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.
In botany, “innovation” describes the formation of a new shoot at the tip or apex of a branch. It’s the point at which growth and change occur. That less common usage of the word provides an apt metaphor for what we do at the Howard Hughes Medical Institute to create favorable environments for innovation among scientists, educators, and students. Sending out new intellectual shoots—in short, creativity and discovery—is what HHMI is all about. This annual report, which marks the 51st year since the Institute’s founding in 1953, provides a sampling of “new shoots” that sprouted in 2003–2004.

Our flagship program in biomedical research is the HHMI investigators program, with more than 300 scientists leading research groups at nearly 70 U.S. universities, research institutes, medical schools, and affiliated hospitals. It rests on the conviction that scientists of exceptional talent, commitment, and imagination will make fundamental biological discoveries if they are given resources, time, and freedom to pursue challenging questions. Over the past 12 months, HHMI investigators have more than lived up to that vision. In areas as diverse as cancer biology, stem cell research, proteomics, immunology, and metabolic engineering, they have transformed our understanding of essential biological processes while also providing their colleagues around the world with tools that will spark future medical discoveries. A more complete picture of the year in science is available on our Web site, www.hhmi.org.

Yet the value we place on innovation extends beyond the work of an individual scientist or laboratory to the Institute as a whole. As a science philanthropy whose explicit goal is the discovery of new knowledge, we seek to use our investments of intellectual and financial capital to seed growth and change, to foster fresh thinking. This past year has been no exception.

Under the leadership of David Clayton, we launched a national competition for up to 50 new investigators who, at an early stage in their careers, have demonstrated exceptional promise. This represents a commitment by HHMI to invest as much as $350 million in additional support for biomedical research over the next seven years.
Janelia Farm, our new research community currently under construction, will probe fundamental biomedical questions that are best addressed through a collaborative, interdisciplinary culture. Janelia Farm will give senior scientists and younger researchers flexible, long-term support and the freedom to explore particularly difficult problems. Initially, research will focus on two broad areas of scientific inquiry: the identification of general principles that govern how information is processed by neuronal circuits, and the development of imaging technologies and computational methods for image analysis. Gerald Rubin, the first director of Janelia Farm, leads the recruitment effort, which begins in 2004 with HHMI’s first open, international competition for group leaders.

Although HHMI has a fine tradition of supporting graduate education, we have given considerable thought to how investments by the Institute can extend beyond the support of individuals and affect the structure of graduate programs. We have found one such approach through a novel partnership with the new National Institute of Biomedical Imaging and Bioengineering (NIBIB), through which we hope to foster development of multidisciplinary programs that integrate the biomedical sciences with the physical sciences, computational sciences, and engineering. Seed funding will come from HHMI with sustained support, for up to five years, from NIBIB. This is just one example of the way in which Peter Bruns, who heads our grants effort, seeks to leverage the Institute’s expertise; other examples are outlined in this report.

If science is about innovation, in the myriad definitions of that word, then it’s fair to say that collaboration is an essential nutrient. Research requires collaboration—at the bench, in debate over data and conclusions, in learning and teaching. Appropriately, the work reported in the pages that follow is as much about collaboration as it is about the discovery of new knowledge. It is a continued honor and privilege to serve as part of this community.

Thomas R. Cech
President
IN MEMORIAM

A Tribute to George W. Thorn

A towering figure in the history of the Howard Hughes Medical Institute and in American medicine, George W. Thorn died on June 26, 2004, in Beverly, Massachusetts, at the age of 98. Thorn played an integral role in the creation and development of the Institute, and his prominent career as a physician, clinical innovator, and academic leader spanned seven decades.

An early adviser to Howard R. Hughes, Thorn helped guide the formation of HHMI, first in helping to select the group of fellows supported by Hughes before the Institute’s official founding in 1953.

Thorn’s formal tenure at HHMI began in 1955, when he was appointed to the Institute’s medical advisory board. The next year, he was also named HHMI’s director of research. Over the ensuing decades, Thorn served the Institute as a member of the Executive Committee, President, Trustee, Chairman of the Trustees, and Chairman Emeritus. He completed his service officially in 1990, but continued as an advisor until 1998.

Thorn’s contributions to HHMI were so varied and his service so long and so vital to the success of the Institute that “it is impossible to measure their full impact,” said Purnell W. Choppin, the Institute’s president emeritus. “He played an incomparable role in shaping the Institute’s future with wisdom, dedication, and great good humor.”

Born in Buffalo, New York, on January 15, 1906, George Widmer Thorn was educated at the College of Wooster in Ohio and went on to receive an M.D. degree from the University at Buffalo School of Medicine in 1929.

A world-renowned endocrinologist, Thorn served for three decades as physician-in-chief at Boston’s Peter Bent Brigham Hospital, a forerunner of Brigham and Women’s Hospital. Thorn pioneered the use of cortisone for treating Addison’s disease and found a treatment for the disease using an extract of the adrenal cortex. Thorn’s work with the extract—and later on with synthetic cortisone and natural adrenal hormones—paved the way for modern treatment of Addison’s disease and also led to advancements in the treatment of hypertension, rheumatoid arthritis, and diabetes.

Other of his notable innovations include bringing the first kidney dialysis machine to the United
States and organizing the medical team that performed the world’s first successful organ transplant (kidney) in 1954.

“[THORN] PLAYED AN INCOMPARABLE ROLE IN SHAPING THE INSTITUTE’S FUTURE WITH WISDOM, DEDICATION, AND GREAT GOOD HUMOR.”

Purnell W. Choppin
HHMI President Emeritus

Thorn’s outstanding medical service resulted in his being named as Hersey Professor of the Theory and Practice of Physic, which is this country’s oldest chair in medicine, at the Harvard Medical School. He was also founding editor and editor-in-chief of the textbook that is now Harrison’s Principles of Internal Medicine, a landmark medical resource. Thorn authored more than 400 publications and taught at Ohio State University, Johns Hopkins and Harvard medical schools, and the Royal College of Physicians in Great Britain.

Thorn was an active tennis player well into his later years, and his interests extended beyond the bounds of science and medicine to include music—he paid for much of his medical school tuition by playing tenor banjo in a dance band—horticulture, and travel. His heightened desire for discovery led him to expeditions into the interior of active volcanoes.

At their meeting following Thorn’s death, the HHMI Trustees adopted a resolution honoring his life and myriad contributions to the Institute. The statement concludes: “His energy, perspicacity, and acumen have been essential to the Institute’s emergence as the nation’s leading scientific philanthropy, a legacy that will continue to inform and reshape the medical and scientific landscape in successive generations. We shall miss this remarkable man and colleague.”

HHMI lost another of its founding Trustees with the death in August 2004 of Helen K. Copley.

Mrs. Copley, 81, was a charter Trustee of HHMI, appointed in 1984 by the Delaware Court of Chancery to oversee the Institute. She served as a Trustee for 11 years, providing wise counsel and thoughtful guidance during a period of sustained growth and transformation for the Institute.

A leading business executive and philanthropist, Copley was chairman and chief executive officer of The Copley Press, Inc., and publisher of the San Diego Union-Tribune for nearly three decades. She retired in 2001 and remained publisher emeritus and chairman emeritus of the company.
KEY SCIENCE FINDINGS OF 2004

Research Highlights

Richard Axel and colleagues successfully cloned a mouse using mature olfactory neurons as the genetic donor.

A team led by Frederick W. Alt, an expert in genomic instability (illus.), discovered unexpected protein interactions in the pathway from genes to antibody production.

Jonathan S. Weissman’s lab helped to establish that different prion strains are characterized by different misfolded conformations of the same protein.

Douglas A. Melton’s laboratory derived 17 new human embryonic stem cell lines and began distributing them for study.

Tom A. Rapoport and Stephen C. Harrison identified the structure of a channel that ferries proteins across cell membranes.

Carolyn R. Bertozzi led researchers who developed a tool for labeling sugar molecules on the surface of cells in living animals without altering the animals’ physiology.

Helen H. Hobbs and colleagues found that certain rare gene mutations can contribute significantly to low levels of a beneficial form of cholesterol in the blood.

Researchers led by Charles L. Sawyers reported a new compound designed to dodge resistance to Gleevec, a drug that virtually halts the progress of chronic myeloid leukemia.

Jack W. Szostak and colleagues discovered that clays may have been catalysts that spurred spontaneous assembly of fatty acids into the small sacs that evolved into the first living cells.

William T. Newsome and colleagues determined how the brain calculates the value of potential behavioral choices as those values change with new experiences.
More than 300 HHMI investigators lead research groups in partnership with nearly 70 U.S. universities, research institutes, and medical schools. Collectively, these scientists have made major discoveries and created new fields of research. Ten have received the Nobel Prize. More than 100 have been elected to the National Academy of Sciences. HHMI invests some $500 million in research annually, a commitment that will grow as the Institute creates Janelia Farm, a new interdisciplinary research community.

This review summarizes HHMI’s robust scientific activity during the 2004 fiscal year.

RECRUITING NEW INVESTIGATORS

In May 2004, HHMI announced a new national competition for investigators in biomedical research. The Institute is looking for candidates from the full range of biological and biomedical inquiry—including clinical research—who demonstrate exceptional promise early in their careers as independent researchers. Between 30 and 50 scientists will be chosen to join the Institute in 2005.

This call for new investigators represents a continued expansion of the Institute’s biomedical research mission. The Institute is committed to investing as much as $350 million in additional support for biomedical research over the next seven years. In addition to expanding its investigator program, HHMI has begun recruiting scientists for the HHMI Janelia Farm Research Campus.
One of the recent success stories in modern cancer treatment is the advent of Gleevec, a drug that virtually halts chronic myelogenous leukemia. Yet for some patients, under some circumstances, Gleevec ultimately fails. In July, HHMI investigator Charles L. Sawyers and colleagues at UCLA’s Jonsson Comprehensive Cancer Center reported the first description of a new compound that in some cases sidesteps the vexing problem.
“The identification of this compound as a drug candidate is a direct by-product of understanding why patients develop resistance to Gleevec,” says Sawyers. HHMI investigators Brian J. Druker, D. Gary Gilliland, John Kuriyan, and Owen N. Witte are among other scientists who have also advanced the understanding of targeted therapies such as Gleevec, including its structure and mechanisms of action.
Research on cancer, infectious diseases, diabetes, eye disorders, degenerative muscle diseases, and Alzheimer’s disease generated a significant number of publications by HHMI investigators this year.

**Tian Xu**, an investigator at Yale University School of Medicine, developed a fruit fly model useful in identifying combinations of gene malfunctions that contribute to metastatic cancer. Previously, researchers had looked for genes that contribute only to metastasis; Xu’s model has shown that genes involved in tumor formation are also directly involved in the metastatic process. Now it makes sense, says Xu, why tumors of different origins can have vastly different and distinctive metastatic potential. “The answer appears to be because it depends on the kind of mutations that it took for them to become tumors.”

For years scientists have tried to stifle cancerous growth by introducing tumor-suppressing proteins into cells, but with little practical success. An ingenious new technique devised by **Steven F. Dowdy**, an investigator at the University of California, San Diego, offers new hope. Dowdy found that introducing a fragment of the protein encoded by the tumor suppressor gene *p53* into mice afflicted with aggressive human tumors selectively killed tumor cells while leaving nearby normal cells undisturbed. Administering the peptide greatly increased survival of mice, in some cases producing apparently disease-free animals.
Working in mice with a progressive muscle degeneration disease similar to human muscular dystrophy, Kevin P. Campbell, an investigator at the University of Iowa Carver College of Medicine, and collaborators found that overexpression of a single protein restored normal muscle function. When the researchers expressed the protein, known as LARGE, in cultured cells from patients with muscular dystrophy, they saw similar benefits.

Researchers led by Gerald I. Shulman, an investigator at Yale University School of Medicine, tracked the potential cause of insulin resistance in the offspring of patients with type 2 diabetes to abnormalities in their mitochondria, the cell’s “power plants.” Impairment of mitochondria, which break down fatty acids, causes buildup of fats and fatty acids inside muscle that can produce insulin resistance. Such buildup can, in turn, contribute to the development of diabetes later in life.

In human studies, Edwin M. Stone and Val C. Sheffield, investigators at the University of Iowa Carver College of Medicine, identified subtle defects in a single gene that underlie a hereditary form of age-related macular degeneration, the leading cause of irreversible vision loss in the developed world. Stone hopes such work eventually will lead physicians to “direct specific treatments to those patient subgroups most likely to benefit from them.”
In August 2004, HHMI investigator Carolyn R. Bertozzi set science abuzz. Working at the University of California, Berkeley, Bertozzi and colleagues found a wholly new way to study chemical reactions in living organisms. The innovative approach tags sugars in a way that does not disrupt a cell’s biology and provides a new tool for labeling specific cells in animals.
How do we unlock the workings of the cell?

“One of the most exciting implications of this work is the prospect for imaging glycosylation in real time within living organisms,” Bertozzi says. “We hope to be able to witness changes in...a tissue as an animal develops through the embryonic stages, as a disease develops, or as tumors become metastatic.” Opening this window onto cellular activity was labeled by a reviewer in Nature as “a major step forward in chemistry.”
Many HHMI investigators seek a better understanding of how cells work. As public interest in stem cells grows, scientists pursue multiple facets of related research. A global team, for example, including investigator Sean J. Morrison at the University of Michigan, demonstrated that adult stem cells can fuse with brain, liver, and heart cells in the body. Their study calls into question the plasticity of adult stem cells, leading Morrison to caution scientists about conducting clinical trials using adult stem cells; the phenomenon of fusion might give the illusion that the stem cells are altering themselves to become mature cells in other tissues when they are not.

Douglas A. Melton and colleagues at Harvard University discovered that insulin-producing beta cells in the pancreas that are attacked in type 1 diabetes are replenished through duplication of existing cells rather than through differentiation of adult stem cells.

Researchers at the Carnegie Institution of Washington led by investigator Allan C. Spradling reported that they had induced differentiating cells to revert to being stem cells. Although such dedifferentiation is known to occur in natural systems, scientists did not have a laboratory model to study the process. The finding suggests that dedifferentiation should be explored as yet another route to generating stem cells for therapeutic purposes.
Researchers led by Mark A. Krasnow developed a fruit fly model for studying mammalian wound healing, a notoriously complex and difficult process to investigate.

Ronald Vale studies molecular motors, called kinesins (red), that transport cargo along highways called microtubules (blue) within the cell.

Thomas M. Jessell and colleagues at Columbia University College of Physicians and Surgeons discovered basic control signals that govern the organization of the spinal cord in the developing embryo. “The developing nervous system doesn’t have to get everything right from the word ‘go,’” Jessell says. “There is a steady nudging of the embryonic neurons in a particular direction of differentiation.” The finding could spark new understanding of inherited neurodegenerative diseases.

HHMI researchers designed and constructed what has been called the world’s first artificial protein—a novel functional protein that is not found in nature. Among other benefits, the finding could lead to the use of artificial protein enzymes for use as medicines or industrial catalysts, says the study’s lead author, investigator David Baker at the University of Washington.

Teams of researchers led by investigators Tom A. Rapoport and Stephen C. Harrison at Harvard Medical School solved the first high-resolution structure of a channel pivotal to protein transportation within cells. The channel aids protein distribution from the site of synthesis to points beyond and helps integrate proteins into the cell membrane, where they function as receptors or other components.
What can we discover from genetics?

**Erin K. O’Shea**, an HHMI investigator at the University of California, San Francisco, studies signaling networks and develops methods for assaying the entire complement of proteins found in an organism. “A major goal of genomics and proteomics is to understand the function of each protein,” she says of work done with investigator **Jonathan S. Weissman**, “and important clues can be gleaned from where each protein is within the cell.”
In separate research also published this year, O’Shea and colleagues reported that “noisy” genes may have a big impact on individuality. The researchers believe they have found the major source of the random “noise” in gene expression that can lead to differences in cells—and people, for that matter—that are genetically identical. The finding has implications for both evolution and biology.
From discoveries of evolutionary relationships between organisms to development of tools and techniques that promise better understanding of disease, HHMI investigators working in the field of genetics and applied genomics reported several significant findings.

In a study that redefined notions of how quickly evolution can occur in nature, David M. Kingsley, an investigator at Stanford University School of Medicine, showed how a small genetic change in the stickleback fish led to a major structural change in skeletal development. The work demonstrates that rapid skeletal changes can occur in one body structure without disrupting the essential role of the same genes elsewhere in the body.

Taking a step well back in evolutionary time, Jack W. Szostak and colleagues at Massachusetts General Hospital reported experimental evidence that clays may have been the catalysts that spurred spontaneous assembly of fatty acids into small sacs that ultimately evolved into the first living cells. “If we can demonstrate more natural ways this might have happened,” says Szostak, “it may begin to give us clues about how life could have gotten started on the primitive Earth.”

As genome sequences of different animals become available, comparative genomic studies broaden our understanding of evolutionary relatedness. Leonid Kruglyak and colleagues at the Fred Hutchinson Cancer Research Center made the first detailed genetic comparison of purebred domestic dogs gives insight to dog breeders and augurs improvements to canine health.
purebred domestic dogs, revealing surprising relationships between ancient and modern breeds and giving insight into more than 350 inherited disorders, including deafness, cancer, and epilepsy.

A team led by David Haussler at the University of California, Santa Cruz, found that the genomes of humans, rats, and mice have hundreds of stretches of DNA that are the same. Evolutionary theory suggests that these “ultraconserved” sequences may be central to mammalian biology.

Stephen J. Elledge, an investigator at Harvard Medical School and Brigham and Women’s Hospital, co-led a research group in creating a vast “library” of short segments of RNA that can be used to turn off individual human and mouse genes to study their function. The RNA interference library, available to researchers worldwide, is expected to be a powerful research tool.

Through work in the roundworm Caenorhabditis elegans, Barbara J. Meyer’s lab at the University of California, Berkeley, shed new light on how global control of all genes on a single chromosome can be established and maintained throughout the lifetime of an organism.
Cornelia I. Bargmann wants to know how genetics and development in the nervous system contribute to specific behaviors. The HHMI investigator at the University of California, San Francisco, studies the roundworm *C. elegans*, which discriminates among hundreds of different compounds that prompt different behaviors. Because the nematode has just 302 well-defined neurons, researchers can identify specific neurons that
generate certain behaviors. Bargmann and collaborators found a molecular mechanism by which *C. elegans* senses oxygen concentrations in soil, which likely helps them locate a hospitable environment. “We do monitor oxygen levels in our bloodstream using a rice grain-sized organ called the carotid body...” says Bargmann. “It might well be that we use a similar oxygen-sensing mechanism as the roundworm.”
Many HHMI investigators work to understand behavior, perception, and cognition.

Richard Axel, at the Columbia University College of Physicians and Surgeons, studies how olfactory information is represented in the brain. He collaborated with Rudolf Jaenisch at the Whitehead Institute for Biomedical Research and a team of researchers to clone a mouse using the nucleus of a single olfactory neuron. The population of neurons in the cloned mouse expressed the full range of odorant receptor molecules, demonstrating that gene rearrangements do not explain how individual neurons come to express only a single odorant receptor.

New studies by a team of researchers led by Jeffrey M. Friedman at the Rockefeller University showed that the appetite-regulating hormone leptin causes rewiring of neurons in areas of the brain that regulate feeding behavior. The discovery provides another important clue about how leptin exerts its effects on the brain to cause decreased food intake and increased energy expenditure.

At the Salk Institute, Terrence J. Sejnowski and collaborators employed a new kind of optical illusion to show that humans use both the timing and spatial context of a visual stimulus to judge brightness.

Two collaborating teams of researchers, one led by Thomas M. Jessell at Columbia University College of Physicians and Surgeons, devised a
HHMI researcher Thomas Jessell made new strides in understanding how walking is coordinated.

Randy Buckner’s group found that frontal brain regions used during a word classification task (red) showed reduced activity with practice (yellow).

genetic technique to distinguish which neurons in the spinal cord control the sequential stepping of left and right limbs. Their findings have literally taken them a step closer to understanding the neural circuitry that coordinates walking movements—one of the main obstacles in developing new treatments for paralysis.

The laboratory of cognitive neuroscientist William T. Newsome at Stanford University School of Medicine reported insight into the neural machinery that animals, possibly including humans, use to weigh the value of one action over another. The researchers determined the strategy by which the brain calculates the value of potential behavioral choices as those values change over time with new experiences.

In mouse studies at the University of California, San Diego, Charles S. Zuker and collaborators furthered our understanding of the molecular mechanisms behind the ability to taste sweet and umami (savory) flavors.

Studies by Randy L. Buckner at Washington University in St. Louis made progress in dissecting the neurological loss experienced by people with Alzheimer’s disease. He found that those affected retain a specific form of memory used for rote learning, even though other types of memories are extinguished.
A leader in molecular immunology, HHMI investigator Frederick W. Alt wants to understand the genetic checks and balances that give rise to immune system diversity. Alt, who works at Children’s Hospital Boston and Harvard Medical School, studies genomic instability and the evolution of genetic errors that can lead to immune cell cancers. This year, Alt and collaborators discovered a new component of the machinery
that immune cells use to generate a diverse array of antibodies from relatively few genes. The discovery reveals important links in the molecular pathway by which complex genetic alterations arm the immune system. “[This cofactor] RPA was never even suspected to be a candidate for such a role…,” says Alt. “Until now, it was only known to be involved in certain DNA replication and repair pathways.”
How do organisms invade the body, and how does the immune system respond? As these representative findings show, HHMI investigators are gaining new insights.

In a surprising twist, Ruslan Medzhitov at Yale University School of Medicine found that the millions of beneficial bacteria living in the human gut might actually help to stave off injury to the lining of the intestines. Among other implications, according to the researchers, this suggests that the practice of giving antibiotics to cancer patients to prevent infections might in fact render the gut more vulnerable to damage. The finding may change the treatment of inflammatory bowel disease, in which the intestine is believed to mount an inflammatory response to benign, or commensal, bacteria.

Led by Wayne M. Yokoyama, researchers at Washington University School of Medicine in St. Louis discovered that when the second line of defense in the mouse immune system is disabled, a normally harmless virus that evades natural killer cells—the first line of defense—can rapidly mutate into a lethal one. “It’s important to note that the virus that comes back is not the virus that was originally put in,” says Yokoyama. The discovery may shed light on why people with compromised immunity sometimes suffer severe infections from viruses that they would otherwise defeat.
MICROMANAGEMENT
Stephen Harrison’s laboratory studies the atomic structures of macromolecular assemblies, such as in this papilloma virus, to understand how they function in cells.

THE 1918 FLU
The late Don C. Wiley and colleagues identified characteristics of a surface protein on the influenza virus that likely explain the ferocity of the 1918 flu epidemic. (Here, Boston Mayor Andrew Peters gets inoculated.)

A CLEAR VIEW
Live transparent zebrafish embryos four days after fertilization, with those in the middle ring stained for hemoglobin to detect red blood cells.

The zebrafish, thanks to its transparent embryo, has provided Leonard I. Zon at Children’s Hospital Boston with a powerful model to study how blood-forming cells develop, which could help shed light on how the immune system is reconstituted following bone marrow transplantation. The information may be especially useful in the cases of cancer patients whose immune systems have been destroyed by chemotherapy.

At the Tufts University School of Medicine, Matthew K. Waldor identified how different cholera bacteria species can share antibiotic resistance genes. The work demonstrates how the use of one therapeutic agent may promote the spread of resistance to many drugs.

Studies of other animal immune systems often give insights into our own. A team of researchers led by Max D. Cooper at the University of Alabama at Birmingham School of Medicine studied the lamprey, a jawless vertebrate, and found a unique adaptive immune response that appears to be a similar but simpler version of the complex human adaptive response.

At the California Institute of Technology, Pamela J. Björkman identified a protein receptor in chickens responsible for transferring antibodies across the yolk sac membrane to the chick embryo in a manner similar to maternal transfer of antibodies across the placenta in humans.
Janelia Farm Research Campus

Janelia Farm, a research community being created by the Howard Hughes Medical Institute, will probe fundamental biomedical questions that require creativity and intellectual courage and are best addressed through a collaborative, interdisciplinary culture. Janelia Farm will nurture explorations in science by providing resident and visiting scientists with resources, independence, and freedom in a stimulating environment that extends HHMI’s commitment to research and discovery.

When it opens in 2006, the HHMI Janelia Farm Research Campus will provide a unique environment for basic biomedical research. Its verdant campus, within 40 minutes of Washington, D.C., will be ideal for scientists who want to remain actively engaged in the direct conduct of science and who seek a high degree of intellectual interaction with their colleagues.

Janelia’s scientists will have unparalleled freedom and resources to explore challenging research questions in a highly interdisciplinary, collaborative culture. In return, they will be expected to conduct research with creativity, passion, and intellectual courage.

HHMI has begun recruiting group leaders—biologists, chemists, computer scientists, engineers, mathematicians, and physicists who are passionate in their pursuit of these problems in basic scientific research and technology development.

Well suited to Janelia Farm’s culture, TWO INITIAL RESEARCH AREAS have been identified:

- The identification of general principles that govern how information is processed by neuronal circuits.
- The development of imaging technologies and computational methods for image analysis.
PARTNERS WITH LOUDOUN COUNTY

Partnering with public schools in Loudoun County, Virginia, where the HHMI Janelia Farm Research Campus will open in 2006, HHMI plans to invest $1 million annually in support of science education. The collaboration affords a new opportunity for HHMI to work closely with an outstanding school district to create a unique science education program linked to HHMI’s Janelia Farm Research Campus. This year, the project has three components: college scholarships, an institute for improving the teaching of science, and a science academy that eventually will link Loudoun County high school students with research at Janelia Farm.

FUTURE PROMISE

HHMI plans to invest $1 MILLION annually in support of science education in Loudoun County

This year, two outstanding seniors from each Loudoun County high school each received a $7,000 scholarship from HHMI. One of the recipients, Adeeb Aghdassi, graduated from Broad Run High School with plans to pursue a pre-med program at the University of Virginia in the fall. His interest in medicine was influenced in part by his work in the histology department at Reston Hospital, where he said he observed firsthand that “the work that [medical professionals] do is out of a love for helping people.”

FROM THE PRESIDENT

JANELIA FARM RESEARCH CAMPUS TOOK SHAPE AS A SKETCH ON THE BACK OF A NAPKIN

“The HHMI Janelia Farm Research Campus took shape as a sketch on the back of a napkin. Now, it is almost a reality. Janelia’s foundation rests on the Institute’s core belief that scientists who demonstrate creativity and imagination can make lasting contributions to benefit humanity when they are given flexible, long-term support, and the freedom to explore.

As HHMI’s first freestanding campus, Janelia Farm will provide a setting in which small research groups can explore fundamental biomedical questions in a highly collaborative, interdisciplinary culture. It will enrich and complement our flagship investigator program, which brings together more than 300 of the nation’s most creative scientists to direct HHMI laboratories at distinguished universities, research institutes, medical schools, and affiliated hospitals.”

— Thomas R. Cech, President
In addition to leading-edge scientific investigation, the Institute also supports innovations in an important complement to bench research—education in science. Supporting students of all ages, HHMI has invested approximately $1.5 billion in a range of activities since it began making grants for science education in 1988.

In institutions of higher learning, science education occurs in an environment of constant and often considerable change. Scientific fields are emerging that blur the lines between disciplines. Biologists, chemists, physicists, engineers, and mathematicians—among others—are finding new possibilities for discovery via interdisciplinary collaborations. Within this shifting culture there is a renewed appreciation for the need to train outstanding researchers to be outstanding teachers.

Similar challenges and opportunities present themselves in science education before and beyond the undergraduate experience—in precollege education and in postgraduate study. HHMI is committed to working to improve science education at all of these levels. Integral to that part of our mission is a commitment to broaden access to opportunities in science. Through this work, we are helping to prepare future generations of scientists and encouraging scientific literacy among all citizens.
The four-year grants, ranging from $500,000 to $1.6 million, highlight several new areas of thematic interest in addition to the four cited above, including inter-institutional collaboration, preparation of future faculty, and the interface of biology with other disciplines. Funds will help develop interdisciplinary laboratory curricula—blending, for example, biological and physical sciences with mathematics. Other grants support fellowships for postdoctoral researchers that include teaching experiences and a mobile teaching laboratory to bring science to disadvantaged students in remote areas.
POSTDOCTORAL FELLOWSHIPS

In a collaborative effort that supports training in teaching, City University of New York Queens College, Occidental College in Los Angeles, and North Carolina’s Davidson College plan to establish postdoctoral fellowships that provide training and experience in teaching as a component of a strong research program.

CARLETON COLLEGE AND ST. OLAF COLLEGE & MICHIGAN’S HOPE COLLEGE

Carleton College and St. Olaf College in Minnesota are working with Michigan’s Hope College to create teams of faculty from biology, the physical sciences, and mathematics who will collaborate on research and develop interdisciplinary courses and labs.

COLLABORATION IN GENETICS RESEARCH

In Ohio, Kenyon College provides students with opportunities to collaborate in genetics research with the University of Wisconsin–Madison.

PARTNERING WITH PHILADELPHIA AREA SCHOOLS

In suburban Philadelphia, Bryn Mawr and Haverford colleges are collaborating to apply their strengths in the life sciences to school children and teachers in the city nearby. Haverford’s Integrated Natural Sciences Center and the Center for Science and Society at Bryn Mawr will use grant support from HHMI to help mentor middle and high school students and to give teachers new tools for science instruction.
Scientist-Educators

THE HHMI PROFESSORS

One of HHMI’s most ambitious grant programs has begun to yield notable outcomes. In 2001, HHMI gave $1 million each to 20 leading research scientists who are deeply committed to making science more engaging for undergraduates. The HHMI Professors, as the grantees are known, infuse undergraduate science with the excitement and rigor of scientific research. Bringing the creativity they have shown in the lab to the undergraduate classroom, the Professors demonstrate through their teaching that active, productive scientists can be especially effective educators. Their work is helping to reform the way undergraduate science is taught at research universities.

"[The undergraduates] will actually produce publishable results with implications for human gene function and disorder."

CELL-TO-CELL COMMUNICATION

Observing the current state of undergraduate science education, Utpal Banerjee laments that “there is a major lack of explicit training of what research is all about.” A biologist and chemist at the University of California, Los Angeles, Banerjee says research is “not just a curiosity, but a way of life, a way of investigation.” Now, as an HHMI Professor, Banerjee has created a program to bring up to 500 undergraduate students in large laboratory courses to work in close cooperation with his lab, where his team studies the nature of cell-to-cell communication among pluripotent cells in Drosophila, the fruit fly. “They will do good work that will actually produce publishable results with implications for human gene function and disorder,” he predicts.
Hilary A. Godwin, a chemistry professor at Northwestern University, wants to see more minorities in science, where only one percent of the faculty in the top 50 chemistry departments is African American or Hispanic. She established an Undergraduate Success in Science program that involves incoming freshmen, among others, in research to assess lead levels in soil around Chicago.

Northwestern University student Rohit Singh (R) discusses lead hazards at a community health fair.

Effective labs function as a community of scholars, where scientists discuss, debate, and learn from each other. A research molecular biologist at Vanderbilt University in Nashville, Tennessee, Ellen Fanning cultivates a science community that extends from freshmen to senior faculty members, all of whom share teaching, mentoring, and learning experiences related to research on DNA replication.

MINORITIES IN SCIENCE

Hilary A. Godwin, a chemistry professor at Northwestern University, wants to see more minorities in science, where only one percent of the faculty in the top 50 chemistry departments is African American or Hispanic. She established an Undergraduate Success in Science program that involves incoming freshmen, among others, in research to assess lead levels in soil around Chicago.

Northwestern University student Rohit Singh (R) discusses lead hazards at a community health fair.

COMMUNITY OF SCHOLARS

21ST CENTURY ENGINEERING

Rebecca Richards-Kortum, a biomedical engineering professor at the University of Texas at Austin, introduces undergraduates to the interdisciplinary nature of 21st century engineering. Physiologists, biomedical engineers, biomathematicians, and physician-scientists collaborate on new courses for engineering majors and non-majors, exploring experimental medicine, human research, and imaging technologies.
STRENGTHENING RESEARCH ABROAD

As the recent SARS crisis demonstrated so vividly, today’s health problems have no respect for national boundaries. They require an immediate global response—and a biomedical research infrastructure capable of generating the knowledge necessary to address them. The challenge is greatest in the developing world, where long-established infectious diseases, such as malaria and tuberculosis, affect millions.

This year, HHMI seeks applicants for a $30 million continuation of two of its long-standing international programs—one for scientists whose work focuses on infectious diseases and parasitology and the second for biomedical researchers in the Baltics, Central and Eastern Europe, Russia, and Ukraine. Approximately 80 recipients, who will receive $50,000 to $100,000 a year for five years, will be announced in 2005.

Building a strong foundation of scientific knowledge and capability beyond the United States is a cornerstone of the Institute’s international programs. Since 1991, HHMI has invested more than $100 million in a global network of scientists in 32 countries who make important contributions outside the U.S. research establishment.

PASTEUR INSTITUTE IN PARIS

At the Pasteur Institute in Paris, HHMI international research scholar Pascale Cossart is painstakingly developing a comprehensive picture of how *Listeria monocytogenes*, a foodborne pathogen responsible for gastroenteritis, meningitis, and other afflictions, crosses three barriers during infection.

UNIVERSITY OF TORONTO

HHMI international research scholar Charles Boone, at the University of Toronto, developed a genetic mapping system for *Saccharomyces cerevisiae* that enables closer, faster study of the yeast’s genetic network.

NATIONAL AUTONOMOUS UNIVERSITY OF MEXICO

At the National Autonomous University of Mexico, HHMI international research scholar Carlos Arias studies the multi-stage process by which rotavirus infection binds to the cell surface and penetrates the cell’s interior.
This year, HHMI international scholars convened in Tallinn, Estonia, for several days of research presentations and discussions. Such meetings lead to collaborative research projects and educational programs that cut across national boundaries. In South and Central America, for example, where a parasitic infection called Chagas disease affects more than 18 million people, HHMI-supported scientists have teamed up to develop potential antiparasitic agents.

Last summer, young scientists traveled to Bangladesh from as far away as Guatemala, Malawi, Peru, and Thailand for a course sponsored jointly by HHMI and Britain’s Wellcome Trust. They worked for two weeks with an international faculty to learn advanced techniques that would help their research in infectious disease. In 2004, HHMI will support comparable programs in Argentina and Uruguay.
Biographies of molecular biologists, physicists, and chemists regularly outline the researcher’s scientific ancestry—his or her tutors, influences, and guides from early schooling through graduate and postdoctoral training. However rich an experience it might be, though, an apprenticeship may not equip a promising postdoc with certain kinds of practical knowledge necessary for making a successful transition to running a lab. Scientific insight, experimental skill, and a passion for discovery are essential, but they provide no guarantee that a newly minted assistant professor will know the first thing about how to recruit and train lab personnel, motivate students, manage a budget, and win funding while maintaining a disciplined focus on his or her own research. Several HHMI initiatives address this problem directly.

1 | HHMI has integrated career-enhancement opportunities for postdoctoral students into each of its seven annual science meetings. Discussions include practical information about everything from starting a lab to conducting science ethically.

2 | HHMI is collaborating with the Burroughs Wellcome Fund (BWF) to disseminate information about scientific management. The partnership began with a five-day course for 128 postdocs and starting faculty members in 2002. The course materials provided the basis for a nuts-and-bolts handbook entitled Making the Right Moves: A Practical Guide to Scientific Management for Postdocs and New Faculty. Demand for the book quickly depleted its first print run, necessitating a 10,000-copy reprint; the book was also downloaded 10,000 times in the first month (see www.hhmi.org/labmanagement). HHMI and BWF are also planning a second, related course for July 2005.

3 | HHMI is well known for several programs that offer research practice at early stages of a scientist’s career. Through its Graduate Science Education and Medical Research Training Program, HHMI seeks to expand the nation’s pool of medically trained researchers and to provide graduate students, postdoctoral fellows, and newly independent scientists with courses and other resources that will help them succeed in their research careers. This year, 64 medical students received HHMI research training fellowships, which they will use at medical research centers nationwide. Another 38 medical students and five dental students were accepted as HHMI-NIH research scholars. They live and work on the National Institutes of Health campus in Bethesda, Maryland, where the research scholars program is based at a facility informally known as the Cloister.
Building on the success of the EXROP program, the HHMI Trustees approved the creation of the James H. Gilliam, Jr., Fellowships in Biological Sciences for Predoctoral Students. The fellowships honor their namesake (left), a charter Trustee of HHMI who passed away in 2003 and who was committed to fostering a diverse scientific community. Up to five fellowships will be awarded annually to students who participated in the Institute’s EXROP program, to help recipients pursue a Ph.D. in biological sciences.
CULTIVATING STUDENT INTEREST
To help prepare the next generation of scientists, to help teachers become better prepared to teach science—and to help ensure that the citizenry as a whole has a better understanding of science—HHMI supports innovative classroom, laboratory, and field activities for pre-K to 12th-grade students. The programs provide opportunities for teacher professional development and outreach activities that reinforce the important role that parents and communities play in science education. In over a decade, the Institute has invested nearly $200 million in projects targeting K–12 students and their science teachers.

Some HHMI precollege programs bring science to schools in the inner cities. Others focus on students and teachers in isolated rural communities. Several target disadvantaged students and those who are underrepresented in the sciences. These examples are illustrative:

• In Washington, D.C., middle school students from one of the city’s most deprived neighborhoods are discovering that they can—and want to—go to college, thanks to a mentoring project at Georgetown University.

• Elementary school teachers in and around Mobile, Alabama, are enhancing science curricula.

• Rural science teachers are forming a support network following summer training at Cornell University.

HHMI awards K–12 science education grants to medical schools, academic health centers, and independent research institutions to engage in community outreach. These institutions have unique resources to share with their communities, including specialized laboratories and the expertise and excitement of their scientists. HHMI has awarded $33 million to biomedical research institutions for programs that have reached more than 400,000 school children and nearly 20,000 teachers.

HOLIDAY LECTURE SERIES

A panel of scientists and bioethicists talk with students about genetic testing.

THE SCIENCE OF MEDICINE
For oncologist Bert Vogelstein, it was Melissa. For neurologist Huda Zoghbi, it was Ashley. These young patients—a four-year-old with leukemia and a two-year-old with Rett syndrome—led the two HHMI investigators to devote their energies to combating human disease. Vogelstein and Zoghbi recounted their experiences in HHMI’s 2003 Holiday Lectures, which focused on how work with patients leads researchers to a deeper understanding of the genetics and biology of human diseases. For the high school students who participate live at HHMI headquarters—and for countless others who see the talks on the Web or via DVD—HHMI’s Holiday Lectures are a guided tour of a compelling topic in biology.
Colleen McDaniel embodies the good that can come from HHMI’s K–12 programs. A second-year graduate student studying molecular and human genetics at Baylor College of Medicine, McDaniel is also a class of fifth graders’ very own scientist. She’s a Science Education Leadership Fellow (SELF), one of a growing cadre of graduate students and postdoctoral fellows who are pairing up with elementary school teachers to improve science teaching and learning in Houston classrooms. The SELF program is a partnership between Baylor and the Houston Independent School District, with support from HHMI.
“Many students attend research universities because of the strength of the science being performed there, but they get turned off in introductory courses and never look back. We need those bright young minds. We want to encourage more students to become scientists, and we want to send non-science majors into society knowing how to confront issues that require analytical and scientific thinking. To achieve scientific literacy in society, we need to teach people how science is done, which means engaging them in science, asking them to be scientists, as part of their university education.”

Peter J. Bruns
Vice President for
Grants and Special Programs
Recognition
HONORS & AWARDS

MACKINNON WINS 2003 NOBEL PRIZE IN CHEMISTRY
In October 2003, HHMI investigator Roderick MacKinnon of the Rockefeller University and Peter Agre of the Johns Hopkins University, a member of HHMI’s scientific review board, were awarded the Nobel Prize in Chemistry. MacKinnon was recognized for work with colleagues that determined the three-dimensional structure of a potassium pore, or channel, that allows cells to control their intake of potassium ions. That work solved a riddle that had perplexed biophysicists for decades: How does a potassium channel admit millions of potassium ions per second, while allowing only one smaller sodium ion to slip through for every 1,000 potassium ions? Without potassium and sodium channels, neurons could not generate electrical signals and hearts could not beat rhythmically.

ELEVEN HHMI INVESTIGATORS ELECTED TO THE NATIONAL ACADEMY OF SCIENCES
Eleven HHMI investigators were elected in April to the National Academy of Sciences. The researchers are Kevin P. Campbell, University of Iowa Carver College of Medicine; Barry Honig, Columbia University College of Physicians and Surgeons; Richard L. Huganir, Johns Hopkins University School of Medicine; Mark T. Keating, Children’s Hospital Boston; Dan R. Littman, New York University School of Medicine; Stephen L. Mayo, California Institute of Technology; Erin K. O’Shea, University of California, San Francisco; Peter Walter, University of California, San Francisco; Xiaodong Wang, University of Texas Southwestern Medical Center at Dallas; Huda Y. Zoghbi, Baylor College of Medicine; and Charles S. Zuker, University of California, San Diego.

ROGER Y. TSIEN
An HHMI investigator at the University of California, San Diego, Roger Y. Tsien shared the 2004 Wolf Prize in Medicine with Robert A. Weinberg of the Massachusetts Institute of Technology. Considered Israel’s Nobel Prize, the award honored Tsien for his “seminal contribution to the design and biological application of novel fluorescent and photolabile molecules to analyze and perturb cell signal transduction.”

ARTHUR L. HORWICH
An HHMI investigator at the Yale University School of Medicine, Arthur L. Horwich was one of five scientists awarded a 2004 Gairdner Foundation International Award, which honors medical scientists whose contributions tangibly improve quality of life. Horwich’s award recognizes “seminal contributions in establishing the principles and discovering the key mechanisms and pathways in cellular protein folding.”

KRISTI S. ANSETH
HHMI investigator Kristi S. Anseth at the University of Colorado at Boulder received the 2004 Alan T. Waterman Award of the National Science Foundation. Criteria for the $500,000 award, which recognizes a young researcher in science or engineering, include originality, innovation, and impact on the field.

THOMAS C. SÜDHOF
An HHMI investigator at the University of Texas Southwestern Medical Center at Dallas, Thomas C. Südhof shared the 2004 MetLife Foundation’s Award for Medical Research in Alzheimer’s Disease.

WILLIAM T. NEWSOME
The 2004 Dan David Prize honored William T. Newsome in the field of brain sciences for his leading discoveries in the fields of neurophysiology and perceptual psychology. Newsome is an HHMI investigator at Stanford University School of Medicine.
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Kathleen L. Gould, Ph.D.

TEXAS

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Brendan Lee, M.D., Ph.D.
John H.R. Maunsell, Ph.D.
Florante A. Quiocio, Ph.D.
Huda Y. Zoghbi, M.D.

Rice University and associated hospitals
Richard H. Gomer, Ph.D.

University of Texas Southwestern Medical Center at Dallas and associated hospitals
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David L. Garbers, Ph.D.
Nick V. Grishin, Ph.D.
Helen H. Hobbs, M.D.
David J. Mangelsdorf, Ph.D.
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SEPTEMBER 1, 2003 - AUGUST 31, 2004

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For information on HHMI investigators active after August 31, 2004, visit www.hhmi.org.
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University of California, San Diego, School of Medicine
(Through December 31, 2003)

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American Cancer Society
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(Through December 31, 2003)

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The Salk Institute

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Francisco, School of Medicine

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Francisco

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NEUROSCIENCE
Baylor College of Medicine

Gregory A. Petsko, Ph.D.
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PROFESSOR OF BIOCHEMISTRY AND
MOLECULAR PHARMACODYNAMICS
DIRECTOR, ROSENSTIEL BASIC
MEDICAL SCIENCES RESEARCH
CENTER
Brandeis University
(Through December 31, 2003)

Joshua R. Sanes, Ph.D.
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Harvard University
(Effective July 1, 2004)

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Dana-Farber Cancer Institute and
Harvard Medical School

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The Scripps Research Institute

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(Through December 31, 2003)

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BIOLOGY AND PHYSICS
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(Effective July 1, 2004)

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CELLULAR PHYSIOLOGY
Stanford University School of
Medicine

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NEUROBIOLOGY
Washington University School of
Medicine

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National Institutes of Health
(Effective January 1, 2004)

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CHIEF, VISUOMOTOR INTEGRATION
SECTION
LABORATORY OF SENSORIMOTOR
RESEARCH
NATIONAL EYE INSTITUTE
National Institutes of Health
(Effective July 1, 2004)
# Fellowships & Grants

SEPTEMBER 1, 2003 - AUGUST 31, 2004

<table>
<thead>
<tr>
<th>Name</th>
<th>University and School of Medicine</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lei Chu</td>
<td>Baylor College of Medicine</td>
</tr>
<tr>
<td>Bidhan B. Das</td>
<td>Yale University School of Medicine (Harvard University) *</td>
</tr>
<tr>
<td>Emily D. Eads</td>
<td>Duke University School of Medicine</td>
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<tr>
<td>Kyle J. Eash</td>
<td>Washington University School of Medicine</td>
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<tr>
<td>Kevin Forsythe</td>
<td>Stanford University School of Medicine</td>
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<tr>
<td>Corinna C. Franklin</td>
<td>Harvard Medical School</td>
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<tr>
<td>Oscar Gonzalez</td>
<td>Stanford University School of Medicine</td>
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<tr>
<td>Rachel N. Grisham</td>
<td>Duke University School of Medicine</td>
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<tr>
<td>Christiane L. Haefele</td>
<td>Duke University School of Medicine</td>
</tr>
<tr>
<td>James J. Harding</td>
<td>Albert Einstein College of Medicine (Stanford University) *</td>
</tr>
<tr>
<td>Daniel Higginson</td>
<td>The Johns Hopkins University School of Medicine</td>
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<tr>
<td>John T. Hinson</td>
<td>Harvard Medical School</td>
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<tr>
<td>Kelley A. Hutcheson</td>
<td>Duke University School of Medicine</td>
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<tr>
<td>Isaac O. Karikari</td>
<td>Duke University School of Medicine</td>
</tr>
<tr>
<td>Diana Katsman</td>
<td>University of California, Irvine, College of Medicine (University of California, Los Angeles) *</td>
</tr>
<tr>
<td>Clara Kim</td>
<td>Brown Medical School</td>
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<tr>
<td>William H. Kitchens</td>
<td>Harvard Medical School</td>
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<tr>
<td>Holbrook E. Kohrt</td>
<td>Stanford University School of Medicine</td>
</tr>
<tr>
<td>Johannes Kratz</td>
<td>Harvard Medical School</td>
</tr>
<tr>
<td>Ameya R. Kulkarni</td>
<td>Yale University School of Medicine</td>
</tr>
<tr>
<td>William B. Kyle</td>
<td>Cornell University, Joan and Sanford I. Weill Medical College and Graduate School of Medical Sciences (Baylor University) *</td>
</tr>
<tr>
<td>Lewis Z. Leng</td>
<td>University of Pennsylvania School of Medicine</td>
</tr>
<tr>
<td>Charles Lin</td>
<td>University of Pittsburgh School of Medicine</td>
</tr>
</tbody>
</table>
Paulina Luczak
Columbia University College of Physicians and Surgeons

Mary-Elizabeth A. Muchmore
Stanford University School of Medicine

Karla N. Munoz
Harvard Medical School

Sheila Naghshineh
Harvard Medical School

Amish A. Naik
University of Rochester School of Medicine and Dentistry

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Duke University School of Medicine

Ivana Nikolic
Duke University School of Medicine

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James Peacock
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Masha Rand
Yale University School of Medicine

Neal M. Rao
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Gordon M. Riha
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Jack R. Schleifarth
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Leroy Sims
Stanford University School of Medicine

Eytan Stein
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Harvard Medical School

Viviany R. Taqueti
Harvard Medical School

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Columbia University College of Physicians and Surgeons

Tracy S. Tylee
University of Washington School of Medicine

Anil S. Vedula
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Chet R. Villa
University of Cincinnati College of Medicine

Annie Wang
University of Rochester School of Medicine and Dentistry (Harvard University)*

Sophia Wang
Mount Sinai School of Medicine (Harvard University)*

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University of California, San Francisco, School of Medicine

Olga K. Weinberg
Vanderbilt University School of Medicine (University of California, Los Angeles)*

Jeremy B. Wingard
Duke University School of Medicine (University of Pennsylvania)*

Hui Xue
Duke University School of Medicine

Adam J. Zucker
Duke University School of Medicine

* A fellowship institution affiliation other than the medical school is indicated in parentheses.
### Continued Awards: Second Year of Research

<table>
<thead>
<tr>
<th>Name</th>
<th>Institution</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lauren M. Kim</td>
<td>Emory University School of Medicine</td>
</tr>
<tr>
<td>Kyle A. Williams</td>
<td>Duke University School of Medicine</td>
</tr>
<tr>
<td>Elias R. George</td>
<td>Baylor College of Medicine</td>
</tr>
<tr>
<td>Petros Giannikopoulos</td>
<td>Harvard Medical School</td>
</tr>
<tr>
<td>Allen S. Ho</td>
<td>University of California, Los Angeles, David Geffen School of Medicine</td>
</tr>
<tr>
<td>Margo C. Funk</td>
<td>Washington University School of Medicine</td>
</tr>
<tr>
<td>Prasanna Jagannathan</td>
<td>Harvard Medical School</td>
</tr>
<tr>
<td>Peter Jun</td>
<td>Stanford University School of Medicine</td>
</tr>
<tr>
<td>Joelle E. Karch</td>
<td>University of Buffalo, State University of New York School of Medicine and Biomedical Sciences</td>
</tr>
<tr>
<td>Jessica C. Karl</td>
<td>University of Buffalo, State University of New York School of Medicine and Biomedical Sciences</td>
</tr>
<tr>
<td>Jocelyn T. Kim</td>
<td>University of Michigan Medical School</td>
</tr>
<tr>
<td>Lauren M. Kim</td>
<td>Washington University School of Medicine</td>
</tr>
</tbody>
</table>

### Continued Awards: Two Years of Support for Completion of Medical Studies

<table>
<thead>
<tr>
<th>Name</th>
<th>Institution</th>
</tr>
</thead>
<tbody>
<tr>
<td>Olujimi A. Ajijola</td>
<td>Duke University School of Medicine</td>
</tr>
<tr>
<td>Joseph T. Azok</td>
<td>Case Western Reserve University School of Medicine</td>
</tr>
<tr>
<td>Maria F. Barile</td>
<td>University of Connecticut School of Medicine</td>
</tr>
<tr>
<td>Monika L. Burness</td>
<td>Pennsylvania State University College of Medicine</td>
</tr>
<tr>
<td>Wendy W. Chang</td>
<td>Duke University School of Medicine</td>
</tr>
<tr>
<td>Kevin J. Cheung</td>
<td>Cornell University, Joan and Sanford I. Weill Medical College and Graduate School of Medical Sciences</td>
</tr>
<tr>
<td>Randi J. Cohen</td>
<td>Stony Brook University Health Sciences Center</td>
</tr>
</tbody>
</table>

### Awards

<table>
<thead>
<tr>
<th>Name</th>
<th>Institution</th>
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<tbody>
<tr>
<td>Sang Do Kim</td>
<td>Harvard Medical School</td>
</tr>
<tr>
<td>Christopher A. Klebanoff</td>
<td>Emory University School of Medicine</td>
</tr>
<tr>
<td>Alexander Langerman</td>
<td>The University of Chicago, Division of Biological Sciences, Pritzker School of Medicine</td>
</tr>
<tr>
<td>Aimee E. Lee</td>
<td>Yale University School of Medicine</td>
</tr>
<tr>
<td>Harrison W. Lin</td>
<td>Keck School of Medicine of the University of Southern California</td>
</tr>
<tr>
<td>Jamie E. McInturff</td>
<td>University of California, Los Angeles, David Geffen School of Medicine</td>
</tr>
<tr>
<td>Jayant P. Menon</td>
<td>University of California, Los Angeles, David Geffen School of Medicine</td>
</tr>
<tr>
<td>William R. Polkinghorn</td>
<td>Harvard Medical School</td>
</tr>
<tr>
<td>Richard Y. Ro</td>
<td>Duke University School of Medicine</td>
</tr>
<tr>
<td>Mohammad M. Siddiqui</td>
<td>Harvard Medical School</td>
</tr>
<tr>
<td>Edward T. Sittler</td>
<td>University of Massachusetts Medical School</td>
</tr>
<tr>
<td>Kien Quang Vuu</td>
<td>University of California, San Diego, School of Medicine</td>
</tr>
</tbody>
</table>
Aaron M. Wieland  
Harvard Medical School

Kyle A. Williams  
University of Minnesota Medical School–Twin Cities

Charles M. Zaremba  
Baylor College of Medicine

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University of Hawaii, John A. Burns School of Medicine

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University of Florida College of Medicine

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Stanford University School of Medicine

Brian C. Capell  
New York University School of Medicine

Benjamin F. Chu  
Texas Tech University Health Sciences Center School of Medicine

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State University of New York at Buffalo School of Dental Medicine

Ingrida Dapkute-Marcus  
University of Pennsylvania School of Dental Medicine

Jason B. Diamond  
Nova Southeastern University, College of Osteopathic Medicine

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New York University School of Medicine

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Tufts University School of Medicine

Parvin Fatheddin  
Duke University School of Medicine

Pauline Funchain  
Ohio State University College of Medicine and Public Health

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Tulane University School of Medicine

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Katherine B. Hobbs  
University of North Carolina at Chapel Hill School of Medicine

Rachel K. Hopper‡  
University of Michigan Medical School

LeRon C. Jackson  
Wake Forest University School of Medicine

Mahim Jain  
Indiana University School of Medicine

Michelle J. Khan‡  
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University of Washington School of Medicine

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Georgetown University School of Medicine

John K. Lee  
Dartmouth Medical School

Yoomi Lee  
Columbia University College of Physicians and Surgeons

Karen M. Likar  
University of Michigan School of Dentistry

Stanley Y. Liu  
University of California, San Francisco, School of Dentistry

Amit R. Majithia  
New York University School of Medicine
<table>
<thead>
<tr>
<th>Name</th>
<th>Institution</th>
<th>Award Amount</th>
</tr>
</thead>
<tbody>
<tr>
<td>Kevin P. Martinez</td>
<td>Charles R. Drew University of Medicine and Science</td>
<td></td>
</tr>
<tr>
<td>Rabie M. Shanti</td>
<td>Harvard School of Dental Medicine</td>
<td></td>
</tr>
<tr>
<td>Xinglei Shen‡</td>
<td>University of Pittsburgh School of Medicine</td>
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<tr>
<td>Michael J. Stone</td>
<td>University of Virginia School of Medicine</td>
<td></td>
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<tr>
<td>Tilak K. Sundaresan</td>
<td>University of Medicine and Dentistry of New Jersey–Robert Wood Johnson Medical School</td>
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<tr>
<td>William C. Van Cleve</td>
<td>The University of Chicago, Division of Biological Sciences, Pritzker School of Medicine</td>
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<td>University of California, San Diego, School of Medicine</td>
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<tr>
<td>Cindy Wei</td>
<td>Washington University School of Medicine</td>
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<tr>
<td>Shakti Ramkissoon‡</td>
<td>University of Medicine and Dentistry of New Jersey–New Jersey Medical School</td>
<td></td>
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<tr>
<td>Anjana Ranganathan</td>
<td>University of Pittsburgh School of Medicine</td>
<td></td>
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<tr>
<td>Rajesh Rao</td>
<td>Yale University School of Medicine</td>
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<tr>
<td>Melissa L. Russo</td>
<td>Georgetown University School of Medicine</td>
<td></td>
</tr>
<tr>
<td>Susan M. Shamimi-Noori</td>
<td>Georgetown University School of Medicine</td>
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</tr>
<tr>
<td>Barnard College</td>
<td>New York, New York</td>
<td>$1,500,000</td>
</tr>
<tr>
<td>Bates College</td>
<td>Lewiston, Maine</td>
<td>$1,200,000</td>
</tr>
<tr>
<td>Bowdoin College</td>
<td>Brunswick, Maine</td>
<td>$800,000</td>
</tr>
<tr>
<td>Bryn Mawr College</td>
<td>Bryn Mawr, Pennsylvania</td>
<td>$1,200,000</td>
</tr>
<tr>
<td>California State Polytechnic University–Pomona</td>
<td>Pomona, California</td>
<td>$1,300,000</td>
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<tr>
<td>Canisius College</td>
<td>Buffalo, New York</td>
<td>$800,000</td>
</tr>
<tr>
<td>Carleton College</td>
<td>Northfield, Minnesota</td>
<td>$800,000</td>
</tr>
<tr>
<td>City University of New York, City College</td>
<td>New York, New York</td>
<td>$1,300,000</td>
</tr>
<tr>
<td>City University of New York, Hunter College</td>
<td>New York, New York</td>
<td>$800,000</td>
</tr>
<tr>
<td>City University of New York, Queens College</td>
<td>New York, New York</td>
<td>$800,000</td>
</tr>
<tr>
<td>College of Wooster</td>
<td>Wooster, Ohio</td>
<td>$800,000</td>
</tr>
</tbody>
</table>

1This program is administered through Grants & Special Programs but is budgeted as a research operation.

2Second year in program as an Advanced Scholar
<table>
<thead>
<tr>
<th>College</th>
<th>Location</th>
<th>Amount</th>
</tr>
</thead>
<tbody>
<tr>
<td>Davidson College</td>
<td>Davidson, North Carolina</td>
<td>$1,300,000</td>
</tr>
<tr>
<td>Florida A&amp;M University</td>
<td>Tallahassee, Florida</td>
<td>$1,200,000</td>
</tr>
<tr>
<td>Grinnell College</td>
<td>Grinnell, Iowa</td>
<td>$1,400,000</td>
</tr>
<tr>
<td>Harvey Mudd College</td>
<td>Claremont, California</td>
<td>$1,200,000</td>
</tr>
<tr>
<td>Haverford College</td>
<td>Haverford, Pennsylvania</td>
<td>$1,600,000</td>
</tr>
<tr>
<td>Hiram College</td>
<td>Hiram, Ohio</td>
<td>$1,200,000</td>
</tr>
<tr>
<td>Hope College</td>
<td>Holland, Michigan</td>
<td>$1,500,000</td>
</tr>
<tr>
<td>Humboldt State University</td>
<td>Arcata, California</td>
<td>$1,300,000</td>
</tr>
<tr>
<td>Kalamazoo College</td>
<td>Kalamazoo, Michigan</td>
<td>$1,100,000</td>
</tr>
<tr>
<td>Kenyon College</td>
<td>Gambier, Ohio</td>
<td>$1,500,000</td>
</tr>
<tr>
<td>Knox College</td>
<td>Galesburg, Illinois</td>
<td>$1,000,000</td>
</tr>
<tr>
<td>Mount Holyoke College</td>
<td>South Hadley, Massachusetts</td>
<td>$1,200,000</td>
</tr>
<tr>
<td>Occidental College</td>
<td>Los Angeles, California</td>
<td>$1,500,000</td>
</tr>
<tr>
<td>Point Loma Nazarene College</td>
<td>San Diego, California</td>
<td>$800,000</td>
</tr>
<tr>
<td>Pomona College</td>
<td>Claremont, California</td>
<td>$1,300,000</td>
</tr>
<tr>
<td>Saint Olaf College</td>
<td>Northfield, Minnesota</td>
<td>$1,400,000</td>
</tr>
<tr>
<td>Smith College</td>
<td>Northampton, Massachusetts</td>
<td>$1,300,000</td>
</tr>
<tr>
<td>Spelman College</td>
<td>Atlanta, Georgia</td>
<td>$1,300,000</td>
</tr>
<tr>
<td>Swarthmore College</td>
<td>Swarthmore, Pennsylvania</td>
<td>$1,500,000</td>
</tr>
<tr>
<td>Trinity College</td>
<td>Hartford, Connecticut</td>
<td>$800,000</td>
</tr>
<tr>
<td>Trinity University</td>
<td>San Antonio, Texas</td>
<td>$1,000,000</td>
</tr>
<tr>
<td>Union College</td>
<td>Schenectady, New York</td>
<td>$1,600,000</td>
</tr>
<tr>
<td>University of Louisiana at Monroe</td>
<td>Monroe, Louisiana</td>
<td>$1,000,000</td>
</tr>
<tr>
<td>University of Puerto Rico–Cayey College</td>
<td>Cayey, Puerto Rico</td>
<td>$500,000</td>
</tr>
<tr>
<td>University of Richmond</td>
<td>Richmond, Virginia</td>
<td>$900,000</td>
</tr>
<tr>
<td>University of Texas–Pan American</td>
<td>Edinburg, Texas</td>
<td>$1,300,000</td>
</tr>
<tr>
<td>Wellesley College</td>
<td>Wellesley, Massachusetts</td>
<td>$1,200,000</td>
</tr>
<tr>
<td>Wesleyan University</td>
<td>Middletown, Connecticut</td>
<td>$1,300,000</td>
</tr>
<tr>
<td>Williams College</td>
<td>Williamstown, Massachusetts</td>
<td>$1,600,000</td>
</tr>
<tr>
<td>Xavier University of Louisiana</td>
<td>New Orleans, Louisiana</td>
<td>$1,300,000</td>
</tr>
<tr>
<td>HHMI’S EXCEPTIONAL RESEARCH OPPORTUNITIES PROGRAM (EXROP)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>2004 EXROP Students</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Jonathan Abraham</td>
<td>Harvard University</td>
<td></td>
</tr>
<tr>
<td>Azeema Ameerally</td>
<td>State University of New York at Stony Brook</td>
<td></td>
</tr>
<tr>
<td>Danielle Andrews-Lovell</td>
<td>Harvard University</td>
<td></td>
</tr>
<tr>
<td>James Araujo</td>
<td>Carnegie Mellon University</td>
<td></td>
</tr>
</tbody>
</table>
Kornelius Bankston  
Morehouse College

Ghofrane Benghanem  
Rensselaer Polytechnic Institute

Irene Blat  
Duke University

Meisha Bynoe  
Massachusetts Institute of Technology

Akanksha Chhabra  
University of California, Los Angeles

Deanna Cochran  
Spelman College

Kelly Cushing  
University of Illinois at Urbana-Champaign

O’Keith Dellafosse  
Louisiana State University and A&M College

Kenneth D’Oyen  
University of California, Berkeley

Naureen Farid  
University of Miami

Debbie Figueroa  
Florida State University

Alodia Gabre-Kidan  
Columbia University

Ashley Grant  
California Institute of Technology

Jennifer Greene  
University of Maryland, Baltimore County

Kathryn Harper  
Cornell University

Diana Herrera  
Purdue University

Brittany Holmes  
University of Colorado at Boulder

Katharine Horbach  
Reed College

Rufus Johnson Jr.  
Tuskegee University

Vanessa Jordan  
University of Illinois at Urbana-Champaign

Silvia Kariuki  
The University of Chicago

Jessica Lee  
University of Washington

Miguel Lopez  
University of California, Los Angeles

Christine Lutan  
Stanford University

Katherine Martin  
Washington University in St. Louis

Aliya McIver  
University of North Carolina at Chapel Hill

Rene Michel  
University of Arizona

Saima Mirza  
Oklahoma State University

Amanda Mitchell  
Vanderbilt University

George Molina  
The Johns Hopkins University

Anderson Morris  
Morehouse College

Tam Nguyen  
Louisiana State University and A&M College

Trang Nguyen  
Indiana University at Bloomington

Emily Olson  
University of Minnesota–Twin Cities

Bundo Onwueme  
University of Wisconsin–Madison

Naira Rezende  
City University of New York, Hunter College

Hubert Roberts  
Massachusetts Institute of Technology

Guadalupe Rodriguez  
University of Texas at Austin

Victoria Rodriguez  
Washington University in St. Louis

Jason Ross  
Stanford University

Joanna Sesti  
New York University

Jason Spears  
Northwestern University

Ai Sumida  
Swarthmore College
Sewell Suon  
California State University, Long Beach

Meriem Gaval  
Florida State University

Antonio Perez  
Harvard University

Anselm Tintinu  
University of Maryland, College Park

Kelley Harris  
Xavier University of Louisiana

Alicia Pinderhughes  
Spelman College

Pansy Tsang  
Yale University

Day Ivy  
California Institute of Technology

Albert Plenty  
The University of Chicago

Christina White  
University of Washington

Keynttisha Jefferson  
Purdue University

Davey Prout  
Louisiana State University and A&M College

Kilangsungla Yanger  
Carleton College

Daniel Jennings  
University of California, Berkeley

Alexander Red Eagle  
University of California, Los Angeles

Rodney Yapi  
Xavier University of Louisiana

Salma Kaochar  
University of Arizona

Jamie Smith  
Florida A&M University

2003 EXROP Students

Michael Kelso  
University of North Carolina at Chapel Hill

Steven Solis  
Duke University

Adrian Alexander  
Washington University in St. Louis

Luis Leon  
University of Washington

Christian Song  
New York University

Imran Babar  
Carleton College

Courtney Lockhart  
Tuskegee University

Heather Sternshein  
Swarthmore College

Georgette Charles  
Massachusetts Institute of Technology

Jacob Manjarrez  
Oklahoma State University

Nancy Van Prooyen  
Reed College

Mara Conrad  
City University of New York, Hunter College

David Mendoza  
Cornell University

Rodney Yapi  
Xavier University of Louisiana

Anderson Morris  
Morehouse College

Nizar Mukhtar  
University of Maryland, College Park

Ana Cortez  
California State University, Long Beach

Vicki Nelson  
The Johns Hopkins University

Ana Cristancho  
University of Miami

Kevin O’Brien  
University of Colorado at Boulder

Emerson Davis  
Yale University
PRECOLLEGE SCIENCE EDUCATION PROGRAM

WASHINGTON, D.C., METROPOLITAN AREA INITIATIVES

Chesapeake Bay Foundation
Annapolis, Maryland
$62,000

Eleanor Roosevelt High School
Greenbelt, Maryland
$29,000

Montgomery County Public Schools Educational Foundation
Rockville, Maryland
$709,000

LOUDOUN COUNTY, VIRGINIA, INITIATIVES

College Scholarships**

Adeeb Aghdassi
Broad Run High School

Remington Below
Stone Bridge High School

Emily Bzdyk
Loudoun Valley High School

Julio C.M. Cruz
Heritage High School

Carolyn A. Davis
Loudoun County High School

Camille Donovan
Stone Bridge High School

Eric Duchon
Loudoun Valley High School

Benjamin D. Fox
Loudoun County High School

Ernesto Gonzalez
Potomac Falls High School

Richard Hang
Park View High School

Donnavon K. Lalputan
Heritage High School

Kathryn Meintel
Park View High School

Yassaman Pourkazemi
Potomac Falls High School

Britany L. Raymond
Broad Run High School

**Each student received a scholarship of $7,000

Loudoun County, Virginia, Educational Programs

Cognitive Learning Institute
Elizabethtown, Pennsylvania
$206,334

Loudoun County Public Schools
Leesburg, Virginia
$214,133

INTERNATIONAL PROGRAM

Institute of Biotechnology,
National Autonomous University of Mexico

COURSES

International Centre for Genetic Engineering and Biotechnology
New Delhi, India
$150,000

Marine Biological Laboratories
Woods Hole, Massachusetts
$8,000

OTHER INTERNATIONAL AWARD

Institute of Biotechnology,
National Autonomous University of Mexico

Grant: Adaptation and Use of the Medical Mystery Festival Program
$30,075, part of a joint grant
with Institute of Biotechnology,
National Autonomous University of Mexico, Cuernavaca, Mexico (see International Program)

OFFICE OF GRANTS AND SPECIAL PROGRAMS

United Way of the National Capital Area
Washington, D.C.
$37,000
DISBURSEMENTS IN FISCAL 2004

Disbursements related to scientific research, grants for science education, and the development of a new research campus at Janelia Farm in the 2004 fiscal year were $653 million. Over the past five years, disbursements by the Institute have totaled approximately $3 billion and have increased by 25 percent since 1999 fiscal-year levels.

SCIENTIFIC RESEARCH

The Howard Hughes Medical Institute is a Medical Research Organization (MRO) within the meaning of section 170(b) of the Internal Revenue Code. In 2004, MRO disbursements were $573 million.

The Institute’s research activities are conducted at Institute laboratories at medical centers, teaching hospitals, and university campuses by investigators who hold faculty or staff 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 for the benefit of the host institution. At the end of the 2004 fiscal year, 318 HHMI investigators were employed in laboratories at approximately 66 academic medical centers.

Total employment at the end of 2004 was 2,699; personnel expense for the year was $268 million. Purchases of supplies and equipment totaled $131 million. The second chart on the following page shows disbursements that qualify for MRO purposes for 2004 and the four preceding years.

As of August 31, 2004, the Institute’s investment in laboratory space, equipment, and other property amounted to $975 million.

JANELIA FARM RESEARCH CAMPUS

In late 2000, the Institute purchased a 281-acre site along the Potomac River in Loudoun County, Virginia, just outside Washington, D.C., upon which it is developing a research campus for a cost of approximately $500 million. Disbursements through fiscal year 2004 were $235 million. The new facility, which is expected to be anchored by a group of Institute investigators complemented by a large number of visiting researchers, is intended to provide the setting for an integrated, multidisciplinary collaborative research, education, and training program focused
on technology development and dissemination. In addition to the ongoing research, training, and education program, the Institute envisions that the research campus at Janelia Farm could play another important and truly unique role in advancing biomedical research by serving as a well-equipped laboratory facility where groups of scientists—including chemists, biologists, physicists, computer scientists, and engineers—can come to work together in a stimulating environment for periods ranging from a few weeks to several years.

**GRANTS AND SPECIAL PROGRAMS**

Through its grants program, the Institute supports science education at all levels, from precollege science education to postdoctoral training. It also awards grants to science museums and similar institutions and directly supports scientists conducting research in the biologic sciences in selected foreign countries. Annual disbursements under the grants program have increased from $40 million in 1988 to $80 million in 2004.

During the period that the program has been in place, a total of approximately $1.5 billion has been disbursed or committed for these purposes.

**DISBURSEMENTS (Dollars in Millions)**

<table>
<thead>
<tr>
<th>Year</th>
<th>Undergraduate Education</th>
<th>Graduate Education</th>
<th>Research Resources</th>
<th>International</th>
<th>Precollege Education, Educational Materials, &amp; Other</th>
</tr>
</thead>
<tbody>
<tr>
<td>2000</td>
<td>100</td>
<td>150</td>
<td>300</td>
<td>50</td>
<td>20</td>
</tr>
<tr>
<td>2001</td>
<td>120</td>
<td>180</td>
<td>350</td>
<td>60</td>
<td>25</td>
</tr>
<tr>
<td>2002</td>
<td>140</td>
<td>200</td>
<td>400</td>
<td>70</td>
<td>30</td>
</tr>
<tr>
<td>2003</td>
<td>160</td>
<td>220</td>
<td>450</td>
<td>80</td>
<td>35</td>
</tr>
<tr>
<td>2004</td>
<td>180</td>
<td>240</td>
<td>500</td>
<td>90</td>
<td>40</td>
</tr>
</tbody>
</table>

**SCIENTIFIC RESEARCH (Dollars in Millions)**

<table>
<thead>
<tr>
<th>Year</th>
<th>Operating</th>
<th>Equipment and Lab Renovation</th>
<th>Lab Construction &amp; Land Acquisition</th>
</tr>
</thead>
<tbody>
<tr>
<td>2000</td>
<td>200</td>
<td>250</td>
<td>150</td>
</tr>
<tr>
<td>2001</td>
<td>220</td>
<td>270</td>
<td>180</td>
</tr>
<tr>
<td>2002</td>
<td>240</td>
<td>290</td>
<td>210</td>
</tr>
<tr>
<td>2003</td>
<td>260</td>
<td>310</td>
<td>240</td>
</tr>
<tr>
<td>2004</td>
<td>280</td>
<td>330</td>
<td>270</td>
</tr>
</tbody>
</table>

**GRANTS AND SPECIAL PROGRAMS (Dollars in Millions)**

<table>
<thead>
<tr>
<th>Year</th>
<th>Undergraduate Education</th>
<th>Graduate Education</th>
<th>Research Resources</th>
<th>International</th>
<th>Precollege Education, Educational Materials, &amp; Other</th>
</tr>
</thead>
<tbody>
<tr>
<td>2000</td>
<td>100</td>
<td>150</td>
<td>300</td>
<td>50</td>
<td>20</td>
</tr>
<tr>
<td>2001</td>
<td>120</td>
<td>180</td>
<td>350</td>
<td>60</td>
<td>25</td>
</tr>
<tr>
<td>2002</td>
<td>140</td>
<td>200</td>
<td>400</td>
<td>70</td>
<td>30</td>
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<tr>
<td>2003</td>
<td>160</td>
<td>220</td>
<td>450</td>
<td>80</td>
<td>35</td>
</tr>
<tr>
<td>2004</td>
<td>180</td>
<td>240</td>
<td>500</td>
<td>90</td>
<td>40</td>
</tr>
</tbody>
</table>
The financial resources available to support the Institute’s research and grants programs are principally generated by its endowment. The net assets of the Institute’s endowment are reflected in the graph below. The Institute’s endowment at the close of FY2004 was $12.8 billion.

The Institute’s long-range investment objective is to provide and maintain inflation-adjusted support for its research and grant program plans. Although investment returns will fluctuate each year, it is anticipated that over time the constant dollar value of the endowment will be preserved, enabling program commitments to be continued and protected against the effects of inflation. The composition of the Institute’s endowment at August 31, 2004, is reflected in the graph below, at right.

The Institute’s endowment is managed under the direction of its Vice President and Chief Investment Officer. Approximately 71 percent of the endowment is managed by external investment managers with the remainder being internally managed.
Statement of Financial Position
AUGUST 31, 2004 AND 2003

ASSETS (IN MILLIONS)

<table>
<thead>
<tr>
<th></th>
<th>2004</th>
<th>2003</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cash and cash equivalents</td>
<td>$460</td>
<td>$532</td>
</tr>
<tr>
<td>Investments</td>
<td>13,200</td>
<td>11,696</td>
</tr>
<tr>
<td>Investment and currencies receivables, and other assets</td>
<td>1,257</td>
<td>1,135</td>
</tr>
<tr>
<td>Laboratory space, equipment and other property — at cost, net of accumulated depreciation and amortization</td>
<td>480</td>
<td>382</td>
</tr>
<tr>
<td><strong>Total Assets</strong></td>
<td>15,397</td>
<td>13,745</td>
</tr>
</tbody>
</table>

LIABILITIES AND COMMITMENTS

<table>
<thead>
<tr>
<th></th>
<th>2004</th>
<th>2003</th>
</tr>
</thead>
<tbody>
<tr>
<td>Accounts payable, accrued expenses and obligations</td>
<td>(160)</td>
<td>(122)</td>
</tr>
<tr>
<td>Grants commitments</td>
<td>(133)</td>
<td>(146)</td>
</tr>
<tr>
<td>Investment purchases payable, repurchase obligations, short sales and currencies payable</td>
<td>(1,667)</td>
<td>(1,483)</td>
</tr>
<tr>
<td>Note and bonds payable</td>
<td>(617)</td>
<td>(617)</td>
</tr>
<tr>
<td><strong>Total Liabilities and Commitments</strong></td>
<td>(2,577)</td>
<td>(2,368)</td>
</tr>
<tr>
<td><strong>Net Assets</strong></td>
<td>$12,820</td>
<td>$11,377</td>
</tr>
</tbody>
</table>

FINANCIAL INFORMATION
The Institute employs the firm of Deloitte & Touche as its independent auditor. A copy of the audited financial statements of the Institute for the year ended August 31, 2004, together with the independent auditor’s report thereon, may be obtained by writing to:

Vice President and Chief Financial Officer
Howard Hughes Medical Institute
4000 Jones Bridge Road
Chevy Chase, MD 20815-6789