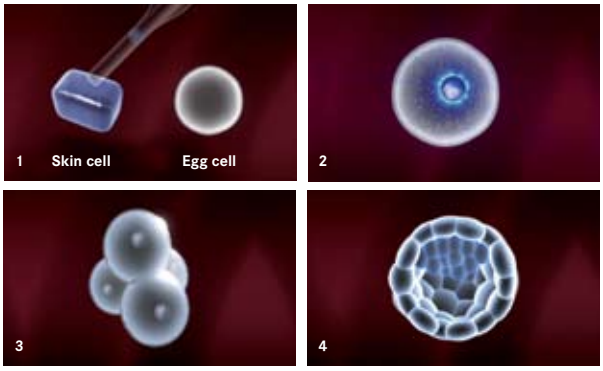
Südhof and Sun generated neurons from two embryonic stem cell lines distributed through the National Institutes of Health and discovered that the cell lines developed into two distinct types of neurons. The neurons from these two cell lines communicated via different neurotransmitters and relied on different regulatory factors. The team suspects that different culture conditions likely played a role in determining these cells' fates.

"There is absolutely no question that these findings mean there need to be more embryonic stem cell lines for research purposes and for use in potential treatments," says Südhof.

OF SKIN AND MICE

The healing of a simple cut demonstrates the skin's profound potential to renew itself. That regenerative ability lies with an adult stem cell—the keratinocyte stem cell, which produces skin cells, hair follicles, and oil glands. In a cloning first, HHMI investigator **Elaine Fuchs** and colleagues at the Rockefeller University used these stem cells to clone viable, healthy mice. The technique delivered a high rate of success compared with other methods for cloning mice. Although the team efficiently cloned mice, Fuchs is more excited about the possibility for keratinocyte stem cells to produce embryonic stem cells and what that might mean for treating human disease.

Elaine Fuchs



CLONING A MOUSE

1. In somatic cell nuclear transfer, or SCNT, the nucleus of an adult body cell—such as a skin cell from a mouse—is plucked out and injected into an unfertilized egg that has had its nucleus removed.
2. A reprogramming phenomenon occurs: the egg cell with the transferred nucleus initiates development.
3. The cell begins to divide, eventually forming a ball of cells called a blastocyst.
4. The blastocyst is implanted in a surrogate mother to create a cloned mouse. Alternatively, embryonic stem cells can be harvested from the inner cell mass (dark blue) of the blastocyst.

CONTROLLING GROWTH
The cells in a plant's epidermis both drive and restrict growth. Left: A wild-type *Arabidopsis* plant (normal). Right: A dwarf plant that has had its receptors for a particular growth hormone blocked. Middle: A former dwarf plant that has had the receptors turned on in the epidermis.

REACHING FOR THE SUN

It's a simple formula for growing plants—sun, soil, and seed. The mystery lies in how a plant decides to put down roots and send up shoots. For more than a century, scientists debated which tissue drove growth in plants: the waxy protective epidermis, the photosynthetic mesophyll tissue, or the central vascular tissues. In studies of dwarf *Arabidopsis* plants, HHMI investigator **Joanne Chory** of the Salk Institute for Biological Studies and postdoctoral fellow Sigal Savaldi-Goldstein settled that debate when they discovered that the epidermis delivers growth instructions to inner tissues. "It took us 10 years to develop the tools to ask the question," Chory says.

Chory's team has shown that the cells of the epidermis communicate with those of the inner plant, both driving and restricting growth. "If we want to feed over 9 billion people by the year 2050, then understanding the basic mechanics of plant growth is required," says Chory. "This knowledge will ultimately lead to our ability to increase yield, while decreasing the need for fertilizer and pesticides."

"If we want to feed over 9 billion people by the year 2050, then understanding the basic mechanics of plant growth is required."

—Joanne Chory

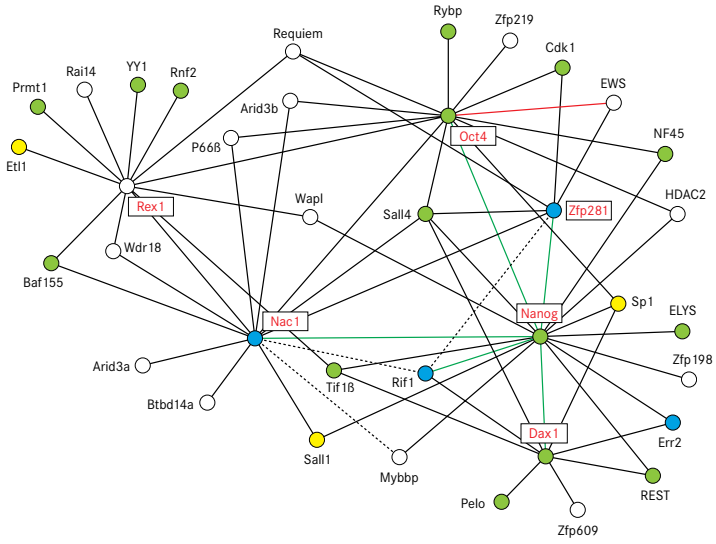
STIMULATING THOUGHT

Nadia Rosenthal

Washington, D.C.–area high school students attended the lectures.

Human embryonic stem cell research is science at its most promising and contentious. The 2006 Holiday Lectures on Science grappled with both in the latest iteration of this popular series. HHMI investigator **Douglas A. Melton** from Harvard University and **Nadia Rosenthal**, senior scientist at the European Molecular Biology Laboratory in Monterotondo, Italy, were the featured speakers at "Potent Biology: Stem Cells, Cloning, and Regeneration." In front of a live audience of 189 high school students from the Washington, D.C., area and a webcast audience in 42 states and 14 countries, Melton and Rosenthal provided primers on developmental biology and explored the potential of embryonic and adult stem cells. Melton and Rosenthal were joined by **Jonathan D. Moreno**, a bioethicist at the University of Pennsylvania and a member of HHMI's Bioethics Advisory Board, and Debra J.H. Matthews, a geneticist and bioethicist at the Berman Institute for Bioethics at the Johns Hopkins University for a spirited discussion of ethical issues. The lectures are available at **www.hhmi.org/biointeractive/lectures.**

MAPPING POTENTIAL



PROTEIN INTERACTIONS
This map sketches out the many protein interactions that give embryonic stem cells their developmental prowess. Each circle represents a different protein, and each line indicates an interaction. The six proteins labeled in red were used as "bait" to fish for additional interacting proteins. The proteins that were "hooked" (green, blue, and yellow) were confirmed by further experiments to be important for stem cell pluripotency.

HHMI investigator **Stuart H. Orkin** and his colleagues at Children's Hospital Boston have created a detailed map of the protein network that regulates an embryonic stem cell's ability to become many different types of cell. They have found that the proteins in the network are controlled as a group during embryonic cell differentiation. Filling in the details of the map may lead to Orkin's ultimate goal: reprogramming a mature cell to resemble as closely as possible an embryonic stem cell. "The major controversy over using human embryonic stem cells is that it requires obtaining oocytes and perhaps destroying embryos," says Orkin. "However, if one could reprogram, say, a skin cell to revert to become identical to an embryonic-type cell, it would obviate these ethical issues."

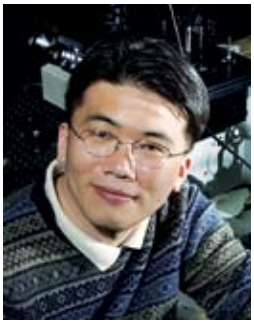
BIG DREAMS ABOUT SMALL THINGS

HHMI INVESTIGATORS are expanding scientific understanding by seeking insight from the infinitesimally small world of nanotechnology. An interdisciplinary science that develops tools on the molecular scale, nanotechnology is providing the means to create test tubes for reactions between single molecules, precisely tag cells, and build miniaturized laboratories. These nano-sized tools are transforming the way researchers observe interactions between molecules, allowing for precise measurements that can help them predict molecular behavior and study cell processes. The interdisciplinary nature of nanotechnology requires that scientists learn to communicate and collaborate with peers from many branches of science. Nanotechnology today offers a big glimpse of the future wrapped up in a tiny package.

SCIENCE AND THE SINGLE MOLECULE

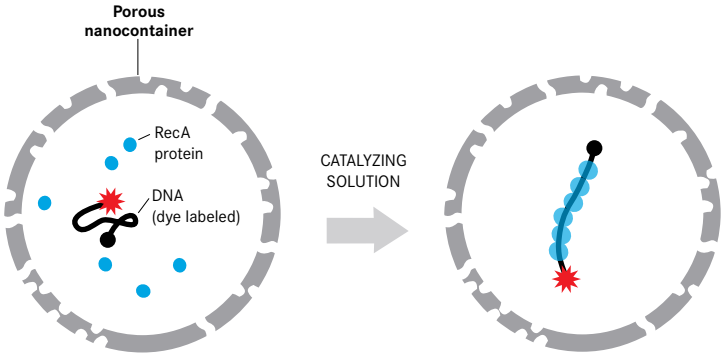
A new kind of "test tube," one-thousandth the diameter of a human hair and small enough to hold only a few molecules of DNA, is revolutionizing the way researchers observe the behavior of single molecules of DNA, RNA, and proteins. The test tubes are in truth bubble-like nanocontainers that are porous to small molecules, permitting researchers to feed ions and other chemicals into the ultra-tiny reaction chambers.

HHMI investigator **Taekjip Ha** at the University of Illinois at Urbana-Champaign and his colleagues are the creative force behind the new technology, which promises to make single-molecule techniques more accessible and more powerful. Currently, scientists extrapolate the behavior of individual molecules by observing the collective behavior of many. Ha, an expert in single-molecule study, believes scientists can learn more about the dynamics of the chemical reactions powering biology by studying the behavior of individual molecules. But techniques for single-molecule studies are limited and often highly specialized. "I think this technique will go a long way toward my goal of commoditization of [single-molecule] techniques, getting them out of specialists' labs to the general research community," Ha said.



"I think this technique will go a long way toward my goal of commoditization of [single-molecule] techniques, getting them out of specialists' labs to the general research community."

—Taekjip Ha



REACTION IN A NANOCONTAINER
The pores in a nanocontainer let small molecules, such as ions and other chemicals, pass through but keep large molecules, such as proteins and DNA, inside. Here, a catalyzing solution infused into the container triggers RecA proteins to interact with DNA, forming a filament.

NANONEEDLE DELIVERS

Tiny tracer molecules are used to study the physics and biochemistry of normal cellular processes. However, introducing such tracer molecules into cells is fraught with peril. Standard methods can damage the cell membrane, and the liquid carrying the tracers can engorge the cell, thereby altering its properties. In an effort to study a cell's normal state, HHMI investigator **Carolyn R. Bertozzi** at the University of California, Berkeley, and the Lawrence Berkeley National Laboratory and her colleagues invented a carbon nanotube needle so small—about one-thousandth the diameter of a human hair—that it can deliver minute amounts of tracer without disrupting the cell.

"Carbon nanotubes have remarkable properties in that they are very rigid, and their overall strength is greater than steel," says Bertozzi. "So, we thought that if you could somehow load cargo onto a carbon nanotube, it could be used to puncture the relatively soft cell membrane and introduce the cargo into the cell without leaving a huge hole in its wake. At the small diameters of carbon nanotubes, the hole should heal readily."

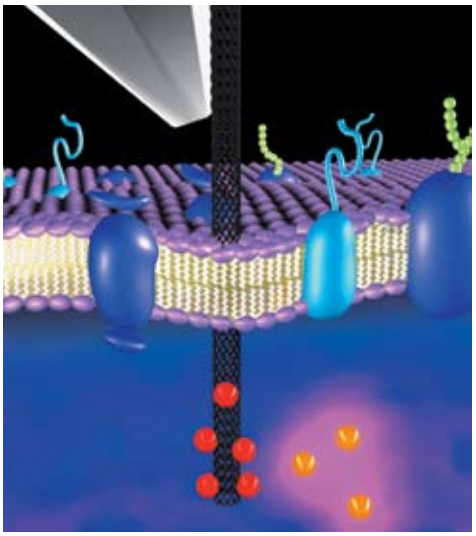
Bertozzi linked tiny fluorescent quantum dot tracers to a carbon nanotube needle via chemical bonds that break when they encounter the intracellular environment. In doing so, they can precisely deliver the quantum dot tracers into the cell without using liquid carriers.

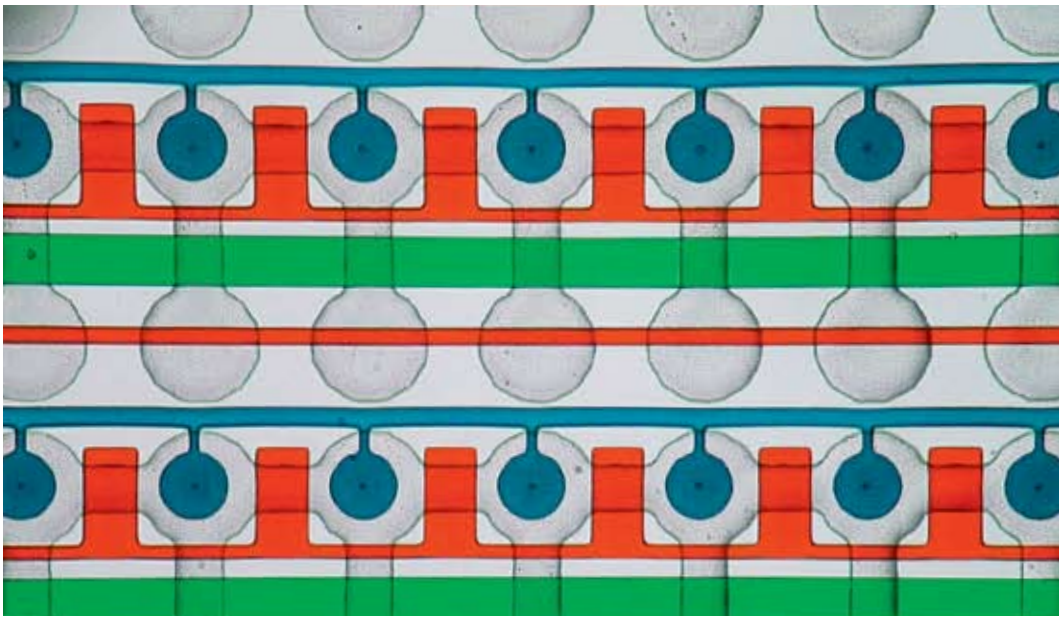
"The good news is that we've shown that the nanoinjector system can introduce such cargoes as quantum dots into cells with little damage," says Bertozzi. "However, the bad news is that we can only deliver a limited number of molecules."

Bertozzi and her group are working on using the nanoinjector to introduce larger molecules, such as DNA, into cells, as well as exploring whether they can target individual components of the cell.

Carolyn R. Bertozzi

INJECTING TRACERS
A carbon nanotube needle (black) pierces the cell membrane and delivers fluorescent quantum dot tracers (red) into the cell. The nanoneedle is so small that it does not disrupt the cell.





MICROLABORATORY
A laboratory about the size of a quarter enables scientists to observe 2,400 chemical interactions simultaneously among molecules such as DNA and proteins. This detail of the microlaboratory shows reaction chambers, each controlled by two valves (orange and green). A button membrane (blue) is used to trap molecules.

LILLIPUTIAN LABS

To understand complex biological systems, scientists must carefully and precisely characterize molecular interactions. It also helps if they like to do a little plumbing–very little, that is. HHMI investigator **Stephen R. Quake** and his colleagues at Stanford University have designed laboratories ranging in size from a quarter to a credit card that are capable of running miniaturized molecular biology experiments. Quake envisions these labs on a chip–made up of dense networks of pipes, valves, and chambers cast in clear rubber–accelerating biological research in the same way the silicon computer chip revolutionized mathematical computation.

Quake's fascination with the Lilliputian world of microfluidics, where scientists manipulate fluids one-hundredth to one-thousandth the volume of a human tear, intersects with his interest in systems biology–the study of how biological networks act in concert. High-throughput technologies have allowed researchers

"We are hoping to open a whole new chapter in how one understands the microbial universe."

–Stephen R. Quake

FOSTERING COLLABORATION

Jennifer L. West

Nanotechnology lies at the intersection of the biological sciences and engineering. Conventional undergraduate science and engineering programs, however, do little to prepare students to conduct research in this field. The Rice Institute of Biosciences and Bioengineering's HHMI Summer Internship in Bionanotechnology is designed to bridge the gap between disciplines. Engineering and physical science undergrads chosen from Rice University and schools around the nation receive an intensive course in biology before they fan out to laboratories to conduct interdisciplinary bionanotechnology research. All the while, the students focus on their ability to communicate with scientists in other disciplines.

Program director **Jennifer L. West**, a bionanotechnologist selected as an HHMI professor to employ her creative science education methods, notes that the undergraduate program is just one of four initiatives the Rice Institute has undertaken. The institute also offers a high school summer academy targeting inner-city and minority teens, an accelerated single-semester cell and molecular biology course, and freshman seminars in bionanotechnology for both science and nonscience majors. Participation in the summer internship program leaves students primed to overcome the communication barriers that hinder interdisciplinary research and ready to participate in the rapidly changing world of nanotechnology research.

to describe *which* molecules interact with each other, but they have been hard-pressed to describe *how* they do it—an observation critical to systems biology. Focusing on measuring the energy required for specialized proteins to bind to their DNA targets, Quake created a lab on a chip capable of conducting 2,400 reactions at once. Using only the physical measurements of binding energies, he could predict the biological functions of the proteins.

Quake's team also used microfluidics techniques to create a laboratory capable of crystallizing minute amounts of proteins. That effort is ongoing as the team tries to refine the crystallization process and eventually generate crystals for X-ray crystallographic analysis.

The labs on a chip provide a means to answer difficult scientific questions. Quake designed a microfluidics laboratory to circumvent the need to culture a bacterial species in order to characterize it. Intrigued by the fact that 99 percent of microbes can't be cultured and therefore studied and characterized in the lab, Quake sought a means to understand this vast microbial universe. "Those unstudied organisms are biology's dark matter," he says.

Because the human mouth is home to more than 700 species of bacteria, most of which haven't been characterized, Quake sought to characterize these members of biology's dark matter. Using the microfluidics lab on a chip, he amplified, sequenced, and characterized 1,000 genes from an organism that had never before been studied. He is now using the chip to isolate, identify, and sequence the community of microbes that dwell in termite hindguts, as well as building custom chips for other researchers seeking to study microbes in other specified environments. "We are hoping to open a whole new chapter in how one understands the microbial universe," Quake says.

BUILDING COMMUNITIES OF LEARNING

OVER THE PAST 20 YEARS of grant making in science education, HHMI has gained an abundance of knowledge and experience and built an unparalleled network of educators and researchers. This provides the foundation for the next generation of Institute initiatives. HHMI grantees are addressing issues such as increasing diversity in the sciences, engaging undergraduates in real research experiences, and improving science education for young students. Their innovative strategies are bringing together communities of learning–scientists, teachers, students, families–both locally and nationally. And the Institute is moving beyond its traditional role as a funder with the creation of its own national program focused on developing groundbreaking approaches to science education.

> **"We hope that giving students a great research experience early on will encourage more of them to become scientists."**
>
> **—Tuajuanda Jordan**

A SEA CHANGE

An experiment that could transform the teaching of college biology is under way at the University of Pittsburgh. Spearheaded by HHMI's new Science Education Alliance (SEA) program, a genomics course is being developed to engage undergraduates from colleges around the country in a research project at the earliest stage in their education.

"The course is primarily geared toward freshmen. We hope they are going to be a national community of undergraduate scholars engaged in authentic research," says SEA director **Tuajuanda Jordan**.

SEA, which will be headquartered at the Janelia Farm Research Campus in Northern Virginia, aims to become a national resource for science education by developing materials and methods and distributing them to the undergraduate education community. SEA will also assemble and support educator networks working on common activities. The national genomics experiment is its first project. "SEA represents the next step in HHMI's education initiatives," says Peter J. Bruns, HHMI vice president for grants and special programs. "Until now, we have been funding programs. Now we will play an active role in their development."

The genomics course was created in collaboration with HHMI professor **Graham F. Hatfull** at the University of Pittsburgh. **Sarah C.R. Elgin** at Washington University in St. Louis, HHMI undergraduate program director **Brad Goodner** at Hiram College in Ohio, and **A. Malcolm Campbell**, director of the HHMI-supported Genome Consortium for Active Teaching at Davidson College in North Carolina, served as advisers. Students in the program will isolate and characterize novel bacteriophages—viruses that infect bacteria—and analyze the viral genomic DNA. The DNA will be sent to the Joint Genome Institute in Walnut Creek, California, for cloning and sequencing. The students will then finish, annotate, and compare DNA sequences. Planning for the pilot project began in summer 2007, and it was launched at the University of Pittsburgh in fall 2007. Jordan will recruit 12 colleges and universities to participate in the project in the 2008–2009 academic year.

"This course is a way to expose students to how science is done in the real world," Jordan says. "In the long term, we hope that giving students a great research experience early on will encourage more of them to become scientists."

Q&A

A. MALCOLM CAMPBELL

ENGAGING UNDERGRADUATES IN GENOMICS RESEARCH

A. Malcolm Campbell is a professor of biology at Davidson College and founding director of the Genome Consortium for Active Teaching (GCAT)—an HHMI-supported program that facilitates the use of modern genomic methods in undergraduate education via a research-based curriculum. GCAT is a community of teachers and students working to improve the education of tomorrow's life-sciences professionals. During the 2007–2008 school year, approximately 5,000 undergraduates in liberal arts and community colleges in the United States and in Canada will participate.

How was GCAT created?

A

The idea for GCAT first came when I learned about microarrays at a conference in 1998. Mary Lee Ledbetter [a biology professor from the College of the Holy Cross] and I realized that our students could do microarray experiments. GCAT came into being because key people were willing to donate services and materials to permit us to develop the protocols, conduct the research, and analyze the data. Foremost are the gutsy small-college faculty who were willing to learn how to do microarray experiments along with their students in order to bring genomics into their curricula. HHMI investigator Patrick O. Brown of Stanford University donated microarrays for the first year, and Leroy Hood, cofounder of the Institute for Systems Biology in Seattle, the next two years. Laurie Heyer [a Davidson mathematics professor] and her undergraduate students developed an open-source, JAVA-based analysis software called MAGIC Tool. GCAT has allowed undergraduates to move from doing single-gene experiments to analyzing whole genomes.

How does GCAT foster the development of a community of learners?

A

GCAT has allowed students and faculty to work as colleagues as they decide what research to pursue and analyze the data derived from the microarrays. This year, two manuscripts authored by faculty and undergraduates have been accepted or published, and at least two more are under review.

What's next for GCAT?

A

We're trying to expose schools to the excitement and feasibility of conducting synthetic biology research in undergraduate classes. Synthetic biology applies engineering principles to genomic circuits to construct small devices—for example, a strain of yeast capable of detecting different concentrations of caffeine. It fosters collaboration and encourages students and faculty to think creatively and across disciplines—and it's much cheaper than microarray experiments. Because the field is so new, it offers opportunities for undergraduates to make real contributions.

DIVERSIFYING SCIENCE

Entering college freshmen from underrepresented minority and disadvantaged groups are just as interested in science as other students. While they represent 23 percent of all college students, at graduation they earn only 13 percent of the science and engineering degrees. "We've been losing them in our own house," says **Michael F. Summers**, a chemist and HHMI investigator at the University of Maryland, Baltimore County.

Inspired by discussions between HHMI professors and undergraduate program directors at a 2004 meeting, HHMI launched a series of symposia on diversity in the sciences to showcase successful diversity programs and encourage institutions to replicate or adapt them. "Diversity in the sciences is about making sure we don't lose the insights that come from a range of experiences and backgrounds," says symposia codirector **Robert Lue** of Harvard University.

Conducted at three locations—Harvard University, the University of Louisiana at Monroe, and the University of Washington, Seattle—76 colleges and universities serving an estimated 915,000 students participated in learning about model programs to increase diversity in the sciences. These programs provide early hands-on research opportunities, promote student-faculty interactions, and build a sense of community. Other strategies to increase academic success include intense mentoring by faculty or peers, summer courses to teach study skills, refocusing the way introductory courses are taught, and having students study in groups.

Students were key participants. Symposia codirector **Wendy Raymond,** an HHMI undergraduate program director at Williams College, notes that their perspectives had a powerful impact on faculty and administration attitudes about diversity.

The series wraps up in early 2008 at a meeting at HHMI's Chevy Chase, Maryland, headquarters.

REACHING THE SCIENTISTS

Since January 2006, HHMI and the journal *Science* have collaborated on a once-monthly section in the publication showcasing innovative approaches to teaching science. The continuing series of peer-reviewed teaching papers has included topics such as using authentic research experiences to teach science, research universities partnering with local schools to raise the level of science education, and innovative methods to teach mathematics.

"The collaboration is valuable because it provides a high profile for science education innovation and gives people who are involved in it a valued publication outlet," says Peter J. Bruns, HHMI vice president for grants and special programs. He points out that the collaboration supports HHMI's efforts to couple education with the way scientists do research. "Besides," he says, "we want to reach scientists, and *Science* is one place where they are."

Education Forum articles are available at **www.sciencemag.org/sciext/educationforum**.

"Diversity in the sciences is about making sure we don't lose the insights that come from a range of experiences and backgrounds."

—Robert Lue

Middle school students at a Duke University summer program isolated DNA from strawberries.

"Many of these institutions are reaching out to traditionally underserved populations. They are also engaging girls in science at a particularly critical time in their educational development."

—Jill Conley

IT'S NEVER TOO EARLY

Medical schools, hospitals, and other biomedical research institutions in communities around the country are sparking a love and understanding of science, particularly among young students. HHMI has committed $22.5 million over five years to 31 institutions to support their outreach efforts to students in kindergarten through 12th grade, as well as teachers, families, and other community members. "These grants provide a unique opportunity for the biomedical research community to provide hands-on experiences and rich content to students and teachers," says Peter J. Bruns, HHMI vice president for grants and special programs.

At Virginia Commonwealth University in Richmond, for example, graduate students and postdoctoral fellows are helping local teachers introduce their students to systems biology—a field focusing on the cell or organism as a whole to better understand disease. In Honolulu, the Queen's Medical Center is presenting a series of health-science evenings for families to improve health literacy and help Native Hawaiian and Pacific Islander students pursue careers in biomedicine.

The Jackson Laboratory in Bar Harbor, Maine, is reaching out to high school students and their teachers. The Summer Student Program encourages minority and underserved students from around the country to spend the summer engaged in cutting-edge research. Locally, the lab hosts high school students for year-long internships. Maine math and science teachers have the opportunity to take research sabbaticals at the lab.

Together, the grants will help broaden access to science across diverse populations. "Many of these institutions are reaching out to traditionally underserved populations," says **Jill Conley**, director of HHMI's precollege science education program. "They are also engaging girls in science at a particularly critical time in their educational development."

SCIENCE POSSES AND BIOPROSPECTORS

Research scientists selected to be HHMI professors receive $1 million each to put innovative ideas for undergraduate science education into practice. Their efforts to ignite and sustain the scientific spark in a new generation of students are taking them from the rain forest to the inner city.

Irving R. Epstein, a chemist at Brandeis University, is working with the Posse Foundation of New York to form a science posse. The foundation has helped more than 1,500 inner-city high school students from diverse backgrounds thrive at top colleges and universities. It provides students with academic and life skills, mentors, and regular support at college. The program has one flaw, however: it hasn't produced scientists.

By tweaking this successful program to include paid laboratory research positions and a two-week "boot camp" during the summer to bring students' science skills up to speed, Epstein hopes the 10 New York City–area students who will enter Brandeis in fall 2008 will one day help to diversify the scientific community. "It's not just the diversity of faces that matters. It's the diversity of ways of looking at the problem," Epstein says. "It's important to get people who don't all think the same way."

Scott A. Strobel, a molecular biophysicist at Yale University, takes undergraduates from the classroom to the Amazon rain forest and then back to the laboratory to immerse them in the processes of science. Developed with his father, Gary Strobel, a plant scientist from Montana State University, the year-long program has students "bioprospecting" for microorganisms that produce biologically active compounds in plants. After a semester-long seminar, students plan their research projects. During the first Amazon expedition, one student collected plants native people used to treat tuberculosis, and another sought out trees producing a potential drug-addiction therapy. When the students return from the jungle, they classify and analyze the microbes and then study bioactive molecules extracted from their cultures. The program began its second of four years in September 2007.

"It's not just the diversity of faces that matters. It's the diversity of ways of looking at the problem."

—Irving R. Epstein

HHMI professor Scott Strobel took undergraduate students "bioprospecting" in the Amazon rain forest.

SEPTEMBER 1, 2006–AUGUST 31, 2007

YEAR IN REVIEW

Janelia Farm Research Campus

JANELIA FARM RESEARCH CAMPUS

Nobel laureates gathered for Janelia Farm's opening symposium. From left: HHMI investigators Roderick MacKinnon and Richard Axel; Janelia Farm senior fellow Sydney Brenner; HHMI Trustees Paul Nurse and Joseph Goldstein; HHMI president Thomas Cech; and HHMI investigators Linda Buck and Eric Kandel.

A NEW SCIENTIFIC COMMUNITY OPENS FOR DISCOVERY

After six years of intense planning, construction, and recruiting, HHMI celebrated the opening of the Janelia Farm Research Campus with five days of events in early October 2006. Nearly 300 scientific, civic, and business leaders gathered on October 3 for a gala dinner to formally open the campus. The following day, a scientific symposium, attended by more than 200 scientists, HHMI Trustees, and guests, focused on major challenges and opportunities in neuroscience. Local officials and other notables from Loudoun County, Virginia, had an opportunity to view the facilities and meet Janelia staff at a reception on October 5. Closing the festivities were an open house for staff from HHMI's headquarters in Chevy Chase, Maryland, and a public open house that attracted more than 3,000 visitors for a day of talks and tours.

Janelia Farm director Gerald M. Rubin spoke to a packed auditorium at the public open house.

"The opening of Janelia Farm is a watershed event in the history of this Institute," says HHMI president Thomas R. Cech. "With the creation of this campus, HHMI has yet another venue from which to implement its core belief—that when creative, imaginative scientists are given the freedom, flexibility, and support to pursue their dreams, they can change the world."

INTERNATIONAL RESEARCH SCHOLARS MEETING

Janelia Farm hosted its first international scientific meeting on September 26–29, 2006. HHMI international research scholars—top biomedical scientists representing 28 countries—gathered to share insights and data from their latest research on some of the world's toughest medical challenges, including tuberculosis, malaria, and antibiotic resistance. "The campus and the culture of Janelia Farm were designed to support and encourage collaborative, interdisciplinary research," says Thomas R. Cech, HHMI president. "Those attributes make Janelia Farm a perfect location to host a meeting where researchers can share ideas about developing new scientific strategies for combating the challenging global problems that HHMI's international scientists have chosen to tackle."

VISITING SCIENTIST PROGRAM

The visiting scientist program encourages individual researchers and teams to work on short- and long-term projects at Janelia Farm. Over the past year, Janelia Farm welcomed more than 20 visiting scientists from the United States, Germany, England, Canada, and France to collaborate with Janelia researchers. About one-fourth were HHMI investigators. Their projects ranged from two weeks to a year or more.

JANELIA GRADUATE PROGRAM

HHMI launched its Janelia Farm graduate program, developed in partnership with the University of Chicago and the University of Cambridge, in September 2006. Students have the choice of earning their doctoral degree from either university, where they generally spend their first year. In most cases, the students conduct research alongside Janelia scientists for the remaining three or four years. "The combination of small labs, an intense research atmosphere, unique resources, and creative people makes Janelia an outstanding place to train as a new scientist," says Gerald M. Rubin, Janelia Farm director. The first student chosen for the graduate program began his studies at the University of Chicago in summer 2007.

Janelia Farm lab

LAB OF THE YEAR AWARD

R&D Magazine, a monthly publication highlighting technologies and strategies for research and development, named the Janelia Farm Research Campus its 2007 Lab of the Year. The criteria for the award include utility, safety, and architecturally distinguished design that enhances the research experience. "Janelia will be a magnet for collaboration and innovation," says Rick Johnson, one of the judges for the award. "The campus offers all the amenities for discovery—interaction, stimulation, collaboration, and a high quality of life and well-being." Ron Garikes, another award judge, adds, "The scale of the structures complements the expansive site. The planners and architects created an elegant design solution that also works from a flow, functionality, and aesthetic perspective."

First level of Janelia Farm's laboratory building

SUMMER RESEARCH PROGRAM FOR UNDERGRADUATES

In summer 2007, four students participated in a 10-week pilot program for undergraduate research at Janelia Farm. Living in on-campus housing, they worked with Janelia scientists on a variety of projects: exploring the neural basis of decision making in mice; improving brightness, signal change, and photostability of a family of genetically encoded glutamate sensors; building an experimental apparatus to study the fruit fly's response to gravity; and studying the anatomy of the fruit fly brain. Julie Simpson, a Janelia Farm scientist who welcomed a student into her lab, hopes the undergraduate program will help "convert smart young minds to neuroscience." Janelia plans to expand the program to at least eight students in summer 2008.

FIRST SEASON OF JANELIA CONFERENCES

More than 300 scientists attended the first season of Janelia conferences in spring 2007. These small, specialized meetings focus primarily on areas central to the research interests of Janelia Farm, and they are intended to foster

collaborative interactions and rapid scientific advances. Participants in the six spring conferences included Janelia Farm scientists, HHMI investigators, HHMI professors, graduate students, and postdoctoral associates. More than 20 percent of the attendees came from outside the United States, including Germany, Japan, the Netherlands, Australia, Italy, China, France, and Switzerland. Topics included "Visual Processing in Insects," "Expanding the Genetic Toolkit in Mouse," and "Neural Circuits and Behavior in *C. elegans*." Plans call for Janelia to hold about 15 such conferences each year.

Scientists attending conferences at Janelia Farm stay in guest housing on campus.

New Janelia Farm Scientists

Five scientists were selected to join Janelia Farm in 2007, bringing the total number of research groups to 24. Resident scientists generally fall into two main categories: group leaders and fellows. Group leaders direct research teams of two to six members, and fellows lead teams of up to two members.

Joshua T. Dudman
Fellow
Neurobiologist
Uses electrophysiological, imaging, and computational techniques to explore sensorimotor integration.

Albert K. Lee
Group leader
Neurobiologist
Studies the neural basis of learning and memory.

Anthony Leonardo
Group leader
Systems neuroscientist
Uses computational and experimental techniques to understand how behaviors emerge from neural circuits.

Lynn M. Riddiford
Senior fellow
Developmental biologist
Studies the hormonal control of insect growth, molting, and metamorphosis.

James W. Truman
Group leader
Developmental neuroscientist
Studies neuronal circuit formation in *Drosophila*.

INSTITUTE NEWS

NEW PUBLIC ACCESS POLICY FOR RESEARCH ARTICLES

After extensive consultation within the HHMI community, the Institute announced in June 2007 that it will require its scientists to publish original research articles in scientific journals that allow the articles and supplementary materials to be made freely accessible in a public repository within six months of publication.

The policy applies to all manuscripts submitted on or after January 1, 2008, and is an extension of existing policies that require HHMI scientists to share published research materials, databases, and software in a timely and useful fashion. Collaborative research articles on which an HHMI scientist is not a major author are not subject to the policy, but HHMI strongly encourages its scientists and collaborators to meet its public access standards.

PubMed Central, the free digital archive of biomedical and life sciences literature maintained by the National Institutes of Health, has been designated as the repository for journals in the biological sciences. Articles published in journals from other fields are expected to be deposited in comparable repositories and made publicly available within six months.

HHMI AND WELLCOME TRUST ESTABLISH INTERNATIONAL POSTDOCTORAL FELLOWSHIPS

HHMI and the Wellcome Trust launched an exchange program that enables postdoctoral researchers in the two institutes' laboratories to spend up to a year working abroad. The program is designed to promote scientific collaboration and research opportunities for scientists beginning their careers. Wellcome Trust postdocs can work in any of the HHMI laboratories in the United States, while those from HHMI labs can work in one of a number of Wellcome Trust laboratories in the United Kingdom. "The knowledge and experience that they will gain through the exchange program will be invaluable to them and will help forge links between international research groups," says Pat Goodwin, head of immunology and infectious disease funding at the Wellcome Trust.

HHMI FORGES PARTNERSHIPS TO SUPPORT POSTDOCTORAL RESEARCH

HHMI increased its support of outstanding young scientists by entering into new collaborations with the Jane Coffin Childs Memorial Fund, the Helen Hay Whitney Foundation, and the Damon Runyon Cancer Research Foundation and renewing its collaboration with the Life Sciences Research Foundation. The Institute will fund up to 16 postdoctoral fellows annually, who will conduct research in the laboratories of HHMI investigators. The fellows receiving HHMI support will be selected competitively by the four fellowship organizations. This funding allows each of the organizations to offer more fellowships than they would otherwise. The fellowships have three-year terms, and fellows will be employed by HHMI.

TWO COMPETITIONS FOR HHMI INVESTIGATORS

HHMI held two national investigator competitions this year. The first was aimed at physician-scientists interested in bridging the gap between basic research and clinical medicine. The other sought early career scientists studying biomedical problems in a broad array of disciplines, including not only biology and medicine but also related areas of chemistry, physics, engineering, and computational biology. The Institute plans to select approximately 15 physician-scientists and 50 general biomedical researchers. Unlike all previous investigator competitions, faculty at eligible institutions were able to apply directly to HHMI—institutional nominations were not part of the process. Selections will be announced in fall 2007 for the physician-scientist competition and in spring 2008 for the general competition.

COLLEGES COMPETE FOR EDUCATION GRANTS

More than 200 baccalaureate colleges and master's-level universities were invited to compete for $60 million in grant funding to support science education. The Institute expects to award approximately 50 grants ranging from $800,000 to $1.6 million to support innovative programs that strengthen undergraduate research, mentoring, interdisciplinary research, and the computational skills of students and faculty. Through this competition, HHMI seeks to buttress the research capacity of college science departments as it relates to teaching, as well as to integrate the life sciences with disciplines such as mathematics and computer science in a way that reflects the increasingly quantitative nature of modern biological research. The awards will be announced in May 2008.

GRANTS & FELLOWSHIPS

FIVE GILLIAM FELLOWS SELECTED

After proving their mettle as undergraduates doing summer research in HHMI-supported laboratories, five promising young scientists received HHMI's 2007 Gilliam Fellowships for Advanced Study. The competitive awards provide support for doctoral studies in the life sciences to students who are from groups underrepresented in the sciences or from disadvantaged backgrounds. The fellowships are named for the late James H. Gilliam Jr., an HHMI Trustee who devoted his life to fostering excellence and diversity in education and science.

Gilliam fellows are selected from a pool of undergraduate students who participated in HHMI's Exceptional Research Opportunities Program (EXROP). Over the past five summers, more than 200 EXROP students have conducted research in the labs of HHMI investigators and HHMI professors.

"The Gilliam fellows are exceptional young people with enormous potential and a burning desire to do biomedical research," says Thomas R. Cech, HHMI president. "Jim Gilliam would be proud to know that fellowships in his name are enabling these talented students to pursue scientific careers and help diversify the ranks of American science professors."

Irene C. Blat

Fluent in Spanish, Blat has volunteered as a translator at free medical clinics in immigrant communities in Charlotte, North Carolina. As an EXROP student, she worked with HHMI investigator Tania Baker at the Massachusetts Institute of Technology to understand how the viral protein MuB facilitates infection. Blat wants to become an academic biomedical researcher and stay involved in helping her community.

Veder J. Garcia

Garcia's interest in plant biology took root during childhood visits to his grandparents' farm in El Salvador. The first in his family to go to college, Garcia graduated with honors and was designated as the Botanical Society of America's 2006 Young Botanist of the Year. He hopes to work with Salvadoran biology professors to improve environmental education.

Nisha M. Broodie

Losing her mother to breast cancer contributed to Broodie's determination to pursue a career in biomedical science. As an EXROP student, her work in the lab of HHMI investigator Li-Huei Tsai at the Massachusetts Institute of Technology helped implicate DNA damage in the progression of neurodegenerative disorders such as Alzheimer's disease.

Eunha Kim

Kim left her family behind in South Korea to pursue an education in the United States. She earned bachelor's and master's degrees in molecular, cell, and developmental biology and envisions one day running her own lab and curing diseases such as the one she suffers from–fibromyalgia, a disorder that causes chronic muscle pain and fatigue.

Jose A. Rodriguez

Arriving in the United States from Jalisco, Mexico, with his family at the age of five, Rodriguez knew no English. In high school, he took advanced-placement science and math classes while working as a busboy 20 hours a week. Now a biophysics major, Rodriguez hopes "to channel the current explosion of technological innovation into the field of biomedical research."

Physician-scientist Charlotte Sumner, recipient of an early career award, in her lab at the Johns Hopkins University.

AWARDS SUPPORT PHYSICIAN-SCIENTISTS' RESEARCH

The Physician-Scientist Early Career Award initiative provides support to promising young physicians who want to pursue careers in academic biomedical research. The 20 awardees selected in 2007 will each receive $375,000 over five years for direct research expenses, and they will devote at least 70 percent of their time to research. The awards are available to alumni of the HHMI Research Training Fellowships for Medical Students and the HHMI–National Institutes of Health Research Scholars Program.

"Physician-scientists are uniquely positioned to translate research discoveries into direct benefits for patients," says Peter J. Bruns, HHMI vice president for grants and special programs. "The research these talented young scientists are doing has the potential to have a tremendous impact on public health."

INTERNATIONAL RESEARCH SCHOLARS RECEIVE AWARDS

Thirty-nine scientists from Argentina, Brazil, Canada, Chile, Mexico, and Venezuela were named HHMI international research scholars for their accomplishments and promising biomedical research. Chosen from 546 applicants, each scholar receives a five-year grant totaling $250,000 to $500,000. "These scientists are recognized pacesetters in their fields," notes Peter J. Bruns, HHMI vice president for grants and special programs.

Launched in 1991, the international research scholars program supports outstanding scientists in their own countries, linking them with each other and with HHMI scientists in the United States to create an international network of scientific excellence. The Institute has awarded more than $100 million in grants to scientists in 32 countries. These new awards are HHMI's fourth round to scientists in Canada and Latin America.

RESEARCH HIGHLIGHTS

In laboratories across the United States, some 300 HHMI investigators and their research groups are advancing knowledge in the most challenging areas of biomedical research today. And in 28 countries around the world, more than 100 international research scholars, who receive grant support from HHMI, are making significant contributions to understanding basic biological processes and disease mechanisms. Highlighted here is a sampling of the important research findings in fiscal year 2007. To learn more about the latest research by HHMI scientists, visit www.hhmi.org/news/research.html.

Switching off Aging in Stem Cells

A single molecular switch induces stem cells in the brain, pancreas, and blood to lose function as they age. Mice without this switch show considerably reduced aging-related decline in stem cell function and tissue regeneration.

Sean J. Morrison, *University of Michigan Medical School*

Fruit Fly Model Mimics Genetic Instability of Human Neurodegenerative Diseases

Researchers developed a fruit fly model that replicates the genetic instability seen in a variety of neurodegenerative diseases, including spinocerebellar ataxia type 3 (SCA3) and Huntington's disease. The model carries the same genetic mutation that affects humans who have SCA3, a disorder that causes loss of motor coordination.

Nancy M. Bonini, *University of Pennsylvania*

Focusing on Cancer's Complexity

In the first large-scale screen of genetic changes in cancer cells, HHMI researchers found that a typical breast or colorectal tumor results from mutations in about 90 genes. Different sets of mutations produce the same type of cancer.

Bert Vogelstein, *The Johns Hopkins University School of Medicine*
Sanford Markowitz, *Case Western Reserve University School of Medicine*

Analysis Reveals Extent of DNA Repair Army

A new database reveals a 700-member army of proteins involved in the DNA repair response. Scientists have already used the database to identify two proteins critical to recruiting BRCA1 to the sites of DNA damage.

Stephen J. Elledge, *Brigham and Women's Hospital*

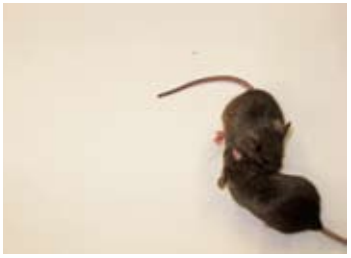
Sleeping Sickness Parasite Can't Live with Stress

The parasite responsible for African sleeping sickness causes its victims plenty of sleepless nights—but the parasite itself does not cope well with stress. New research shows that the parasite's natural response to stress is enough to kill it, a weakness that researchers may be able to exploit.

Shulamit Michaeli, *Bar-Ilan University, Israel*

Disabling a Sensory Organ Prompts Female Mice to Act Like Male Mice

By short-circuiting the sensory organ that detects the chemical cues mice use to attract mates, HHMI researchers prompted female mice to behave like male mice in the throes of courtship. The finding suggests that the neural circuits that govern gender-specific behaviors, such as aggression and



courtship, are similar in male and female brains.
Catherine Dulac, *Harvard University*

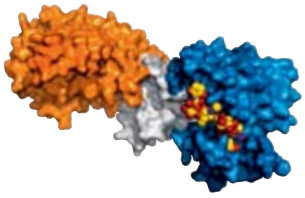
Structural Biology Reveals How T Cells Recognize Transplanted Tissue

HHMI researchers established how the structure of receptors on the surface of T cells enables them to recognize self and foreign cells. The research could lead to ways to improve the body's acceptance of transplanted tissue.
K. Christopher Garcia, *Stanford University School of Medicine*

A Genetic "Gang of Four" Drives Spread of Breast Cancer

Studies of human tumor cells implanted in mice show that the abnormal activation of four genes drives the spread of breast cancer to the lungs. The studies reveal that the aberrant genes work together to promote the growth of primary breast tumors.
Joan Massagué, *Memorial Sloan-Kettering Cancer Center*

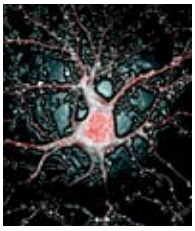
Bacterial Walls Come Tumbling Down



The first detailed images of an elusive drug target in an enzyme produced on the outer wall of bacteria may provide scientists with enough information to aid design of novel antibiotics. The drugs are needed to treat deadly infections initiated by *Staphylococcus aureus* and other bacterial pathogens. The enzyme above has an antibiotic bound to the blue region.
Natalie C.J. Strynadka, *University of British Columbia, Canada*

Gene Helps Distinguish Self from Non-Self During Neural Development

The dendritic limbs of developing nerve cells must organize themselves to cover as much space as they can evenly and efficiently. They must also take care to avoid over-

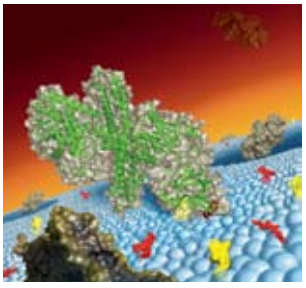


lapping with their sister dendrites. Researchers found that a much-studied gene provides branches of nerve cells with the ability to recognize one another and grow apart.
S. Lawrence Zipursky, *University of California, Los Angeles*
Yuh Nung Jan, *University of California, San Francisco*
Lily Y. Jan, *University of California, San Francisco*

Handicapping Tuberculosis May Be the Way to a Better Vaccine

A genetically altered strain of tuberculosis developed by HHMI scientists and their colleagues elicits a stronger immune response than the current vaccine, bacillus Calmette-Guérin. The new vaccine improves survival of infected mice and may help put scientists on track to replace bacillus Calmette-Guérin, which has been used for nearly a century.
William R. Jacobs Jr., *Albert Einstein College of Medicine*

Seeing a Neurotoxin's Deadly Grip



Two HHMI research teams working independently discovered new information about how the botulinum neurotoxin (gray and green above) shuts down neurons with deadly efficiency. By providing detailed views of the toxin plugged into its neuronal receptor, the studies could aid efforts to engineer specialized versions of botulinum neurotoxin for treating a wide array of medical problems.

Axel T. Brunger, *Stanford University*
Edwin R. Chapman, *University of Wisconsin–Madison*

Study Reveals Primates, and Their Neurons, in the Act of Reasoning

Every day, humans make thousands of decisions using the information at hand and their assessment of the potential outcome of those choices. In a pioneering study of rhesus macaque monkeys, HHMI researchers caught primates in the act of probabilistic reasoning. They measured the electrical activity in brain cells as the animals made choices on the basis of their interpretation of a set of visual cues and the potential for reward.

Michael N. Shadlen, *University of Washington School of Medicine*

Enhanced Environment Restores Memory in Mice with Neurodegeneration

Mice whose brains were devastated by neurodegeneration regained long-term memories and the ability to learn after their surroundings were enriched with toys and other sensory stimuli. Scientists achieved the same results when they treated the mice with a specific type of drug that encourages neuronal growth. The studies suggest two promising avenues for treatment that might alleviate learning deficits and memory loss in humans with Alzheimer's disease or other neurodegenerative diseases.

Li-Huei Tsai, *Massachusetts Institute of Technology*

Lithium Eases Symptoms of Fatal Neurological Disorder

Studies in mice have shown that lithium, a drug widely used to treat mood disorders in humans, can provide relief from the crushing symptoms of a fatal brain disease. HHMI researchers did a series of experiments in mice that showed lithium can ease the symptoms of spinocerebellar ataxia type 1, an inherited neurodegenerative disorder.

Huda Y. Zoghbi, *Baylor College of Medicine*

Muscle Repair Depends on Multiple Cell Types

Researchers identified a population of stem cells that repair muscle after damage. Researchers had assumed that all these cells, called satellite cells, had similar properties. They all seemed to follow the same developmental path to becoming mature muscle. The new discoveries show that the developmental fate of a given satellite cell depends on its physical orientation immediately after cell division.

Michael A. Rudnicki, *Ottawa Health Research Institute, Canada*

HONORS & AWARDS

Jack W. Szostak

SZOSTAK WINS LASKER AWARD

The 2006 Albert Lasker Award for Basic Medical Research was awarded to HHMI investigator **Jack W. Szostak** of Massachusetts General Hospital, Carol W. Greider of Johns Hopkins University, and Elizabeth H. Blackburn of the University of California, San Francisco, for their research on telomerase, the enzyme responsible for maintaining the ends of chromosomes. Telomerase is closely tied to human cancers and aging. The award, given by the Albert and Mary Lasker Foundation, honors "outstanding contributions in basic and clinical research."

Ronald M. Evans

TWO INVESTIGATORS RECEIVE ALBANY PRIZE

HHMI investigators **Ronald M. Evans**, The Salk Institute for Biological Studies, and **Robert J. Lefkowitz**, Duke University Medical Center, were awarded the Albany Medical Center's 2007 Prize in Medicine and Biomedical Research, the largest prize in medicine in the United States. The Albany Prize recognizes extraordinary and sustained contributions to improving health care and promoting biomedical research with translational benefits for patient treatment. Evans and Lefkowitz, along with Solomon H. Snyder of the Johns Hopkins School of Medicine, shared the $500,000 award. The three researchers were recognized for discoveries that reveal how cells use receptor molecules to communicate with their environment.

STEITZ WINS GAIRDNER AWARD

HHMI investigator **Thomas A. Steitz** of Yale University and his colleague Harry F. Noller of the University of California, Santa Cruz, were among the five recipients of the 2007 Gairdner Foundation International Award. Each awardee received a $30,000 prize. Steitz and Noller are credited with identifying the detailed structure and function of the ribosome, the subcellular structure where proteins are synthesized. Their work has led to the development of antibiotics that have the potential to circumvent resistance. The Gairdner Award is presented to medical scientists whose work is expected to significantly improve quality of life.

Thomas A. Steitz

LEFKOWITZ AWARDED SHAW PRIZE

Robert J. Lefkowitz, an HHMI investigator at Duke University Medical Center, was awarded the $1 million Shaw Prize in Life Science and Medicine. The international award is given to researchers whose work has achieved worldwide significance. Lefkowitz was recognized for "his relentless elucidation of the major receptor system that mediates the response of cells and organs to drugs and hormones." He is renowned for his work on G protein–coupled receptors, transmembrane receptors found throughout the body that are the targets of many well-known pharmaceuticals.

Robert J. Lefkowitz

Gerald M. Rubin

Morgan Sheng

HHMI SCIENTISTS ELECTED TO ROYAL SOCIETY

The Fellowship of the Royal Society, the national academy of science of the United Kingdom, elected two HHMI scientists in 2007. **Gerald M. Rubin**, HHMI vice president and director of the Janelia Farm Research Campus, was elected as a foreign member for his contributions to the field of *Drosophila* genetics and development. HHMI investigator **Morgan Sheng**, who studies synaptic ion-channel complexes at the Massachusetts Institute of Technology, was elected as a fellow.

EIGHT ELECTED TO THE INSTITUTE OF MEDICINE

The Institute of Medicine of the National Academies elected seven HHMI investigators and one HMMI professor in October 2006. Members are elected through a highly selective process that recognizes people who have made major contributions to the advancement of medical sciences, health care, and public health. The investigators are **Linda B. Buck**, Fred Hutchinson Cancer Research Center; **Stephen J. Elledge**, Brigham and Women's Hospital; **Richard A. Flavell**, Yale University School of Medicine; **Stephen P. Goff**, Columbia University College of Physicians and Surgeons; **Susan L. Lindquist**, Massachusetts Institute of Technology; **Joan Massagué**, Memorial Sloan-Kettering Cancer Center; and **Charles S. Zuker**, University of California, San Diego. The HHMI professor is **Baldomero Olivera**, University of Utah.

NATIONAL ACADEMY OF SCIENCES ELECTS 11

In May 2007, 11 HHMI investigators were elected to the National Academy of Sciences. The investigators are **David A. Agard**, University of California, San Francisco; **David J. Anderson**, California Institute of Technology; **Tania A. Baker**, Massachusetts Institute of Technology; **Sean B. Carroll**, University of Wisconsin–Madison; **Brian J. Druker**, Oregon Health & Science University; **Scott D. Emr**, University of California, San Diego; **David Ginsburg**, University of Michigan Medical School; **Helen H. Hobbs**, University of Texas Southwestern Medical Center at Dallas; **Christopher Miller**, Brandeis University; **Gerald I. Shulman**, Yale University School of Medicine; and **Wayne M. Yokoyama**, Washington University School of Medicine in St. Louis.

NATIONAL ACADEMY OF SCIENCES HONORS SIX HHMI RESEARCHERS

The National Academy of Sciences (NAS) honored six HHMI scientists in April 2007 with various awards for their outstanding scientific achievements.

Xiaodong Wang, HHMI investigator at the University of Texas Southwestern Medical Center at Dallas, received the Richard Lounsbery Award for his pioneering work on apoptosis.

The NAS Award in Molecular Biology was given to HHMI investigator **Gregory J. Hannon** of Cold Spring Harbor Laboratory for "elucidation of the enzymatic engine for RNA interference."

Randy L. Buckner, an HHMI investigator at Harvard University, received one of the Troland Research Awards for

his "substantive contributions to understanding of the neural mechanisms of memory formation and retrieval."

HHMI investigator **Jeffrey M. Friedman** at Rockefeller University was given the Jessie Stevenson Kovalenko Medal for his work with leptin and its implications for obesity.

The Alexander Hollaender Award in Biophysics went to **Barry H. Honig**, an HHMI investigator at Columbia University, for his theoretical and computational studies of macromolecular interactions and protein folding.

HHMI professor **Richard M. Losick** of Harvard University was honored with the Selman A. Waksman Award in Microbiology for "discovering alternative bacterial sigma factors and his fundamental contributions to understanding the mechanism of bacterial sporulation."

AMERICAN ACADEMY OF ARTS AND SCIENCES ELECTS 12

The American Academy of Arts and Sciences elected 10 HHMI investigators and 2 HHMI professors in April 2007. The investigators are **Brenda L. Bass**, University of Utah School of Medicine; **Bonnie L. Bassler**, Princeton University; **Nancy L. Craig**, The Johns Hopkins University School of Medicine; **Barry H. Honig**, Columbia University; **Lily Y. Jan**, University of California, San Francisco; **Yuh-Nung Jan**, University of California, San Francisco; **Robert A. Lamb**, Northwestern University; **Gail Mandel**, Oregon Health & Science University; **Michel C. Nussenzweig**, The Rockefeller University; and **Helen Piwnica-Worms**, Washington University School of Medicine in St. Louis. The professors are **Baldomero Olivera** of the University of Utah and **Susan R. Wessler** of the University of Georgia.

TWO WIN BRUCE ALBERTS AWARD

HHMI professor **Sarah C.R. Elgin**, Washington University in St. Louis, and HHMI undergraduate program director **A. Malcolm Campbell**, Davidson College, received the 2006 Bruce Alberts Award for Excellence in Science Education from the American Society for Cell Biology. Both were recognized for giving undergraduate students hands-on experience with genomics. Elgin is founder of the Genomics in Education Program, which engages students in sequencing and annotating genomes. Campbell started the Genome Consortium for Active Teaching, which aims to bring functional genomics into the undergraduate curriculum through research.

Sarah C.R. Elgin

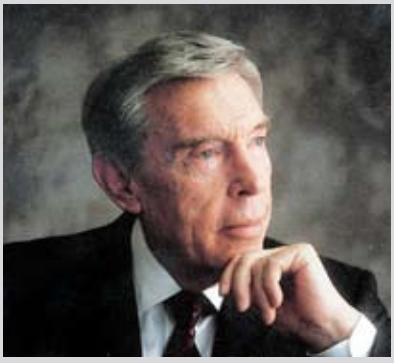
A. Malcolm Campbell

PASSAGES

David L. Garbers, a distinguished scientist and an HHMI investigator for more than 30 years, died on September 5, 2006. He was 62 years old.

Garbers was a professor of pharmacology and director of the Cecil H. and Ida Green Center for Reproductive Biology Sciences at the University of Texas Southwestern Medical Center in Dallas. His science focused on sperm biology and signal transduction. While at the Vanderbilt University School of Medicine early in his career, he discovered a novel family of receptors on the sperm cells of sea urchins that enable sperm to swim in the right direction. He later found the same receptors in higher organisms, including mammals. More recently, Garbers identified proteins expressed only on sperm cells, including an ion channel that gives a sperm the wiggle it needs to penetrate the egg membrane. His research has opened opportunities for new contraceptives and ways to increase fertility. Garbers's scientific interests also extended to stem cell biology and the development of techniques to grow male germ cells in the laboratory.

Garbers was a member of the National Academy of Sciences, as well as the American Academy of Arts and Sciences and the Academy of Medicine, Engineering, and Science of Texas.



Frank William Gay, a business executive and retired HHMI Trustee, died on May 21, 2007, in Kingwood, Texas. He was 86.

Gay's association with HHMI extended over more than 30 years. A business associate of Institute founder Howard R. Hughes Jr., he was one of the eight original Trustees appointed by the Delaware Court of Chancery to oversee HHMI. He served as a Trustee from 1984 to 2006, providing thoughtful guidance and counsel during a period of transformation and growth for the Institute. Before being appointed as a Trustee, Gay served on the Institute's executive committee from 1971 to 1984. A successful business executive, Gay held a number of positions during his career and association with Howard Hughes. He was chairman of the board of directors of the Hughes Air Corporation, a senior vice president and member of the board of directors of the Hughes Tool Company, and president and chief executive officer of Summa Corporation. Gay was active in a number of organizations, including the Boy Scouts of America. A veteran of the U.S. Army and the Marine Corps, he was a graduate of Brigham Young University and was honored with its Distinguished Alumni Award in 1976.

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Washington University School of Medicine

Paula D. McPoland
University of Washington School
of Medicine

Charles B. Mikell
Columbia University College of Physicians
and Surgeons

Eric Milner
Washington University School of Medicine

Camille M. Minder
Duke University School of Medicine

Steven C. Minear
Stanford University School of Medicine

Sandy Mong
Harvard Medical School
(Massachusetts Institute of Technology)*

Anvy T. Nguyen
University of California, San Francisco,
School of Medicine

Krishna N. Parekh
Duke University School of Medicine
(University of Pennsylvania School
of Medicine)*

Tanvi N. Parikh
Cornell University, Joan and Sanford
I. Weill Medical College and Graduate
School of Medical Sciences
(Memorial Sloan-Kettering Cancer Center)*

Nishant D. Patel
Johns Hopkins University School
of Medicine

Priyesh A. Patel
Duke University School of Medicine

Bradford A. Perez
Duke University School of Medicine

Joshua Schulman
Harvard Medical School

Andrew D. Schweitzer
Mount Sinai School of Medicine
(Albert Einstein College of Medicine)*

Alexandra Snyder
Mount Sinai School of Medicine

Sheela C. Toprani
Cleveland Clinic Lerner College
of Medicine of Case Western
Reserve University
(Case Western Reserve University
School of Medicine)*

Ryan Ungaro
Mount Sinai School of Medicine

Luis A. Verduzco
Harvard Medical School

Kyle L. Viani
University of Michigan Medical School

Shoshana J. Weiner
Case Western Reserve University School of Medicine
(Cleveland Clinic Foundation)*

Elizabeth L. Whitlock
Washington University School of Medicine

Robert Wirka
Cleveland Clinic Lerner College of Medicine of Case Western Reserve University
(Cleveland Clinic Foundation)*

Ambrose H.W. Wong
Washington University School of Medicine
(Harvard Medical School)*

Ashley Wysong
Duke University School of Medicine
(University of North Carolina at Chapel Hill School of Medicine)*

Ai-ris Yonekura
Harvard Medical School

Charles Q. Yu
University of California, Davis, School of Medicine

Harras B. Zaid
University of California, San Francisco, School of Medicine

Elizabeth A. Zambricki
Stanford University School of Medicine

Continued Awards: Second Year of Research

Sudeb Dalai
Stanford University School of Medicine

Andrew Hoover
University of Iowa, Roy J. and Lucille A. Carver College of Medicine

Charles Rickert
Washington University School of Medicine

HHMI-NIH Research Scholars†

Amana Akhtar
University of Michigan Medical School

Sonny Batra
Stanford University School of Medicine

Steven Beaudry
West Virginia School of Osteopathic Medicine

Christina Bennett
Indiana University School of Medicine

Kristin Berg
Creighton University School of Medicine

Jim Boonyaratanakornkit
University of California, San Francisco, School of Medicine

Steven Brauer
Harvard Medical School

Christina Brezing
University of Florida College of Medicine

Jorge Caballero
Stanford University School of Medicine

Paul Campion‡
New York University School of Medicine

Jessica Choe‡
Drexel University College of Medicine

David Chou‡
University of Pittsburgh School of Medicine

Jonah Cohen
Brown Medical School

Kelly Cushing
Rush Medical College of Rush University

Fei Dong
Case Western Reserve University School of Medicine

Reza Ehsanian‡
Stanford University School of Medicine

Chibawanye Ene
Indiana University School of Medicine

Haven Garber
Ohio State University College of Medicine and Public Health

Joshua Gordon
David Geffen School of Medicine at UCLA

†This program is administered through Grants & Special Programs but is budgeted as a research operation.

‡Second year in program as an advanced scholar.

Fellowships & Grants

Rohit Gupta
Duke University School of Medicine

Kirsi Hakkinen
Harvard University School of Dental Medicine

Julie Hall
University of California, San Francisco, School of Medicine

Jesse Hanisch‡
Creighton University School of Medicine

Victor Harrison
University of Hawaii John A. Burns School of Medicine

Brett Jagger
Indiana University School of Medicine

Osamu Kaneko
David Geffen School of Medicine at UCLA

Adam Kern
University of Chicago, Division of Biological Sciences and Pritzker School of Medicine

Mohammed Khan
David Geffen School of Medicine at UCLA

Jung Eun Lee
Duke University School of Medicine

Quan Lan Lew
University of Chicago, Division of Biological Sciences and Pritzker School of Medicine

Michelle Longmire
University of New Mexico School of Medicine

Elise Meoli
University of Rochester School of Medicine and Dentistry

Eric Muñoz
Oregon Health and Science University School of Medicine

Derek Narendra
University of Michigan Medical School

Giang Nguyen‡
Albany Medical College

Josiah Orina
Emory University School of Medicine

Lavanya Palavalli
University of Missouri–Columbia School of Medicine

Mrinali Patel
Duke University School of Medicine

Katie Pricola
Stanford University School of Medicine

John Quick
New York University School of Medicine

Abigail Rao
Dartmouth Medical School

Andrea Russo
Dartmouth Medical School

Shashank Sinha
University of Chicago, Division of Biological Sciences and Pritzker School of Medicine

Mariel Solares
University of California, San Francisco, School of Medicine

Scott Steward-Tharp
University of Iowa College of Dentistry

Matthew Swisher
Duke University School of Medicine

Brian Sworder‡
Boston University School of Medicine

Ashesh Thaker
David Geffen School of Medicine at UCLA

Nicholas Zwang
Harvard Medical School

James H. Gilliam Jr. Fellowships for Advanced Study

Irene C. Blat
Massachusetts Institute of Technology

Nisha Broodie
Harvard University

Veder J. Garcia
University of California, Berkeley

Eunha Kim
Massachusetts Institute of Technology

José A. Rodriguez
University of California, Los Angeles

Physician-Scientist Early Career Awards

Nicholas M. Boulis
Emory University School of Medicine

Katherine de Castro Crew
Columbia University College of Physicians and Surgeons

Sarah M. Fortune
Harvard University School of Public Health

Paul J. Galardy
Mayo Clinic Rochester

Aram Hezel
Massachusetts General Hospital
(2006 awardee)

Farouc A. Jaffer
Massachusetts General Hospital

Eric C. Johannsen
Brigham and Women's Hospital

Aarif Y. Khakoo
University of Texas M.D. Anderson Cancer Center

Nerissa U. Ko
University of California, San Francisco, School of Medicine

Ross L. Levine
Memorial Sloan Kettering Cancer Center

Emanual Maverakis
East Bay Institute for Research and Education

Sridhar Ramaswamy
Massachusetts General Hospital

Vicente A. Resto
University of Texas Medical Branch

Manish Sagar
Brigham and Women's Hospital

Sean I. Savitz
University of Texas Medical School at Houston

Costi D. Sifri
University of Virginia Health Sciences Center

Jonathan A. Stiber
Duke University Medical Center

Charlotte J. Sumner
Johns Hopkins University School of Medicine

Matthew J. Walter
Washington University School of Medicine

Rebekah R. White
Duke University

Allan D. Wu
David Geffen School of Medicine at UCLA

Other Graduate Science Education Awards

Association of American Medical Colleges
Washington, D.C.
Grant: AAMC-HHMI Scientific Foundation for Future Physicians Committee
$105,000

Cold Spring Harbor Laboratory
Cold Spring Harbor, New York
Grant: Graduate and Postgraduate Educational Programs
$3,000,000

The Jackson Laboratory
Bar Harbor, Maine
Grant: Graduate and Postgraduate Educational Programs
$2,000,000

Marine Biological Laboratory
Woods Hole, Massachusetts
Grant: Graduate and Postgraduate Educational Programs
$4,000,000

Fellowships & Grants

UNDERGRADUATE SCIENCE EDUCATION PROGRAM

HHMI's Exceptional Research Opportunities Program (EXROP)

Nkosi Adejola
University of Miami

Jose Arevalo
University of California, Berkeley

Ashley L. Bolden
University of Colorado at Boulder

Christina Brown
University of California, San Diego

Flavian D. Brown
Carleton College

Tiara T. Byrd
Florida A&M University

Silvia G. Caballero
City University of New York, Hunter College

Scott S. Chilton
Massachusetts Institute of Technology

Akanni Y. Clarke
University of Massachusetts

Karla I. Claudio Campos
University of Puerto Rico–Cayey

Elias J. Cornejo
University of Colorado at Boulder

Kylie S. Durand
Louisiana State University and A&M College

Jasmine R. Ellis
Princeton University

Jasmine D. Garrett
Arizona State University

Daniel B. Gilmer
Howard University

Laura A. Gonzalez
University of Texas at Austin

Jessica Gutierrez
New Mexico State University

Tyanna Hadley
University of Delaware

Reginald S. Hurtt
University of Michigan–Ann Arbor

Shani K. Isaac
University of Florida

Christina M. Jones
Louisiana State University and A&M College

Doris O. Jones
Virginia Commonwealth University

Adebimpe Kasumu
Spelman College

Kristopher J. Kennedy
University of California, Los Angeles

Maureen W. Kimani
Emory University

Marissa K. Lee
Massachusetts Institute of Technology

Tim M. Mahanes
Georgia State University

Bertrade C. Mbom
Carnegie Mellon University

Tyra N. McCray
University of California, Davis

Juan P. Mena-Gonzalez
University of Arizona

Evin K. Nembhard
Harvard University

Nghi K. Nguyen
Stanford University

Oluwatobi A. Ogbechie
Harvard University

Ujunwa C. Okoye
State University of New York at Stony Brook

Maria K. Ortega
University of California, Los Angeles

Jose M. Pena
University of California, Berkeley

Markeith A. Pilot
University of California, Riverside

Sacha L. Prashad
University of California, Los Angeles

Enrique I. Ramos
University of Texas at El Paso

Jaime X. Ramos
University of California, San Diego

Juan M. Romero
California State Polytechnic University–Pomona

Quinn L. Sievers
Williams College

Devin Sok
Stanford University

Joshua J. Solano
Duke University

Beryl E. Swanson
University of Washington

Constantin N. Takacs
Yale University

Gloria R. Tavera
University of Florida

Brittany Taylor
University of Maryland, College Park

Dyese Taylor
Dartmouth College

Steven Tuyishime
University of Maryland, Baltimore County

Jeffrey Uribe
City University of New York, City College

Natalia Vasco
Rice University

Valerie M. Villanueva
College of William and Mary

Kimberley M. Watson
Swarthmore College

Other Undergraduate Science Education Awards

East Tennessee State University
Johnson City, Tennessee
Grant: Quantitative Biology–Curricular and Institutional Transformation at the Math/Biology Interface
$25,000

Hiram College
Hiram, Ohio
Grant: Web-Accessible Genomics Tools and Research Challenges for Undergraduate Education
$50,000

University of Wisconsin–Madison
Madison, Wisconsin
Grant: Summer Institute on Undergraduate Education in Biology
$92,000

PRECOLLEGE SCIENCE EDUCATION PROGRAM

Initiative for Biomedical Research Institutions

Baylor College of Medicine
Houston, Texas
$749,627

Cold Spring Harbor Laboratory
Cold Spring Harbor, New York
$746,243

Dartmouth Medical School
Hanover, New Hampshire
$749,958

Duke University School of Medicine
Durham, North Carolina
$749,957

Fred Hutchinson Cancer Research Center
Seattle, Washington
$696,000

Indiana University School of Medicine
Indianapolis, Indiana
$661,958

Institute for Systems Biology
Seattle, Washington
$721,734

The Jackson Laboratory
Bar Harbor, Maine
$749,000

Lovelace Respiratory Research Institute
Albuquerque, New Mexico
$742,678

Marine Biological Laboratory
Woods Hole, Massachusetts
$725,225

McLaughlin Research Institute
Great Falls, Montana
$529,308

Oregon Health and Science University School of Medicine
Portland, Oregon
$738,955

Purdue University West Lafayette School of Veterinary Medicine
West Lafayette, Indiana
$749,755

Fellowships & Grants

Queen's Medical Center
Honolulu, Hawaii
$747,644

Stanford University School of Medicine
Palo Alto, California
$748,330

University of California, Los Angeles, School of Dentistry
Los Angeles, California
$748,337

University of California, San Diego, School of Medicine
San Diego, California
$750,000

University of Cincinnati College of Medicine
Cincinnati, Ohio
$696,000

University of Florida College of Medicine
Gainesville, Florida
$676,543

University of Mississippi School of Medicine
Jackson, Mississippi
$695,923

University of Missouri–Columbia School of Medicine
Columbia, Missouri
$750,000

University of Texas M.D. Anderson Cancer Center
Houston, Texas
$750,000

University of Texas Medical Branch at Galveston
Galveston, Texas
$750,000

University of Texas Southwestern Medical Center at Dallas
Dallas, Texas
$749,908

University of Toledo College of Medicine
Toledo, Ohio
$749,820

University of Utah School of Medicine
Salt Lake City, Utah
$750,000

University of Wisconsin School of Medicine and Public Health
Madison, Wisconsin
$745,500

Virginia Commonwealth University School of Medicine
Richmond, Virginia
$750,000

Wake Forest University School of Medicine
Winston-Salem, North Carolina
$696,000

Washington University School of Medicine
St. Louis, Missouri
$736,852

West Virginia University School of Medicine
Morgantown, West Virginia
$696,000

Washington, D.C., Metropolitan Area Initiatives

Audubon Naturalist Society
Chevy Chase, Maryland
Grant: Greenlabs Environmental Teacher Workshops
$25,000

Chesapeake Bay Foundation
Annapolis, Maryland
Grant: Maryland Environmental Education Program
$150,000

Eleanor Roosevelt High School
Greenbelt, Maryland
Grant: Science and Technology Program
$29,000

Montgomery County Public Schools Educational Foundation
Rockville, Maryland
Grant: Elementary Science Leadership Program; Student and Teacher Internship Program; Teacher Professional Development
$651,000

Loudoun County, Virginia, Initiatives

Loudoun County Public Schools
Leesburg, Virginia
Grant: Teacher Professional Development Institute; Academy of Science; and College Scholarships**
$1,000,000

** College scholarships: $7,000 for each student.

College Scholarships

Chelsea A. Bradley
Loudoun County High School

Grace Chen
Briar Woods High School

Candace L. Garramone
Loudoun County High School

Caroline S. Higgins
Broad Run High School

Christina K. Holl
Freedom High School

Dina T. Khalf-Allah
Briar Woods High School

Saadia L. Khan
Dominion High School

Nicholas A. Lopez
Potomac Falls High School

Stutay Monga
Heritage High School

John T. Nguyen
Park View High School

Matthew E. Parker
Loudoun Valley High School

Jasmine B. Paul
Heritage High School

Nghi B. Phung
Park View High School

Jacquelyn A. Piccolo
Stone Bridge High School

Nicole A. Poltash
Broad Run High School

Candace D. Rubenstein
Stone Bridge High School

Emily S. Ryan
Potomac Falls High School

Annemarie C. Thomas
Dominion High School

Tae I. Um
Freedom High School

Emily C. Willis
Loudoun Valley High School

INTERNATIONAL PROGRAM

Canada and Selected Countries of Latin America

Argentina

Diego de Mendoza, Ph.D.
Institute of Molecular and Cellular Biology of Rosario, CONICET

Ana B. Elgoyhen, Ph.D.
Institute for Research on Genetic Engineering and Molecular Biology, CONICET

Alberto Carlos Frasch, D.D.S., Ph.D.
Institute for Research in Biotechnology, National University of General San Martin

Fernando A. Goldbaum, Ph.D.
Leloir Institute Foundation

Alberto R. Kornblihtt, Ph.D.
University of Buenos Aires

Javier F. Palatnik, Ph.D.
Institute of Molecular and Cellular Biology of Rosario, CONICET

Armando J. Parodi, Ph.D.
Leloir Institute Foundation

Marcelo Rubinstein, Ph.D.
Institute for Research on Genetic Engineering and Molecular Biology, CONICET

Alejandro F. Schinder, Ph.D.
Leloir Institute Foundation

Alejandro J. Vila, Ph.D.
Institute of Molecular and Cellular Biology of Rosario, CONICET

Pablo Wappner, Ph.D.
Leloir Institute Foundation

Marcelo J. Yanovsky, Ph.D.
University of Buenos Aires

Brazil

Maria F. Leite, Ph.D.
Federal University of Minas Gerais

Pedro L. Oliveira, Ph.D.
Federal University of Rio de Janeiro

Alexandre A. Peixoto, Ph.D.
Oswaldo Cruz Foundation

Fellowships & Grants

Canada

Mark Glover, Ph.D.
University of Alberta
(Effective January 1, 2008)

Lea Harrington, Ph.D.
Ontario Cancer Institute
(Through December 31, 2007)

Philip Hieter, Ph.D.
University of British Columbia

Timothy R. Hughes, Ph.D.
University of Toronto

Robert G. Korneluk, Ph.D.
Children's Hospital of Eastern Ontario Research Institute
(Effective January 1, 2008)

Freda D. Miller, Ph.D.
Hospital for Sick Children

Dana J. Philpott, Ph.D.
University of Toronto

Richard A. Rachubinski, Ph.D.
University of Alberta

Michael A. Rudnicki, Ph.D.
Ottawa Health Research Institute

Michael W. Salter, M.D., Ph.D.
Hospital for Sick Children

Erwin A. Schurr, Ph.D.
McGill University

Eric A. Shoubridge, Ph.D.
McGill University

Nahum Sonenberg, Ph.D.
McGill University

Peter St George-Hyslop, M.D., F.R.C.P.
University of Toronto

Natalie C. Strynadka, Ph.D.
University of British Columbia

Michael D. Tyers, Ph.D.
Samuel Lunenfeld Research Institute, Mount Sinai Hospital
(Through December 31, 2007)

André Veillette, M.D., F.R.C.P.
Clinical Research Institute of Montreal

Yu Tian Wang, Ph.D.
University of British Columbia

Richard W. Wozniak, Ph.D.
University of Alberta

Jeff Wrana, Ph.D.
Samuel Lunenfeld Research Institute, Mount Sinai Hospital

Chile

Miguel L. Concha, M.D., Ph.D.
University of Chile

Mexico

Luis G. Brieba de Castro, Ph.D.
Center for Research and Advanced Studies of the National Polytechnic Institute
(Mexico City)

Luis R. Herrera Estrella, Ph.D.
Center for Research and Advanced Studies of the National Polytechnic Institute
(Irapuato)

Ranulfo Romo, M.D., D.Sc.
Institute of Cellular Physiology, National Autonomous University of Mexico

Jean-Philippe Vielle-Calzada, Ph.D.
Center for Research and Advanced Studies of the National Polytechnic Institute
(Irapuato)

Venezuela

Raul A. Padron, Ph.D.
Venezuelan Institute for Scientific Research

Courses

Center for Research and Advanced Studies of the National Polytechnic Institute
Irapuato, Mexico
$150,000

University of KwaZulu-Natal
Durban, South Africa
$150,000

EDUCATIONAL RESOURCES

WGBH Educational Foundation
Boston, Massachusetts
Grant: NOVA scienceNOW
$1,500,000

OFFICE OF GRANTS AND SPECIAL PROGRAMS

HHMI Investigator Education Grants

David Baker, Ph.D.
University of Washington
Grant: Rosetta@home—A Protein Modeling Program
$100,000

Sean B. Carroll, Ph.D.
University of Wisconsin–Madison
Grant: Work on NOVA evolution program
$100,000

Roger Y. Tsien, Ph.D.
University of California, San Diego
Grant: BioBridge—Translating Today's Research for Tomorrow's Scientists
$74,876

Ronald D. Vale, Ph.D.
University of California, San Francisco
Grant: iBioseminars
$100,000

OTHER AWARDS

American Association for the Advancement of Science
Grant: *Science*'s Education Forum
$40,000

National Academy of Sciences
Grant: Follow-up activities related to the report *Guidelines for Human Embryonic Stem Cell Research*
$60,000 (fiscal year 2006)

National Research Council
Grant: Understanding Interventions That Encourage Minorities to Pursue Research Careers—Major Questions and Appropriate Methods
$5,000

American Academy of Arts and Sciences
Cambridge, Massachusetts
Grant: Support of the study *Federal Funding of Science*
$100,000

United Way of Loudoun County and Other Community Organizations in Loudoun County
Leesburg, Virginia
$31,425

United Way of the National Capital Area
Washington, D.C.
$50,000

FINANCE & INVESTMENTS

SEPTEMBER 1, 2006–AUGUST 31, 2007

The Howard Hughes Medical Institute is the nation's largest private supporter of academic biomedical research. The endowment is the Institute's principal source of funding. The investment objective is to manage the endowment in a prudent manner that will maintain its purchasing power and will fund the Institute's research and grants programs on an ongoing basis. At the end of the fiscal year on August 31, 2007, the endowment was $18.7 billion. Classified as a medical research organization by the Internal Revenue Service, the Institute is required to spend at least 3.5 percent of its endowment each year on direct medical research activities and related overhead, exclusive of grants and investment management.

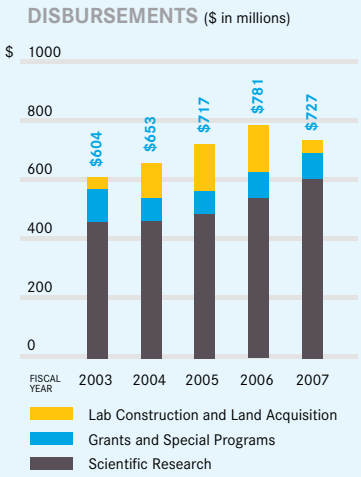
Disbursements in Fiscal Year 2007

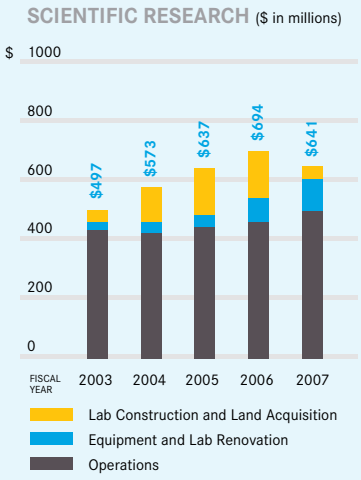
Disbursements during the fiscal year totaled $727 million: $599 million for HHMI scientific research, including the first year of operations of the Janelia Farm Research Campus in Ashburn, Virginia; $42 million for the completion of Janelia Farm and for headquarters expansion; and $86 million for grants for science education and international research scholars. Over the past five years, disbursements by the Institute totaled nearly $3.5 billion.

Scientific Research

HHMI's research activities are conducted principally at Institute laboratories at medical centers, teaching hospitals, and universities in the United States by investigators who hold faculty appointments at the host institutions. These individuals, together with their support staffs, are HHMI employees and are compensated directly by the Institute. Investigators may spend up to 25 percent of their time on teaching, administration, or other activities that benefit the host institutions. At the end of fiscal year 2007, the Institute supported 297 investigators at 64 academic medical centers.

As of August 31, 2007, the Institute's investment in laboratory space, equipment, and other property amounted to nearly $1.4 billion, with a current replacement value of approximately $1.7 billion.





Janelia Farm Research Campus

In August 2006, HHMI opened its Janelia Farm Research Campus. Situated on a 689-acre site along the Potomac River in Ashburn, Virginia, just outside Washington, D.C., the campus provides the setting for interdisciplinary, collaborative research focused on two areas: identifying the general principles that govern how information is processed by neuronal circuits; and developing imaging technologies and computational methods for image analysis. The total development cost was $500 million.

In its first year of operation, research expenditures at Janelia Farm totaled approximately $67 million, of which $15 million represented personnel expenditures and approximately $32 million was for equipment and outfitting. When Janelia Farm is at full capacity, it will house a permanent research staff of about 250—including 24 group leaders and 20 fellows—and up to 100 visiting scientists.

Grants and Special Programs

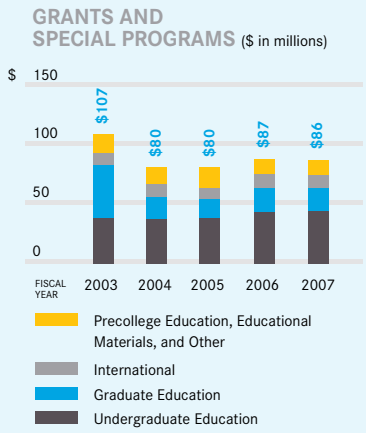
Through its grants program, the Institute supports science education at all levels, from the earliest grades through advanced research training. It also directly supports scientists conducting research in the biological sciences in selected foreign countries. The Institute disbursed $86 million to support the activities of 577 grantees in 29 countries during fiscal year 2007.

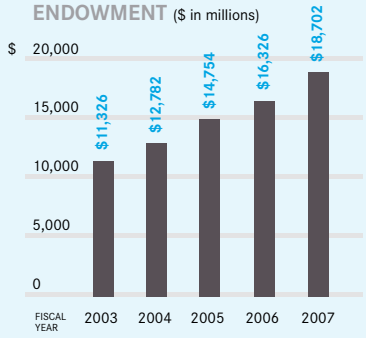
Endowment

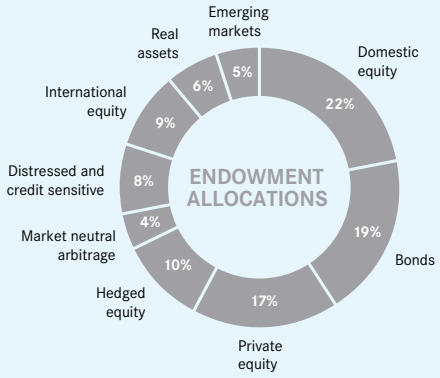
The Institute's endowment is managed under the direction of its vice president and chief investment officer. Approximately 69 percent of the endowment is invested by external fund managers; the remainder is internally managed. External managers are used principally to manage alternative investments, including hedge funds, private equity, and derivatives.

At the close of fiscal year 2007, the endowment was $18.7 billion, an increase of $2.4 billion from the end of fiscal year 2006. The endowment's return for fiscal year 2007 was 18.6 percent.

The composition of the Institute's endowment by investment category on August 31, 2007, is reflected in the graph to the right.







STATEMENT OF FINANCIAL POSITION

AUGUST 31, 2007, AND 2006

ASSETS ($ in millions)	**2007**	**2006**
Cash and cash equivalents	$ 105	$ 190
Investments	19,353	16,896
Investment and currency receivables, and other assets	1,421	297
Laboratory space, equipment, and other property—at cost, net of accumulated depreciation and amortization	796	755
Total Assets	$ **21,675**	$ **18,138**
LIABILITIES ($ in millions)		
Accounts payable, accrued expenses, and obligations	(208)	(209)
Grants commitments	(158)	(162)
Investment purchases payable, repurchase obligations, short sales, and currency payable	(2,049)	(858)
Notes and bonds payable	(627)	(624)
Total Liabilities	**(3,042)**	**(1,853)**
Net Assets	**$ 18,633**	**$ 16,285**

Financial Information

The Institute employs the firm of PricewaterhouseCoopers LLP as its independent auditor. The audited financial statements of the Institute for the year ended August 31, 2007, and the independent auditor's report thereon are available on the Institute's Web site at www.hhmi.org/about, or they may be obtained by writing to:

Controller
Howard Hughes Medical Institute
4000 Jones Bridge Road
Chevy Chase, Maryland 20815-6789

CREDITS

Page 1
Illustration by Riccardo Vecchio
Page 3
Bruce Weller
Page 6
Illustration by Riccardo Vecchio
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Page 10
Mello: Erika Larsen; Hannon: Zack Seckler/AP, © HHMI; Lowe: Zack Seckler/AP, © HHMI
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Todd Hido/Edge
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Svoboda: Paul Fetters; Ehlers: Karen Tam/AP, © HHMI; Neurons: Yifan Xu/Ehlers Lab
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Poliovirus: Boerries Brandenburg/Zhuang Lab; Zhuang: Joshua Dalsimer
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Zuker: Jeffrey Lamont Brown; Fruit fly eyes: David Yarmolinsky and Andrew Zelhof/Zuker Lab; Animation image: © 2006 The President and Fellows of Harvard College
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Gerald Jacobs/Nathans Lab
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Lindquist: Justin Knight; Prions: Courtesy of Peter Tessier and Tom DiCesare/Lindquist Lab
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Paul Fetters
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Pancreas: Qiao Zhou and Douglas Melton; Melton: Joshua Dalsimer
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Südhof: Paul Fetters; Fuchs: Matthew Septimus; SCNT images: Blake Porch and Chris Vargas/HHMI
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Arabidopsis: Laboratory of Joanne Chory; Chory: Courtesy of Salk Institute
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Rosenthal: Paul Fetters; Students: Paul Fetters; Map: Reprinted by permission from Macmillan Publishers, Ltd.: *Nature* vol. 444/16 November 2006/ doi:10.1038/nature05284, © 2006
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Bertozzi: Barbara Ries; Nanoneedle image: Courtesy of Gautam Rangan and Xing Chen/Bertozzi Lab
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Sebastian Maerkl/Quake Lab
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Donna Carson/AP, © HHMI
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Paul Fetters
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