Howard Hughes Medical Institute
2008 Annual Report

Uncommon Curiosity

Mission statement

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

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Letter from the President

For nearly a decade, I have had the honor and privilege of serving as president of the Howard Hughes Medical Institute. This office, which I will relinquish on March 31, 2009, to return to full-time research in Colorado, has allowed me to think deeply about the future of science and how best to educate successive generations of scientists. I treasure the experience.

The theme of this annual report is "Uncommon Curiosity," because out-of-the-ordinary inquisitiveness is an absolute requirement for achieving success in research. We begin with Mario Capecchi of the University of Utah, whose unusual trajectory prompted him to leave the cozy academic confines of Cambridge, Massachusetts, and head west. Salt Lake City was hardly a frontier in the classical sense, but it provided just the right environment to enable Capecchi to make discoveries that have paved the way for the development of animal models for human disease. For this, he shared the 2007 Nobel Prize in Physiology or Medicine with Oliver Smithies and Sir Martin Evans.

Capecchi's deep curiosity and drive have him pressing ahead with new research challenges, and that's my goal as well. Much as I have delighted in leading HHMI, I also want to get back to my laboratory at the University of Colorado at Boulder—and it's not simply the view of the Rocky Mountains that's drawing me back. For me, nothing is more invigorating than hashing out new experimental approaches with students and delving into the structure and function of telomeres—those all-important caps at the ends of our chromosomes that keep them healthy and functioning properly. Come to think of it, they keep my intellect healthy and functioning properly as well!

In Colorado, I will also direct a new institute in interdisciplinary science. This role will bring me full circle, back to the conversations about the importance of breaking down the barriers between research disciplines that I had with Gerry Rubin and David Clayton as I began my

Out-of-the-ordinary inquisitiveness is an absolute requirement for achieving success in research.

tenure as HHMI's president. Those conversations—which began in Boulder the year before my move to HHMI's headquarters in Maryland—culminated in development of the Janelia Farm Research Campus. Now directed by Rubin, this new community enables chemists, computer scientists, and physicists to work side by side with biologists in a vibrant environment enriched by students, visitors, and collaborating scientists from around the world. Janelia Farm represents a big step for HHMI, and we set big goals. Were we realistic or excessively bold? Only time will tell, but we're certainly excited by the progress so far.

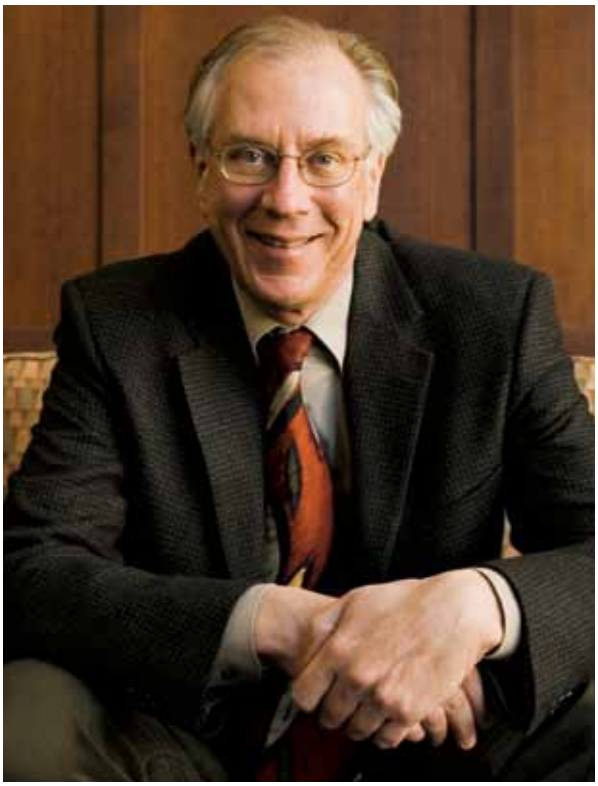
When I succeeded Purnell Choppin as HHMI's president nine years ago, the Institute's flagship investigator program was a powerful force for discovery and innovation in American science, and it remains so today. The program's basic principles—people not projects, generous resources, extended time horizon—remain unaltered. Nonetheless, we made modest yet significant changes that have altered the composition of the investigator community and brought new scientific disciplines, as well as institutions, into the fold. At the urging of Joseph Goldstein, David Nathan, and Craig Thompson of our Medical Advisory Board, we undertook two focused competitions to expand the number of patient-oriented physician-scientist investigators in the Institute.

More recently, under the leadership of Jack Dixon as HHMI's chief scientific officer, we opened up the process for selecting new investigators by allowing scientists to apply directly, replacing the previous process of institutional nominations. The new mechanism has enhanced the perception of HHMI's fairness and openness and has also resulted in a wonderful diversity among institutions,

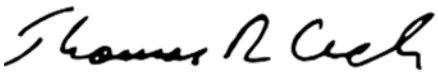
scientific disciplines, and the new investigators themselves. I have equally high hopes for our newest initiative—another open-access competition, this time designed to select highly talented scientists at the very outset of their independent research careers.

At HHMI, our experiments are not limited to the laboratory. Our grants program, led by Peter Bruns, actively encourages colleges and universities to seek more effective ways to engage students. For example, we created the HHMI professors program to support accomplished research scientists in their efforts to implement high-impact, inquiry-based undergraduate education at their own institutions, and to share with the broader community the methods, curricula, and materials they create.

Another new effort has focused on building connections between HHMI investigators and our educational programs to achieve an important goal: increasing diversity among the ranks of academic scientists. The exceptional research opportunities program (EXROP for short) allows us to provide summer research experiences in HHMI laboratories for promising college students who are disadvantaged or from groups that are underrepresented in the sciences. We've taken it one step further, building a community among these students by bringing them together and providing additional mentoring. Fully half of our EXROP students are now in graduate school—and that doesn't count those who opted for medicine! A decade from now, I fully expect to see many of them in front of classrooms and in the ranks of accomplished scientists.



As president, my first obligation has been to be a wise steward—of the intellectual freedom that our scientists require to do their best work, of the potential embodied by the students we reach through our grants, of the financial resources that make it possible for us to carry out our mission. To the extent that I have succeeded, it is a tribute to the many gifted collaborators—including the staff at our administrative headquarters and HHMI's Trustees—who have joined me in this work. Together, we have set the Institute's course for a new and no doubt fascinating future.

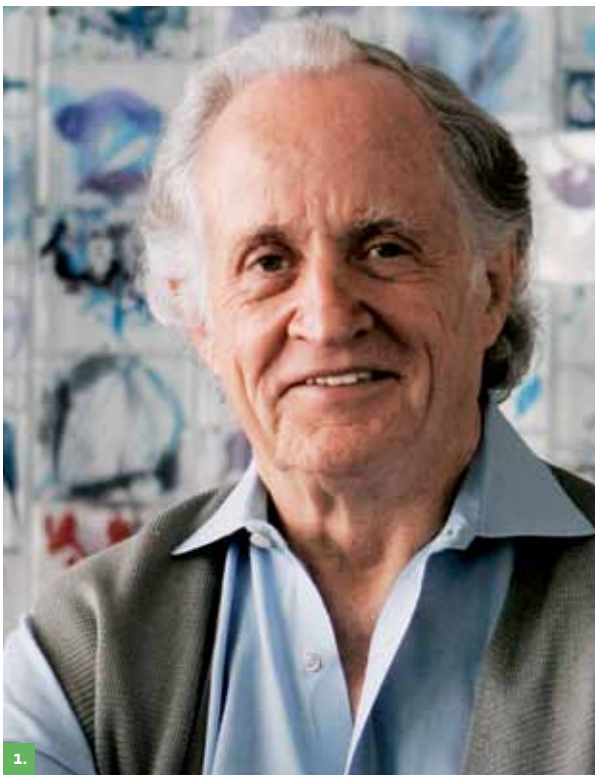


Thomas R. Cech, Ph.D.
President

James Watson, who shared the Nobel Prize for discovering the structure of DNA with Francis Crick and Maurice Wilkins, is well known for thinking big. Indeed, he often admonished graduate students and postdocs "not to waste time asking small questions." Many HHMI investigators have taken that advice to heart.

Ask Big Questions

1. **Mario R. Capecchi**
2. **Embryonic Stem Cells**
   Using mouse ES cells, Capecchi created the first knockout mouse.
3. **DNA**
   Deoxyribonucleic acid carries the genetic information of a cell.



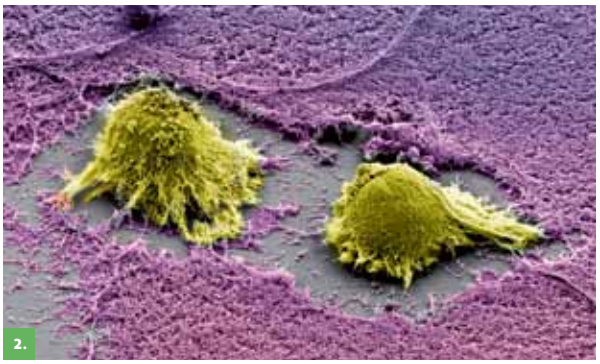
1.

A Bold Approach

HHMI investigator Mario R. Capecchi, a former student of James Watson, profited from his mentor's advice to think big. Capecchi's relentless curiosity about seemingly unanswerable questions has changed the way scientists explore mammalian genetics. His research earned him the 2007 Nobel Prize in Physiology or Medicine. Now in his 70s, Capecchi, at the University of Utah, is preparing to ask another big question: what makes a mouse a mouse?

"Scientific questions are often exceedingly complex," Capecchi says. "Then a new technology comes in and it changes what questions are accessible. Hopefully, when you ask a question that is beyond your technological capability, that leap is within the realm of possibilities."

Capecchi himself is a technology developer. In the 1980s, he described how to use the cell's machinery to target and alter genes. Spurred by a 1977 report from Richard Axel (now an HHMI investigator) and Michael Wigler at Columbia University demonstrating that cells in culture would occasionally take up and incorporate DNA, Capecchi created a nuclear injection procedure to make the uptake process more efficient and then study it. He and his students discovered that sometimes cells used "homologous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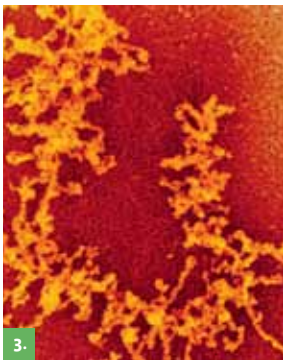
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Capecchi's relentless curiosity about seemingly unanswerable questions has changed the way scientists explore mammalian genetics.

recombination"—the physical rearrangement of genetic material between two strands of DNA—to stitch together multiple copies of the same DNA.

With that finding Capecchi submitted a grant proposal to the National Institutes of Health (NIH) to use the cells' homologous recombination machinery to target and alter genes. The NIH reviewers told him to focus on the less risky aspects of the proposal. Capecchi gambled his career by ignoring that dictate and used the funds on the very high-risk—and ultimately high-reward—effort to target genes in mammalian cells. By the time his NIH grant was up for renewal, he had succeeded.

Through collaborations—and some friendly competition—Capecchi, Sir Martin Evans at Cardiff University in the United Kingdom, and Oliver Smithies at the University of North Carolina at Chapel Hill revolutionized mammalian genetic techniques. Evans cultured mouse embryonic stem (ES) cells, Capecchi created a targeted mutation in those cells, and Smithies corrected a genetic defect in ES cells. The work culminated in 1989 when Capecchi announced he had created a mouse lacking a gene entirely—the first "knockout" mouse. Today, knockout mice are used extensively to study mammalian genetics. The men shared the 2007 Nobel Prize in Physiology or Medicine for their efforts.

Not content to focus on a single field or question, Capecchi changes the direction of his lab every 8 to 10 years. His group has studied bacteriophages, neuroscience, and cancer. "I enjoy thinking about new things," Capecchi says. "It's a challenge. It shakes up your neurons.

"You are sort of naïve when you enter a new field." Capecchi views this as an advantage that permits him to ask the big questions that scientists immersed in a given subject might not ask.

His latest foray is an exploration of the genetic basis for how nature evolved the great diversity of life on the planet. "When molecular biologists compare enzymes from two different species, they are looking at what makes us similar," Capecchi says. "I want to know what happened in evolution to make us different."

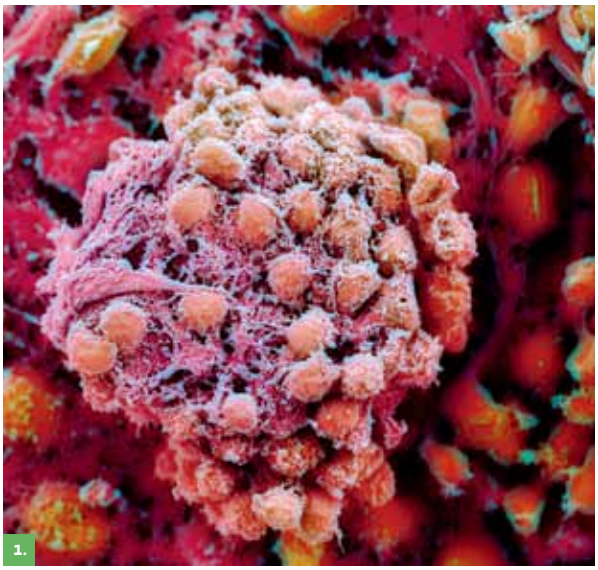
Capecchi believes that most differences among species arise as a result of additive mutations, and he wants to use bats and mice to test the mechanics of evolution. The two animals are about the same size and share physiological similarities, including body temperature and heart rate. Yet they are profoundly different: bats

fly and use echolocation to navigate the world; mice scurry on all fours and rely on smell. "However," Capecchi points out, "the genetic content is nearly identical between the two animals."

Because individually inserting bat genes into mice would require approximately 25,000 mouse strains, Capecchi is taking a bolder approach. In work supported by HHMI, he plans to transfer large spans of bat genome into mouse embryos and see if the resulting mice have new characteristics. He doesn't expect to make the mice fly or echolocate, but he does think that his team may find mice with elongated fingers or changes in their auditory systems that make them more similar to bats. He doesn't rule out profound changes, however; animals can evolve new characteristics quite rapidly.

"One of the things that is nice about nature is that if something works, nature will use it," Capecchi says. "And it is possible that, when a change is so rapid, only a handful of genes are involved."

Even so, his plan to explore evolution in this fashion is ambitious—he is still developing the technology that will allow him to insert such large swaths of bat genome into mice. If he does find



1.

"One of the things that is nice about nature is that if something works, nature will use it," Capecchi says.

mice displaying batlike characteristics, he will break them down gene by gene. Capecchi recognizes the project may not bear fruit for 10 to 20 years. Still, he was optimistic enough to submit the project for an NIH grant shortly before his Nobel Prize was announced. The NIH reviewers flatly turned him down.

"I sent them a letter back saying, 'Déjà vu,' and resubmitted the grant without the speculative parts," Capecchi laughs, noting that the second version received funding. But he sees a loss in focusing on projects deemed most likely to succeed. "One of the things that's unpredictable about science is the science itself."

1. **Pluripotent**
Human embryonic stem cells can mature into any cell type depending on the biochemical signals they receive.

2. **George Q. Daley**

3. **Douglas A. Melton**


3.


2.

Disease-specific stem cell lines

George Q. Daley, a new patient-oriented HHMI investigator at Children's Hospital Boston, and colleagues created a powerful resource that allows scientists to replicate human diseases in a Petri dish. They added four genes, called reprogramming factors, to cells from patients with 10 genetic disorders—including Parkinson's disease, muscular dystrophy, and type 1 diabetes. And the cells reverted to the embryonic state. These cells, which are being made widely available to other researchers, should offer lots of new ways to address the root causes of the diseases, Daley says. "We think, we hope, we'll be able to make lines from just about any patient with any disease."

Is there an easier way to rebuild a pancreas?

The discovery of human embryonic stem (ES) cells—the source material for every cell in the body—has given great hope to people struggling with degenerative disorders such as diabetes and Parkinson's disease. ES cells offer the potential to replace damaged tissues and eradicate disease. Those cures, however, lie in the future.

Researchers have been trying to coax ES cells along precise pathways to become specific nerve, cardiac, or pancreatic cells. HHMI investigator Douglas A. Melton, who is committed to curing diabetes, asked whether it was really necessary to start with ES cells to make insulin-producing pancreatic β cells. Could there be a shortcut? Melton started with neighboring cells—fully differentiated pancreatic exocrine cells that produce digestive enzymes—and attempted to repurpose them in mice: stop making enzymes, start making insulin. He and his postdoctoral fellow Qiao "Joe" Zhou discovered they needed to deliver only three regulatory genes to the mice to complete the "extreme makeover" efficiently and quickly.

The researchers changed the function of adult cells without using ES cells or relying on techniques to reverse a cell's genetic programming. The work demonstrates that regenerating tissues may not require a march back to the beginning to reach the end, but could allow physicians to alter nearby cells to replace damaged tissue. "My obsession to find a new treatment for diabetes [drove this work]," says Melton, who is codirector of the Harvard Stem Cell Institute. "I wake up every day trying to think of a new way to make a β cell."

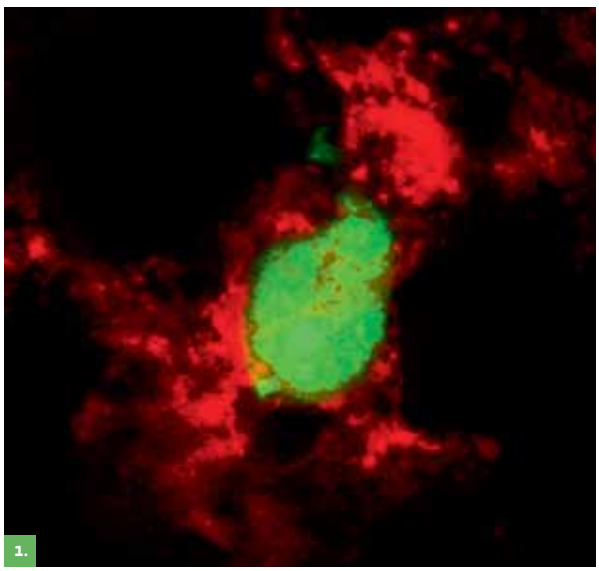
1. **Metastasis**
A human breast cancer cell (green) lodged in a mouse lung capillary can spread when surrounded by weakened endothelial cells (red).

2. **Joan Massagué**

3. **Anna Marie Pyle**

4. **Jumping RNA**
An electron density map of the group II intron.

Massagué and his colleagues found that the most invasive, aggressive human breast tumors are missing three critical microRNA molecules.



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What drives cancer's spread?

Metastasis is a problem as big as any in cancer research. HHMI investigator Joan Massagué continues to make inroads on cancer's deadly spread to other organs since it became the focus of his work in 2000. Massagué and his colleagues at Memorial Sloan-Kettering Cancer Center first identified different sets of genes that collude to permit breast cancer to spread to various tissues, like the lungs and bone. Silencing four of the genes that work together to encourage metastasis to the lungs, for example, eliminated tumor growth and spread. This year the team found that the most invasive, aggressive human breast tumors are missing three critical microRNA molecules. When the three molecules were added back to human breast cancer cells in mice, the tumors lost their ability to spread.

"The tiny RNAs prevent the spread of cancer by interfering with the expression of genes that give cancer cells the ability to proliferate and migrate," Massagué says. His team's findings may lead to drugs that interfere with metastasis and perhaps form the basis of tests to determine which breast cancers are most likely to spread.


3.

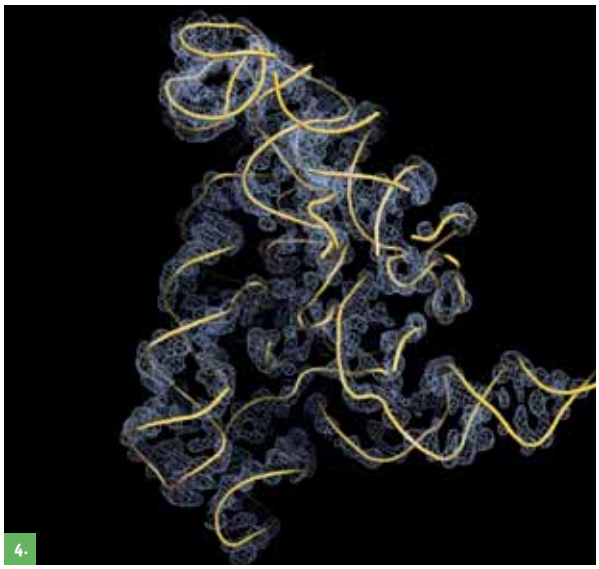
How does an RNA parasite escape?

HHMI investigator Anna Marie Pyle of Yale University took a snapshot of a genetic parasite isolated from a deep-sea bacterium and found answers to how specialized stretches of RNA escape from the genome. Once free, these wandering bits of RNA, called group II introns, invade new RNA and DNA, and that mobility has had a profound influence on evolution by promoting diversity among the world's most ancient organisms.

For the past 16 years, Pyle has worked to reveal the structure of group II introns to understand how they free themselves. Painstaking biochemical analysis led her to seek the detailed information available from x-ray crystallography.

Pyle chose to explore the stable group II intron from the alkaline-loving deep sea bacterium *Oceanobacillus iheyensis*. She found that these movable RNAs folded into a globular shape with a central portion containing the parts of the RNA needed for splicing RNA and DNA with metal ions. "This genetic parasite really has fangs," Pyle says. "It's ready to go out and react with something."

What's more, the shape is remarkably similar to the cell's spliceosome—a structure of proteins and RNA that normally removes unneeded sections of RNA. Pyle's work confirmed many anticipated similarities between the group II intron and the RNA in the spliceosome and hints that the spliceosome may have derived from an ancient group II intron.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"This genetic parasite really has fangs," Pyle says. "It's ready to go out and react with something."

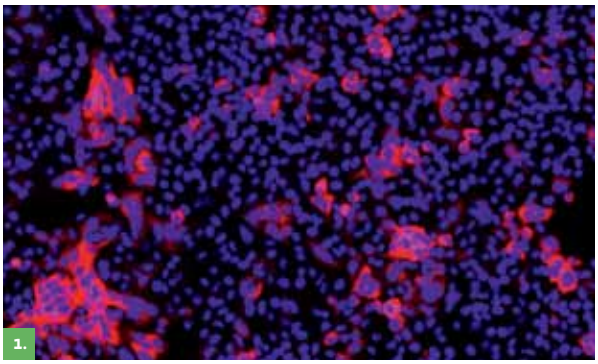
Innovative science benefits from connections between the cultures and styles of diverse disciplines. Whether it means seeking the physicist down the hall or the biochemist across the globe, HHMI scientists are reaching beyond their usual disciplinary boundaries to answer pressing questions in science and medicine.

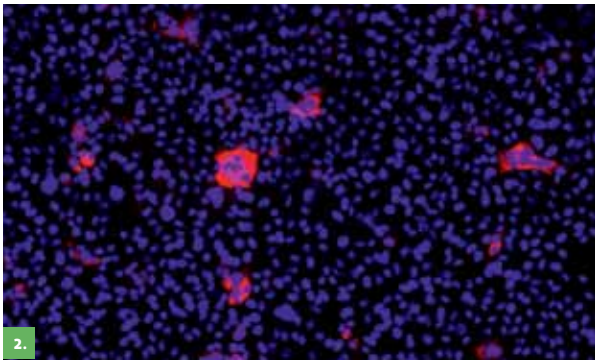
Creative Connections

1/2. **Blocking Disease**
Levels of HIV (red) dropped when scientists blocked a protein in human cells (blue).

3. **Stephen J. Elledge**

4. **Gregory J. Hannon**





Massive Screens

HHMI investigator Stephen J. Elledge found more than 200 new targets for blocking the human immunodeficiency virus (HIV) because he saw a problem—outside his field—and thought he could help.

In his first foray into HIV biology, Elledge, at Brigham and Women's Hospital, provided a detailed road map describing how HIV hijacks 273 human cellular proteins to infect critical immune cells and destroy the immune system.

Viruses are needy. They lean heavily on their host cells to invade successfully. HIV is no different—it has a mere 9 genes that make only 15 proteins. Every one of the human proteins that aid HIV's assault on the immune system is a potential new therapeutic target to stop the virus. Researchers had discovered some of the pathways Elledge and his team identified, but more than 200 of the proteins were new finds.

"This is a tremendous resource for the entire field of HIV research," says Dan R. Littman, HHMI investigator and an HIV expert at New York University Langone Medical Center. "It's been known for a long time that these host factors were out there, but there had never been a systematic approach to identify them. I don't think anyone could have imagined how many would turn up." Elledge, who studies the cell cycle, used his expertise in RNA interference—a process by which

"We wanted to get this information out to the field," Elledge says. "It will allow people to think more deeply about the life cycle of HIV and how to impede it."

small RNA molecules shut off genes—to disrupt genes one by one and observe whether HIV could still establish itself and reproduce. The team plodded through 21,000 disrupted genes to isolate the ones HIV required. Now drug developers can try to shut down those proteins, or at least go after the proteins that the host can live without.

"We wanted to get this information out to the field," Elledge says, noting that pharmaceutical companies are doing similar work privately. "It will allow people to think more deeply about the life cycle of HIV and how to impede it."

3.

4.

The Full Genome Approach

Stephen J. Elledge has taken on cancer too, partnering with HHMI investigator Gregory J. Hannon at Cold Spring Harbor Laboratory to reveal new target proteins for anticancer drugs. The two invented a genetic screening method that quickly and inexpensively probes breast and colon tumors for genes that help them thrive. They generated a library of short hairpin RNAs (shRNAs) that trigger RNA interference and turn genes off. They inserted the shRNAs into retroviruses and used them to infect normal and cancer cells. The shRNA binds to similar stretches of RNA in the cell and shuts off the corresponding gene, preventing its translation into protein. If the protein is critical to survival, the cell dies. If the protein is a growth inhibitor, the cell multiplies and thrives. Screening thousands of RNAs and their related genes would normally require thousands of experiments. But Hannon and Elledge devised a genetic barcoding method to track the effects of thousands of RNAs in a single pool of cells in a single lab dish. They found dozens of genes that, when shut down by the shRNAs, damaged the cancer cells but didn't harm normal cells.

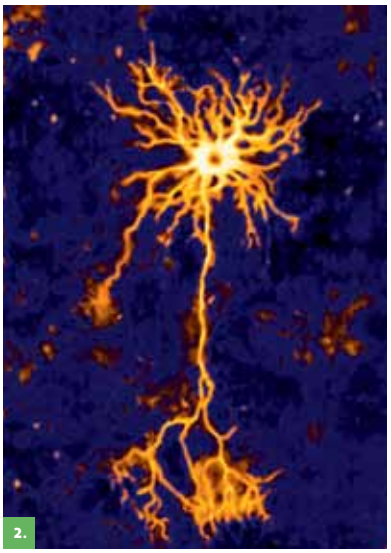
1.

"I love to roll up my sleeves and write the code," Myers says, noting that the unique atmosphere at Janelia Farm encourages cooperative work.

Six Degrees of Gene Myers

For a man who has never taken a biology course, Janelia Farm group leader Gene Myers is immersed in complex biological questions. Trained as a mathematician, computer scientist, and engineer, Myers has a growing network of collaborators throughout Janelia and the world. The principal architect of a tool that permitted Craig Venter and Celera Genomics Corporation to sequence the human genome in three years, Myers has turned his focus to image analysis. Current projects include:

- Developing software with Janelia's Julie Simpson, Jim Truman, and Gerry Rubin for cataloguing images of stained fly brains.
- Refining and improving the interpretation of raw data produced by the PALM microscope, a powerful light microscope developed by group leader Eric Betzig and Harald Hess for discerning the precise location of proteins within cells.
- Developing software and a microscope with Janelia's Karel Svoboda, Jeff Magee, and Scott Sternson that track sets of stained neurons in 3-D stacks tiling the cerebral cortex of the mouse. By creating enough data sets, the researchers hope to develop a neural atlas of the mouse brain revealing how neurons connect to each other.



2.

- Creating methods for tracking and measuring cellular processes during the first anterior/posterior mitotic division in *Caenorhabditis elegans* with Tony Hyman of the Max Planck Institute of Molecular Cell Biology and Genetics, Dresden.
- Producing with Stuart Kim of Stanford University 3-D stacks of in situ worm preparations in which all 81 muscle cell nuclei are stained a different color.

This range of collaborations suits Myers just fine. "I'm a very hands-on kind of guy. I have lots of ideas. I love to roll up my sleeves and write the code," he says, noting that the unique atmosphere at Janelia Farm encourages cooperative work. "We have the opportunity to do really exciting science."

1. **Gene Myers**
2. **Human Neuron**
   The spindly ends at the bottom of this neuron connect to muscle fibers.
3. **David Baker**
4. **Protein Folding**
   The complex three-dimensional structure of HIV reverse transcriptase.

3.

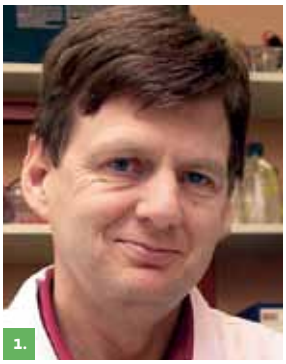
4.

"My dream is that a 12-year-old in Indonesia turns out to be a prodigy and builds a cure for HIV," Baker says.

Gamers, Protein Scientists Unite!

It may not be as hot in the online gaming community as *World of Warcraft*, but the new game *Foldit* enlists gamers to "solve puzzles for science." The brainchild of HHMI investigator David Baker at the University of Washington and colleagues, *Foldit* (www.fold.it) is a free online game that pits players against each other to design proteins rather than battle evil orcs.

Rosetta@home, Baker's distributed computing network aimed at protein folding, was humming along, using downtime on people's computers around the world to perform trillions of random calculations to fold proteins. But participants saw lots of useless calculating going on and suggested the program could use some human intervention. *Foldit*, developed with a special grant from HHMI, brings human brainpower to the effort by allowing players to solve protein structures from nature after successfully completing a few training levels. This fall, gamers will be able to design all-new proteins that ultimately could become useful tools for developing new agents to cure disease or clean the environment. "My dream is that a 12-year-old in Indonesia turns out to be a prodigy and builds a cure for HIV," Baker says.



1. **Alan F. Cowman**
2. **Geoffrey McFadden**
3. **Sergey Lukyanov**
4. **Fluorescent Frogs**
   Katushka, a new red fluorescent protein, lights up muscle fibers in this frog.
5. **Gerald M. Rubin**

On a Mission Against Malaria

HHMI international research scholar Alan F. Cowman longs to work himself out of a job, if it means the end of malaria, and he's formed several collaborations to make it happen. The malaria expert from Australia's Walter & Eliza Hall Institute of Medical Research most recently teamed up with HHMI international research scholar Geoffrey McFadden, at the University of Melbourne, to explore how a gatekeeper inside the malaria parasite decides which proteins gain entry. McFadden and Cowman discovered that this cellular gatekeeper enforced rather lax rules: as long as a given protein was at least 24 amino acids long, had a positive charge, and included the amino acid asparagine, it could gain entry into the parasite's cellular compartment called a plastid. The researchers were able to sneak their own engineered protein past the gatekeeper, making them think it should be relatively simple to trick the gatekeeper into letting an invader inside to kill the malaria parasite.

Pet Shop Beauty

The bright red fluorescent protein Katushka outshines other existing fluorescent proteins 10 to 1. And it exists because HHMI international research scholar Sergey Lukyanov spied a brilliant red sea anemone at his local Moscow pet shop and wouldn't go home without it. He won a bidding war against another customer and returned to the lab with the sea creature to develop the protein. His colleague at the Shemyakin-Ovchinnikov Institute of Bioorganic Chemistry, HHMI international research scholar Andrey Zaraisky, established Katushka's suitability as a tracer in live animals, such as this African clawed frog *Xenopus laevis*. And the pet-store anemone? Just a piece of one tentacle was needed to isolate the protein. The animal resides in one of Lukyanov's aquariums, with other anemones and marine fish.

Q&A


5.

Gerald M. Rubin
Sowing Seeds of Collaboration

Gerald M. Rubin, the *Drosophila* biologist and former HHMI investigator who now directs the Janelia Farm Research Campus, likes to think big and to work collaboratively. As he noted some years ago, "I have a knack for dealing with highly creative, quirky, high-maintenance people and getting them to work together." Those specific qualities came into play when Rubin led a novel effort to sequence the *Drosophila* genome, and they're very much on display as he strives to create a collaborative research community at Janelia Farm.

Q Why do you believe Janelia Farm Research Campus is more conducive to collaborative efforts than academia?

A Academia rewards individual achievement, not collaboration. Certain scientific problems are best studied in an interdisciplinary environment where collaboration is the expectation, and research groups are encouraged to self-assemble to solve problems.

Q What does it take to change a culture?

A The ability to collaborate readily is a vital tool, but our scientists need the mind-set to use that tool. It requires constant reinforcement.

Q Janelia Farm is fairly small compared to a university. Does that limit collaborations?

A No, the small size facilitates collaboration, as individuals working in different fields are not segregated into departments. That said, many of our projects benefit from wider expertise than we can have at Janelia Farm, a deficiency we address through our visiting scientist program. Scientists come for three weeks, a full sabbatical year, or a series of short visits spread over multiple years—we're open to any arrangement that makes sense.

Q Are the scientists at Janelia Farm connecting as you envisioned?

A When we were planning Janelia, we asked: what important biological problem would you tackle if you could assemble 100 people for 10 years with generous funding? None of our projects has reached that scale, but I can see the seeds in some.

Q Can you give an example?

A There's an attempt to create a map of the fly brain and then relate specific neurons to specific sensory and motor activities. The project requires the development of new anatomical methods, numerous high-throughput behavioral assays, and developments in molecular genetics and in methods that allow physiological measurements of the function of individual neurons in flies as they perform various behaviors. It's a wide-ranging project in which nine resident labs and several visiting scientists currently participate.

The pursuit of science begins with curiosity, but real insight comes from forming and testing hypotheses. To spark an inquisitive fire and train the next generation of scientists to take up research in an ever more complex and interdisciplinary scientific world, HHMI is undertaking some experiments of its own.

Putting New Approaches to the Test

1.

"We want students to experience science as the creative, challenging, and rewarding endeavor that it is," says Tom Cech.

Undergraduate Variations

HHMI issued a challenge to the nation's top undergraduate institutions: identify creative new ways to engage students in biological sciences. Close to 200 replied, and now 48 liberal arts colleges in 21 states and Puerto Rico will test their resourceful, imaginative approaches to science education with newly won HHMI grants. This is the largest number of new grantees in a decade; more than a quarter of the institutions have never received an HHMI grant before.

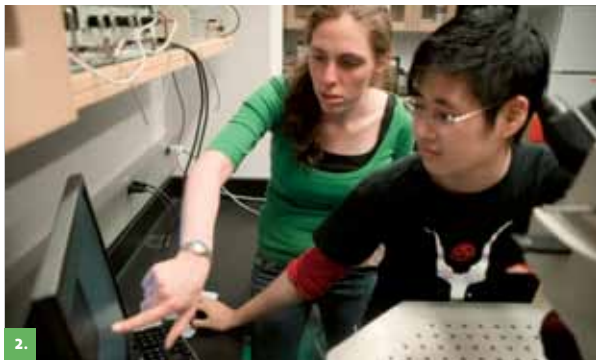
"The undergraduate years are vital to attracting and retaining students who will be the future of science," says HHMI President Thomas R. Cech. "We want students to experience science as the creative, challenging, and rewarding endeavor that it is."

HHMI has pledged a total of $60 million to support the programs devised by the colleges and universities. The institutions include traditional liberal arts colleges, historically black colleges and universities, small religious schools, and larger state institutions. Using grants ranging from $700,000 to $1.6 million, they will focus on teaching modern laboratory techniques, designing interdisciplinary classes, and boosting outreach. Some are entirely redesigning their biological science majors. The following are a few of the new programs:

Franklin & Marshall College in Lancaster, Pennsylvania, is taking advantage of a genomic science resource in its backyard: the D. Holmes Morton Clinic for Special Children specializes

1. **Liberal Arts Education**
Darrylynn Nelson and Elizabeth Adeyemi, students at Spelman College, evaluate the role of a gene in yeast.

2. **Hands-On Science**
Barnard College students Christine Chang and Ayelet Spitzer use fluorescent microscopy and digital imaging to see if cells are dividing in fruit fly testes.



in diagnosing and treating inherited metabolic disorders in children from Amish and Old Order Mennonite communities. The clinic has gathered genetic data on more than 80 different metabolic disorders. Thirty-two students from the college will work at the clinic and on campus to mine and analyze this wealth of information looking for distinctive patterns of mutation, deletion, or repetition that might underlie these disorders. The grant will also support an additional 32 students to work on other projects in bioinformatics and genomics.

The Spokane Tribe of Wellpinit, Washington, taught *Gonzaga University* biology professor Brook Swanson and his colleagues that Native Americans don't view science as a discrete topic: everything is interconnected. "How you interact with your environment is an integral part of your community and your spirituality," Swanson says. Now Gonzaga University's biology department is using part of its first HHMI grant to strengthen its outreach to a community that is not often attracted to science careers. The grantees are developing a new curriculum for the tribe's K–12 school that is filled with context and nuance conveyed through stories, case studies, and the history of science. They hope the project will attract more Native Americans to science as well as other students who benefit from learning in context.

Through "learning communities," the *College of Charleston* will encourage and support first-year students interested in computational biology, chemical biology, and neuroscience. About 30 to 40 students with similar interests will study, take classes, and live together during their first year. Each learning community will be assigned a junior or senior who is doing research in a relevant area. This student will serve as a peer facilitator and coordinate weekly discussion sessions. The college has used learning communities in other disciplines and successfully improved grades and increased retention, particularly among underrepresented groups.

Spelman College in Atlanta is going Hollywood and using some of its grant to fund student filmmakers as they create a full-length documentary examining the lives of recent Spelman graduates who are pursuing successful scientific careers. The historically black women's college is also revamping its mentoring program in the biological sciences to pair successful alumni in the sciences with female high school students from the Atlanta area. In addition, the mentoring program will expand to place Spelman students during the summer in the labs of top minority women scientists at research universities across the United States.

"This diverse pool of grant recipients and large numbers of first-time awardees shows that HHMI is committed to funding new ideas and new ways of approaching science education," says Peter J. Bruns, HHMI's vice president for grants and special programs. "We want to help create successful models for teaching science that can spread throughout the higher-education community."

1.

Sink-or-Swim Proteomics

HHMI professor Pavel A. Pevzner believes that without more bioinformatics specialists, researchers will either drown in genetic and protein sequence data or, worse, miss the key connections that undergird human health or disease. Pevzner's solution is to push undergraduate students into the deep end of bioinformatics to see if he can train them to be experts in genome annotation.

In a University of California, San Diego, course innocently titled "Research Experience for Undergraduates," Pevzner thrust students into the lab to figure out the genome of three species of *Shewanella*, an important "metal-munching" genus of bacteria. Armed with raw mass spectroscopy data for the bacterium's proteins plus genomic sequence information, the students set to work designing experiments and writing computer algorithms to link the two sets of data.

Pevzner and seven undergraduates from the class published their results in the July 2008 issue of *Genome Research*. In that paper they unveiled an entirely new branch of bioinformatics that Pevzner calls "comparative proteogenomics."

2.

"Instead of meeting with the students in a room, we will meet them on the Web. Students in India and China and in whatever place in the world can collaborate with each other," says Pevzner.

With a proof of principle in hand, Pevzner and graduate student Nitin Gupta are taking the experiment worldwide via their UBER-GRID—the Undergraduate Bioinformatics E-Research Grid. "We will put our projects on the Web and invite every student in the world to collaborate," Pevzner says.

"Instead of meeting with the students in a room, we will meet them on the Web. Students in India and China and in whatever place in the world can collaborate with each other." The lab will post links to required data sets, genome repositories, downloadable software tools, prediction programs, and literature references.

1. **Pavel A. Pevzner**
2. **Metal Muncher**
Shewanella oneidensis grows on the iron oxide mineral hematite.
3. **Analyzing Insect Sounds**
Janelia Farm's Gus Lott (right) describes his software to students from Singapore and Virginia.

Engineering a Class

Summer break for a group of college students from some of the best engineering colleges in the country meant returning to their Greenbelt, Maryland, high school to design a top-flight engineering curriculum. Students at *Eleanor Roosevelt High School*, a science and technology magnet, will pilot-test several of the new modules this fall. They will redesign the Taj Mahal, build an SUV, and guide a robot using the latest in computer programming.

Faced with a high school engineering curriculum that hadn't been revised since 1976, science and technology program coordinator Jane Hemelt and teachers Rocco Mennella and Michael "Pudge" Samordic turned to a group of alumni who've been excelling in college engineering programs. Supported in part by HHMI, these 10 students culled their knowledge and that of almost 50 engineering professors to develop course modules that focus on the practical aspects of engineering while including as much physics and mathematics as possible. And because science and technology teachers can be hard to find, they designed the modules to be taught by teachers who are not engineering experts.

With refinements based on feedback from pilot testing, and development of more modules over the next several years, Hemelt hopes to make the curriculum widely available. "Who knows, this could become a model for the state and maybe a model for the country," Hemelt says.

3.

Collaborations Across the Oceans

How crickets evolved different songs is a research question bringing together students from Loudoun County, Virginia, and the island nation of Singapore. Through this HHMI-supported project, these students are getting their first taste of international scientific collaboration.

Pairs of students from the *Academy of Science* (AOS) at Dominion High School and the prestigious Hwa Chong Institution (HCI) teamed up to explore six research questions. The cricket project even drew in Janelia Farm scientist Gus Lott, who brought to the table software he developed to analyze insect sounds.

The international collaboration experiment is the brainchild of AOS director George Wolfe, a former Peace Corps volunteer who traveled three years ago to train teachers in Singapore. On a later trip, he suggested to HCI's principal research consultant that "our students collaborate like real scientists." Last fall, the HCI students visited Loudoun County for some face-to-face interaction. The AOS students went to Singapore this summer and the teams presented their final results together.

1. **Steven E. Jacobsen**
2. **Ronald M. Evans**
3. **David Asai**


1.


2.

A Wide-Screen View of Silence

Turning on the wrong gene at the wrong time can wreak havoc in a cell. Scientists have known for decades that cells use DNA methylation to keep unneeded genes turned off, but their understanding of how DNA methylation accomplishes this critical task has been stymied because they could examine methylation only one gene at a time. HHMI investigator Steven E. Jacobsen at the University of California, Los Angeles, has given the scientific community an important new tool to explore the gene silencing process: a molecular and computational approach that delivers a wide-screen, whole-genome view of DNA methylation.

"There's lots of evidence that when genes' methylation patterns are not properly maintained, that is a major cause of cancer," says Jacobsen. "So if we can learn enough about these methylation mechanisms, we may someday learn to manipulate them and treat cancer."

During DNA methylation, small molecules called methyl groups attach to specific sites on DNA where they signal the cellular machinery to silence genes in a specific region. Using the plant *Arabidopsis thaliana*, Jacobsen and his computational biologist colleagues Matteo Pellegrini and Shawn Cokus, with researchers from the biotechnology companies Illumina and New England BioLabs, developed novel techniques to rapidly and correctly identify more than 90 percent of the methylation sites across the plant's entire genome. With their validated tool in hand, Jacobsen and colleagues are analyzing other organisms to see how widely conserved methylation patterns are.

Exercise in a Pill

The genetically engineered mice ran longer and faster than normal mice and they resisted weight gain even when fed a high-fat diet. HHMI investigator Ronald M. Evans at the Salk Institute for Biological Studies pursued the next obvious—and electrifying—question: is it possible to create a drug to duplicate the athletic abilities of his "marathon" mouse?

Evans' team found two drugs that target the critical gene *PPAR-delta*, which serves as a master regulator of several genes. The two compounds, GW1516 and AICAR, increased the activity of *PPAR-delta* in mice. Treated mice also had higher endurance than untreated mice. GW1516 had a more dramatic effect, but only when combined with exercise. Sedentary mice receiving AICAR ran longer and farther than those receiving exercise training. Like exercise, the two drugs trigger a variety of changes such as an increase in the number of energy-generating mitochondria in cells and a shift in metabolism to favor burning fat. "We have now created the potential for a really simple intervention in an area of major health problems," Evans says.

The drugs could also be used by athletes seeking an advantage over their competitors—especially the exercise-enhancing GW1516. For that reason, Evans has developed a test to detect whether the drugs are being used for performance enhancement. He has provided it to the World Anti-Doping Agency, for retroactively testing samples from athletes who competed in the 2008 Olympics.

Q&A


3.

David Asai
Experiments in Education

David Asai has served as a program director at Purdue University and most recently at Harvey Mudd College. He joins HHMI as Director of Precollege and Undergraduate Science Education, calling it a once-in-a-lifetime opportunity to encourage educators to test new ideas.

Q The Undergraduate Science Education program and the Precollege Science Education program just merged. What's the benefit?

A Your knowledge about science doesn't begin as a freshman in college. Merging the two programs means we can focus on collaborating across the continuum of science education from pre-K through college rather than emphasizing discontinuities. Now, we just need a clever acronym for the program!

Q As an HHMI program director, what is the biggest thing you've learned about undergraduate teaching and learning?

A I've been very fortunate to have served as a program director at a large research institution and an undergraduate liberal arts college. I've learned that big research universities and little liberal arts colleges have things to teach each other. Research institutions obviously have more resources, but liberal arts colleges can be more nimble when it comes to trying out new ideas. We need to encourage exchange between the two so they can learn from each other.

Q How is the transition from Harvey Mudd proceeding?

A My National Science Foundation (NSF) grant was just renewed, and back at Harvey Mudd, I have four seniors, three sophomores, and two postdocs studying the dynein motors responsible for intracellular transport. There will be a lot of videoconferencing and traveling back and forth, but I think it is important that our grantees understand that those of us who work at headquarters also have labs and teach. This perspective helps us understand the challenges they face.

Q What goals do you hope to achieve in the next year?

A Long term, I want to find ways to consider the entire continuum of science education from pre-K through college in a holistic way. I would also like to encourage institutions to do more hypothesis-based experiments in science education and give them the opportunity and incentive to try new and sometimes risky ideas. Even if the hypothesis fails, it will be useful as long as we do it right and disseminate the results.

Short term, we have two program officer openings in our group. I would like to fill the positions with people who have been successful in academic teaching and research. For one of the positions, we plan to use the NSF model where people take a leave from their home institutions for a couple of years and then return to academia. This "rotator" model provides the opportunity for the regular and frequent refreshing of our perspectives.

With scientific curiosity and advancing technology, researchers have begun exploring problems of enormous complexity. Several HHMI investigators have made exciting new discoveries about some mystifying diseases, such as autism.


Probing Complexity

1. **Christopher A. Walsh**
2. **Communication Breakdown** Nerve cells reach out to each other to exchange information at the synapse.
3. **Thomas C. Südhof**
4. **Huda Y. Zoghbi**
5. **Li-Huei Tsai**

Revealing the Roots of Autism

Autism strikes with heartbreaking timing. Just as a toddler should be gleefully interacting with family members, the child regresses and pulls away from the world. Most children with autism are slow to develop language, have poor social skills, and repeat stereotypical behaviors, but the extent of their difficulties can range from subtle to devastating. This wide variability has confounded attempts to understand the disorder.

In just the past year, however, several HHMI investigators and others have made key discoveries about the autistic brain. Their findings have zeroed in on the synapses—the tiny chemical-filled gaps between neurons. Synapses create powerful information-processing networks that enable humans to think and remember, interpret sensory information from the outside world, and navigate the challenges of social relationships. Synapses also appear to be central to Rett syndrome and fragile X syndrome, two rare genetic disorders with autistic features.

"There's lots of evidence to suggest that this process of synaptic learning is key to autism," says HHMI investigator Christopher A. Walsh at Beth Israel Deaconess Medical Center. In 2008, Walsh and clinical collaborators in the Middle East found six synapse-related genes that, when mutated, contribute to autism. They made the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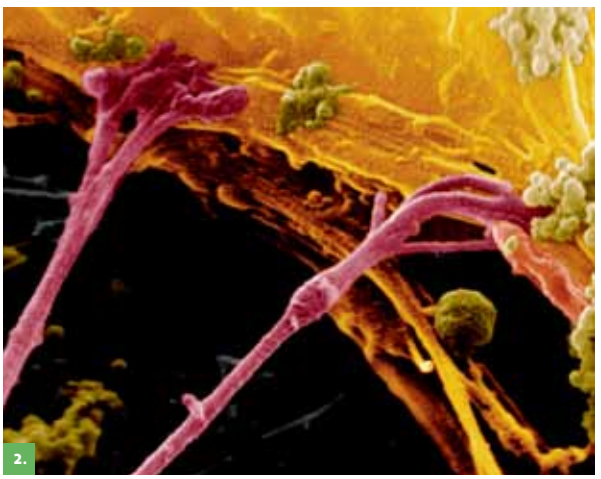

2.

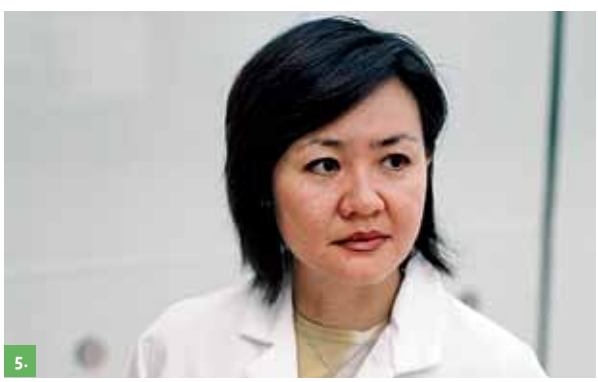
discovery by using a new strategy to compare genes from autistic and nonautistic siblings from 88 large Middle-Eastern families. Most of the mutations were found in regions that serve as on-off switches to nearby genes that are involved in learning. Walsh posits that these broken on-off switches could serve as targets for therapeutics or could help identify children likely to respond to intensive behavioral intervention.


3.

Another dramatic development in autism research came in 2007 when HHMI investigator Thomas C. Südhof, then at the University of Texas Southwestern Medical Center at Dallas, and colleagues developed a mouse model of autism spectrum disorders. He engineered the mice with a mutation in the human gene *neuroligin-3*, part of a family of genes (along with the neurexins) that he linked to synapses in the 1990s. These genetically altered mice were far less social than normal mice, but they were also smarter—they learned the location of a platform submerged in murky water in fewer days than normal mice. "Usually, when you impair mouse cognitive function, they're just stupid," says Südhof, now at Stanford University. He adds that the results "validate the whole idea that autism is related to synapses."

HHMI investigator Huda Y. Zoghbi has continued her investigations of the gene mutations involved in Rett syndrome, a devastating disorder that robs (mostly) girls of their speech, motor control, and social development after 6 to 18 months of normal development. Zoghbi, a pediatric neurologist and geneticist at Baylor College of Medicine, discovered in 1999 that 95 percent of all Rett cases involve a mutation in a gene on the X chromosome called *MECP2*. Zoghbi's group reported in 2008 that the MECP2 protein interferes with the regulation of 2,500 genes, which she says helps explain the broad and varied symptoms of the disorder.


4.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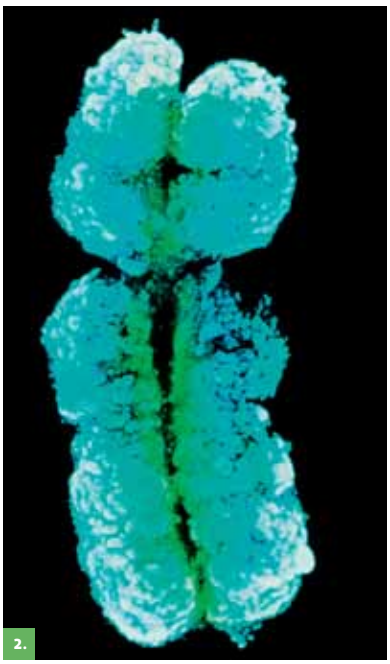
By genetically engineering mice deficient in a protein called Cdk5, HHMI investigator Li-Huei Tsai at the Massachusetts Institute of Technology (MIT) also drew attention to the role of the synapse. Without Cdk5, a second protein called CASK does not interact with neurexin proteins and synapse formation is profoundly defective. "Proteins implicated in autism all seem to overlap in this particular area of synaptic development," Tsai says.

1. **Mark F. Bear**
2. **Fragile Tip**
   In fragile X syndrome, the X chromosome holds a mutation that makes it easily break near one tip.
3. **Philip S. Perlman**

1.



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Autism-associated defects in synapses may be reversible, according to recent mouse studies of Rett syndrome and of the most common form of inherited mental retardation, fragile X syndrome. HHMI investigator Mark F. Bear, also at MIT, devised a new strategy for treating fragile X. Bear had previously established that a neurotransmitter called mGluR5 weakens neural connections by increasing the amount of protein made at a synapse. He and his colleagues also established that the fragile X mental retardation protein (FMRP), which is mutated in fragile X syndrome, serves as a foil to mGluR5 and puts the brakes on protein synthesis. When FMRP is absent, protein synthesis at the synapse goes unchecked.

Bear and his colleagues tested whether eliminating one copy of mGluR5 in mice with fragile X syndrome would reduce seizures and memory impairment. In December 2007, they reported that indeed the mice with dampened mGluR5 expression showed few fragile X symptoms. mGluR5 antagonists have been moved into human studies.

With these and other findings that place the synapse front and center, researchers are showing the first signs of optimism that they may find a way to treat autism and related disorders.


3.

Philip S. Perlman
Herding Mice

When **Philip S. Perlman** joined HHMI as a senior scientific officer in 2004, he brought years of research experience on mitochondrial genes in yeast. Naturally, he was charged with finding a way to help HHMI investigators manage the costs of mouse research.

With input from 18 HHMI mouse researchers from around the country, Perlman learned a thing or two about mice, and devised an Institute-wide initiative to address the investigators' top concerns: the costs of genotyping, colony management, and problems getting the Jackson Laboratory repository to accept mice that were no longer being used for active research, but needed to be maintained for future studies.

Now, mouse genotyping is outsourced through Memphis-based company Transnetyx: more than 70 researchers have used the service at a special price negotiated by HHMI. Sixty-five investigator labs have completed training on the Jackson Lab's Colony Management System, developed by HHMI investigator Simon W.M. John. And, with HHMI support, the Jackson Lab repository has accepted more than 200 new mouse strains. The price came down significantly when the lab found a way to switch from freezing mouse embryos from each breeding pair to sperm cryopreservation. Perlman is not stopping there. Etched ear tag identifiers are in the works, as is research to identify the optimal number of mice per colony cage.

Top 10 Things Yeast Geneticist Philip Perlman Learned About Mice

1 Mouse research is slow. Mice take 4 months between generations; yeast reproduce 18 times in 24 hours.

2 Mice need clean cages, food and water, air conditioning, and toys. You can store yeast in the freezer.

3 A mistake in mouse research sets you back months. *See number 1.*

4 Mice are much better models than yeast for human diseases such as diabetes, cancer, and cardiovascular disease.

5 Mice are harder to share with your colleagues. You can send yeast via regular mail the same day the request comes in. Mice take six months to breed and genotype before they can be shipped—special delivery.

6 Mice have cute, furry faces. Yeast are just furry.

7 Mouse studies need institutional approval. Yeast are not animals, so no animal care or ethics rules are involved.

8 Mice have better health care than many humans.

9 Mouse research is irresistible. Once it enters an investigator's program, it never leaves.

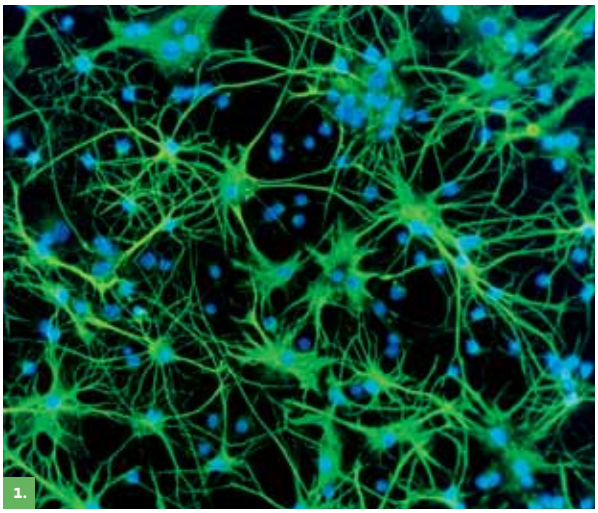
10 Yeast smell like bread and beer; mice smell like …

Two Approaches to Protecting Motor Neurons

Everyday tasks like getting out of bed or stepping into a car require coordination of dozens of muscles, guided by hundreds of motor neurons that connect the muscles with the spinal cord. Amyotrophic lateral sclerosis (ALS), or Lou Gehrig's disease, is one neurodegenerative disease that destroys motor neurons.

In work that could help aid drug discovery for ALS, HHMI investigator Thomas M. Jessell, at Columbia University College of Physicians and Surgeons, working with Jeremy Dasen of New York University and Philip Tucker of the University of Texas at Austin, identified a key gene responsible for making motor neurons and ensuring they make critical connections between the spinal cord and muscles.

FoxP1 is required to generate motor neurons, according to the new research. And, importantly, the level of the protein FoxP1 expressed by developing neurons dictates the precise subtype they will form. FoxP1 is an essential cofactor for many of the Hox proteins that, according to Jessell's previous work, orchestrate motor neuron development and connectivity. Hynek Wichterle and Mirza Peljto at Columbia are using this Fox-Hox recipe to develop "a promising screening for identifying drugs that prevent or slow the degeneration of motor neurons," says Jessell.



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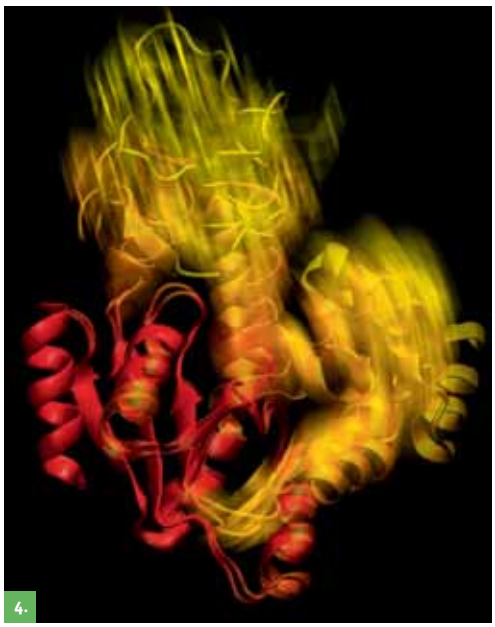
HHMI international research scholar Rafael Radi is taking a different approach to ALS, based on an unexpected result of his research on the immune system's macrophages. Motor neurons rely on companion cells, called astrocytes, for nourishment and protection. Radi's lab found that peroxynitrite, used by macrophages to kill bacteria, can also turn astrocytes into motor neuron killers and lead to ALS. Radi and his team at the Universidad de la República in Uruguay used an antioxidant to reverse peroxynitrite buildup and block motor neuron destruction in rats with a form of ALS. "I think peroxynitrite is a central mediator in cell death," he says. "It can kill pathogens, but it can also kill your own cells."

1. **Astrocyte Cells**
Immunofluorescent light micrograph of mammalian brain cells.
2. **Rafael Radi**
3. **Thomas M. Jessell**
4. **Fidgeting Enzyme**
Three-dimensional structure of adenylate cyclase.
5. **Dorothee Kern**

Twitching Proteins

HHMI investigator Dorothee Kern has changed the way scientists think about enzymes. To draw out the dynamic personality of adenylate kinase, Kern and her team at Brandeis University used x-ray crystallography for structural information, examined the internal motion of the enzyme with nuclear magnetic resonance, and used a supercomputer to generate a movie of the enzyme opening and closing.

Kern called on her brother, physicist Christian Huebner, at Martin Luther University Halle-Wittenberg in Germany, to make sense of discrepancies between methods. Huebner had designed and built a unique ultrasensitive laser that allowed precise measurements and time resolution in microseconds. The new measurements showed that, contrary to conventional wisdom, the enzyme doesn't always wait for its substrate to change shape. It adopts an intermediate half-open, half-closed state every few nanoseconds. It only rarely closes all the way, snapping its lid shut in milliseconds. "That's when the enzyme is getting down to business and can bind with its substrates to perform catalysis," says Kern. It took a technological tour de force, but Kern and her team ultimately revealed the enzyme's hidden moves.



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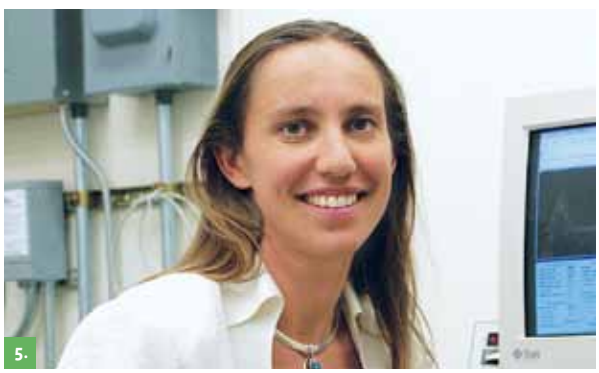
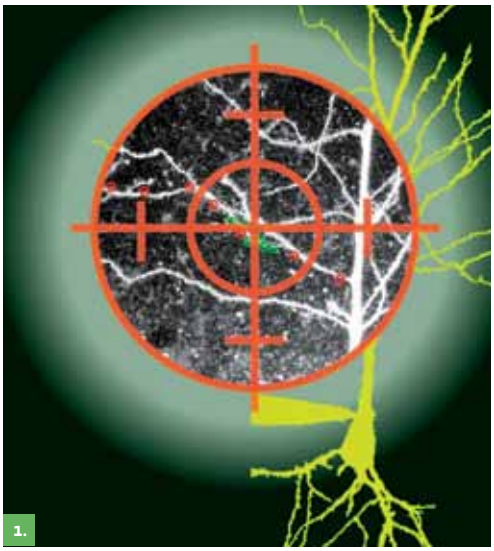


5.

HHMI investigator Dorothee Kern has changed the way scientists think about enzymes.

1. **Dendrite Targets**
Two-photon image of a neuron showing different spatial patterns of excitatory input onto a dendrite branch. Target shows location of neurotransmitter uncaging.

2. **Jeffrey C. Magee**



Information Storage in the Brain

The human brain is composed of 100 billion neurons, each sporting roughly 10,000 synaptic connections to other neurons. The signals that flood through these myriad connections become stored information through a process called synaptic plasticity, which occurs when the strength of input changes because of what we experience or the thoughts we produce.

Group leader Jeffrey C. Magee and colleagues at the Janelia Farm Research Campus used a new technique to show that neurons fine-tune their information processing through a second type of plasticity that he calls "dendritic plasticity." Dendrites, the large branches that extend from the main body of a neuron, represent the receiving end of nerve impulses. They are covered with receptors for chemical signals, or neurotransmitters. As neurotransmitters flood the dendrites, they trigger an electrical wave called a dendritic spike that, when powerful enough, can propagate a nerve impulse through the body of the neuron.

Using neurotransmitters sequestered in a molecular "cage" that Magee could release with a laser pulse, his team targeted the exact spot on a dendrite they wished to stimulate. Just as synaptic inputs can be strengthened or weakened to presumably transmit and later store information, Magee's group showed that neurons use dendritic plasticity to adjust how they respond to incoming signals from other neurons. "This form of plasticity is distinct from—and complementary to—the more traditional synaptic plasticity," he says.

Year in Review

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New Trustee
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Shaping the Future

The past year was one of remarkable growth and renewal for HHMI's research programs. The Institute announced three major initiatives, representing a total investment of roughly $1 billion over the next six to eight years, which will shape the character of HHMI research for years to come.

October 2007 saw the selection of 15 patient-oriented researchers as HHMI investigators, a powerful reaffirmation of the Institute's commitment to ensuring that basic research discoveries are translated into improved treatment for patients. These physician-scientists are a special breed; their scientific work is guided by their interaction with patients. The 15 new investigators were selected in a nationwide competition that drew close to 250 applicants. HHMI has completed two such targeted competitions for patient-oriented translational research in the last six years.

Exceptional ingenuity and curiosity were also distinguishing features of the 56 scientists selected in May 2008 to become HHMI investigators. That group, which included 42 men and 14 women, represented 31 institutions nationwide, including 7 institutions that added an HHMI investigator for the first time: the Aaron Diamond AIDS Research Center, Boston University, Cornell University–Ithaca, Purdue University, Texas A&M University, Cincinnati Children's Hospital Medical Center, and the University of Texas at Austin. The group includes scientists with roots outside the United States, including Argentina, China, Israel, and the Netherlands, and with equally diverse intellectual backgrounds in fields as varied as bioengineering, immunology, and synthetic biology.

"We decided to focus on scientists who have led their own laboratories for several years because many of these scientists are at a high point of their creativity just as they see their start-up funds and early-career awards ending," says Cech.

Just as HHMI impels its scientists to take on high-risk, high-reward projects, it asks the same of itself in considering programs to add to its scientific portfolio. In early 2008, the Institute unveiled a bold initiative to provide much-needed support to about 70 of the nation's best early-career faculty at a time when they most need the help. The Early Career Scientist Program was carefully conceived to provide a lifeline to researchers who have run their own labs for two to six years and are at a critical point in establishing their own vibrant, independent research programs. Each Early Career Scientist appointed in spring 2009 will receive a six-year, nonrenewable appointment to HHMI as well as the substantial support necessary to move his or her research in creative, new directions.

When deliberating where the Institute's resources could have the greatest impact outside its core HHMI Investigator Program, President Thomas R. Cech and others saw a clear opportunity. "We decided to focus on scientists who have led their own laboratories for several years because many of these scientists are at a high point of their creativity just as they see their start-up funds and early-career awards ending," Cech says. "Some of them may still be in line for their first NIH R01 grant, while others may have their first grant but are facing the very challenging first renewal of that grant. It is this period of career vulnerability that the HHMI Early Career Scientist Program aims to bridge."

1.

"We know our pool of candidates has been excellent in past competitions," says Cech, "but how can it not be even deeper and broader if we open up the process?"

Apply Directly

Two years ago, HHMI's scientific leadership began to examine the nomination and application processes for the Investigator Program. Although the Institute's flagship program has been undeniably successful—producing 12 Nobel laureates and 124 members of the National Academy of Sciences—President Thomas R. Cech and others wondered whether the process of picking investigators could be improved. And so began a series of discussions that led to a radical reworking of the process.

Instead of inviting research institutions to nominate the very best of their faculty for HHMI investigator positions—as HHMI has done since 1994—the new model would ask eligible researchers to nominate themselves directly. Many factors played a role in the policy shift, but one stood above all others: "We know our pool of candidates has been excellent in past competitions," says Cech, "but how can it not be even deeper and broader if we open up the process?"

HHMI used the direct application process for the first time in the 2007 Investigator Competition in Patient-Oriented Research and in the 2008 HHMI Investigator Competition. The results were so positive that the Institute has decided to use direct application for the 2009 HHMI Early Career Scientist Competition.

15 New Patient-Oriented Researchers

Vivian G. Cheung
The Children's Hospital of Philadelphia

Arul M. Chinnaiyan
University of Michigan Medical School

George Q. Daley
Children's Hospital Boston

1.

Elizabeth C. Engle
Children's Hospital Boston

Joseph G. Gleeson
University of California, San Diego, School of Medicine

Daniel A. Haber
Massachusetts General Hospital

Friedhelm Hildebrandt
University of Michigan Medical School

S. Ananth Karumanchi
Beth Israel Deaconess Medical Center

Christopher V. Plowe
University of Maryland Medical School

Kerry J. Ressler
Emory University School of Medicine

David H. Rowitch
University of California, San Francisco, School of Medicine

Charles L. Sawyers
Memorial Sloan-Kettering Cancer Center

"We would like to identify as many primary causes of kidney diseases in children as possible," says Friedhelm Hildebrandt, University of Michigan Medical School, who analyzes patient blood samples for disease genes. "Then, we finally might be able to do something about the disease itself, and not just treat the symptoms."

Erol Fikrig
Yale School of Medicine

Beth Levine
University of Texas Southwestern Medical Center at Dallas

Andrey S. Shaw
Washington University School of Medicine in St. Louis

1. Translating Discoveries into Treatments

People often talk about translating laboratory discoveries into patient care, but inspiration can flow in the reverse direction as well. In 1992, an encounter with a toddler whose eyes were frozen in a downward gaze led pediatric neurologist Elizabeth C. Engle to a trove of previously unrecognized congenital disorders that rob patients of normal control of their eye movements. Exploring the clinical and genetic features of these disorders, Engle and her colleagues have defined a new category of syndromes resulting from errors in brain-stem motor neuron development.

Engle pored over journals looking for case reports and families with similar conditions and contacted clinicians around the world. She eventually located more than 700 families affected by this newly described disorder or others related to it. Using DNA linkage and mutation analysis, Engle identified the genetic causes for a series of these disorders and found that each perturbed development of one or more cranial nerves. These syndromes are now termed congenital cranial dysinnervation disorders. Among them: Duane syndrome, horizontal gaze palsy, Moebius syndrome, and congenital ptosis.

Engle, based at Children's Hospital Boston, became a new HHMI investigator in 2007, along with 14 other distinguished physician-scientists.

In July 2008, she led an international team of researchers that identified a gene mutated in Duane syndrome, a common disorder that restricts movement of the eyes. Engle's team zeroed in on the Duane syndrome gene by studying DNA extracted from blood or saliva samples provided by multiple members of different families. The gene mapped to the locus identified in the genetic linkage studies. By screening genes in the linked region, Engle's group identified a unique mutation in the gene *CHN1* in each of seven families. *CHN1* encodes a signaling molecule, 2-chimaerin, which is essential for normal upper motor neuron axon guidance.

Engle says she hopes her research will one day have a direct impact on her patients' lives. "One of my ultimate goals as a clinician-scientist," she says, "is to move our research back to the bedside by finding better treatments for these early defects in brain-stem motor neuron development."

1. A Rewarding Obsession

There are many paths by which scientists find their calling and retain their curiosity about the world. In May 2008, that sense of exploration was palpable as 56 new HHMI investigators descended on HHMI headquarters for a two-day orientation.

One of those in the crowd, Jue Chen, Purdue University's first HHMI investigator, exemplifies the tenacity and perseverance characteristic of this new group of investigators. For seven long years, Chen was obsessed with the maltose ABC transporter, which ferries life-sustaining sugar molecules through a cell's membrane to its interior. She wanted to produce detailed pictures of the transporter in action.

Chen is a structural biologist and an expert in x-ray crystallography. Like all structural biologists, she wants to see cells or parts of cells going about their business resolved in exquisite detail at the atomic and molecular levels. Chen crystallizes the proteins she is interested in and then bombards them with x-rays. Computers help capture the diffraction patterns that bounce off the atomic lattice. By rotating the crystallized protein complexes through multiple exposures, Chen gradually builds three-dimensional computer models that expose the architecture of these natural nanomachines.

When Chen joined Purdue in 2002 for her first faculty position, she set up a new crystallography laboratory. Solving the structure of the maltose transporter became the central goal of her new research group. Scientific mentors suggested that it might be too narrow a project. One adviser warned that as a junior researcher, Chen could be "betting the farm" on a problem that was beyond current technology.

Chen listened to their advice but stayed the course. Her decision paid off five years later. In 2007, she and her colleagues published a complete structure of the maltose transporter in its elusive midaction position, putting Chen's lab on the leading edge of the ABC-transporter field.

Looking back, Chen says that it wasn't obstinacy or the chance of having a high-profile publication that motivated her. "I was doing this because I was just so interested in the molecule," she recalls. "I told people that I was obsessed. I just had to see it."

Sangeeta N. Bhatia
Massachusetts Institute of Technology

Jue Chen
Purdue University

Catherine L. Drennan
Massachusetts Institute of Technology

"My philosophy is slightly different; I tend to follow my nose. **If I find something interesting and I think I can solve a problem, I'll go ahead and tackle it**," says Paul D. Bieniasz, Aaron Diamond AIDS Research Center at Rockefeller University. As a result, our understanding of HIV is much deeper.

Paul D. Bieniasz
Aaron Diamond AIDS Research Center

Carlos D. Brody
Princeton University

David C. Chan
California Institute of Technology

Christopher J. Chang
University of California, Berkeley

James J. Collins
Boston University

Yang Dan
University of California, Berkeley

Abby F. Dernburg
University of California, Berkeley, Lawrence Berkeley National Laboratory

Andrew Dillin
Salk Institute for Biological Studies

Michael B. Eisen
University of California, Berkeley

Michael B. Elowitz
California Institute of Technology

Adrian R. Ferré-D'Amaré
Fred Hutchinson Cancer Research Center

L. René García
Texas A&M University

Jay T. Groves
University of California, Berkeley

Lora V. Hooper
University of Texas Southwestern Medical Center at Dallas

Darrell J. Irvine
Massachusetts Institute of Technology

Christine Jacobs-Wagner
Yale University

Scott Keeney
Memorial Sloan-Kettering Cancer Center

Seung K. Kim
Stanford University

Leonid Kruglyak
Princeton University

Wendell A. Lim
University of California, San Francisco

Dianne K. Newman
Massachusetts Institute of Technology

Phillip A. Newmark
University of Illinois at Urbana-Champaign

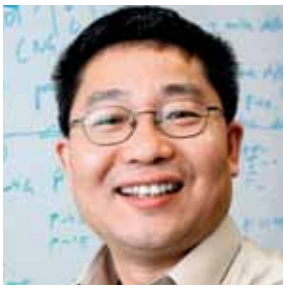
Michele Pagano
New York University School of Medicine

Duojia Pan
The Johns Hopkins University School of Medicine

"The intestinal immune system is **radically different** from the more familiar immune cells that police invaders in the bloodstream," says Lora V. Hooper, University of Texas Southwestern Medical Center at Dallas. "Although much has been learned over the past several years, it's still a big black box."

Erich D. Jarvis
Duke University Medical Center

Grant J. Jensen
California Institute of Technology



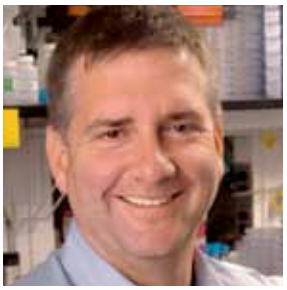
Youxing Jiang
University of Texas Southwestern Medical Center at Dallas

Leemor Joshua-Tor
Cold Spring Harbor Laboratory

Zhe Lu
University of Pennsylvania School of Medicine

Danesh Moazed
Harvard Medical School

Jeffery D. Molkentin
Cincinnati Children's Hospital Medical Center



John V. Moran
University of Michigan

Mercedes Pascual
University of Michigan

Tanya T. Paull
University of Texas at Austin

David S. Pellman
Dana-Farber Cancer Institute

Samuel L. Pfaff
Salk Institute for Biological Studies

"I want to understand **how thought and sensation are organized in time and space**," says Massimo Scanziani, University of California, San Diego.

Jonathan K. Pritchard
The University of Chicago

Bernardo L. Sabatini
Harvard Medical School

David M. Sabatini
Massachusetts Institute of Technology

Massimo Scanziani
University of California, San Diego

Kang Shen
Stanford University

Yigong Shi
Princeton University

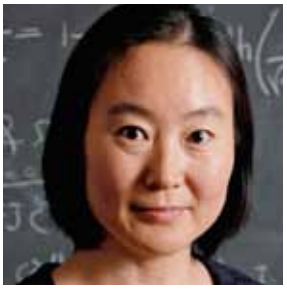
David L. Stern
Princeton University

Jack Taunton
University of California, San Francisco

Wilfred A. van der Donk
University of Illinois at Urbana-Champaign

Leslie B. Vosshall
The Rockefeller University

Thomas Walz
Harvard Medical School



Michelle D. Wang
Cornell University

2. Don't Know Much Biology

As a graduate student in HHMI investigator Stuart L. Schreiber's lab at Harvard University, Jack Taunton exhibited an early penchant for following his own scientific instincts—and curiosity. A chemist by training, Taunton knew he needed to learn more biology before he could tackle projects that interested him.

He began reading the "classics": *The Journal of Cell Biology*, *Cell*, and other journals. "I didn't take classes in biology, but I was surrounded by very talented biologists who taught me everything I know," Taunton says.

After he learned to synthesize molecules found in nature, a "dramatic career turn" steered Taunton away from making compounds to understanding how they function, which he found more challenging intellectually.

His next project led to the synthesis of trapoxin, a biologically fascinating compound. "Trapoxin influenced cancer cells to change shape and look more like normal cells—and they stopped dividing," he explains. He also identified its protein target, histone deacetylase, an enzyme that had been widely sought but never purified or cloned. He cloned the human histone deacetylase gene and revealed its identity as a regulator of gene expression. Not bad for a chemist.

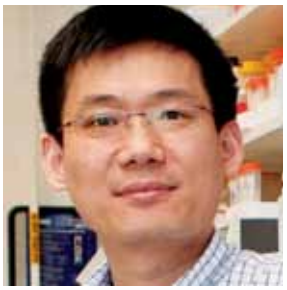
Taunton, a new HHMI investigator at the University of California, San Francisco, is designing novel molecules that reveal how human diseases develop and progress.

He is creating a cache of small molecules to explore the inner workings of the cell. Protein kinases were squarely in his sights from day one because they regulate nearly all cellular processes and are intimately involved in many human diseases. The real challenge, however, is that there are 500 or so kinases encoded by the human genome, and all are remarkably similar. "Distinguishing one kinase from the other 500 with a small molecule is very challenging in terms of molecular recognition," he says. His preference is to go after kinases with no known inhibitor.

As Taunton expands beyond kinases to other enzymes and protein-protein interactions, he'll continue to aim for uncharted waters. "Part of the success I've had has been choosing problems that others aren't working on," he says.

Mark J. Schnitzer
Stanford University

Julie A. Theriot
Stanford University
School of Medicine



Hongtao Yu
University of Texas
Southwestern Medical
Center at Dallas

Phillip D. Zamore
University of Massachusetts
Medical School

Ning Zheng
University of Washington
School of Medicine

New Trustee: Charlene Barshefsky

Ambassador Charlene Barshefsky, senior international partner at the law firm WilmerHale in Washington, D.C., and former U.S. Trade Representative during the administration of President William Clinton, was elected a Trustee of the Institute in January 2008.

Barshefsky served as the nation's principal trade negotiator and policy maker from 1997 to 2001 and as acting and deputy trade representative from 1993 to 1996. She is best known internationally as the architect and negotiator of China's historic World Trade Organization agreement. A 1972 graduate of the University of Wisconsin–Madison, Barshefsky received a law degree from the Columbus School of Law at Catholic University in 1975 and has been named one of the 50 most influential women lawyers in the United States by *The National Law Journal*.

Flood Recovery

During the severe flooding that devastated much of the Midwest in 2008, the Iowa River surged over its banks and across the University of Iowa campus. The university's *Roy J. and Lucille A. Carver College of Medicine* escaped direct damage, but the biomedical research being conducted within suffered with the shutdown of the campus power plant. The plant provides the steam that is essential for air conditioning and heat, plus hot water and autoclave operations.

HHMI contributed $1 million to the university's recovery efforts to help ensure the continuity of biomedical research at the Carver College of Medicine—home to four HHMI investigators. The money is helping pay for temporary systems to provide steam and chilled water to the college's facilities while the university spends several months to restore its power systems.

Renovating Places of Learning

For more than a century, scientists have gathered at the *Marine Biological Laboratory* in Massachusetts and *Cold Spring Harbor Laboratory* in New York to work together and exchange ideas. Both institutions have thriving research training programs, and thousands of scientists come to the campuses each year to teach and learn. As their programs grow, both institutions face the need to provide additional laboratory and classroom space and renovate existing facilities. This year, HHMI contributed $15 million toward major infrastructure upgrades at each institution.

The funds will enable Cold Spring Harbor Laboratory to build six new research buildings and a 12,241-square-foot building with course laboratories and a computer classroom, and to renovate a teaching laboratory building erected in 1926. It will also help purchase major equipment for high-resolution microscopy and protein analysis. The Marine Biological Laboratory will use the HHMI support to renovate its Loeb Building, which is used for summer courses and lectures. The building, built in 1970, suffers from inadequate heating, ventilation and air-conditioning systems, and an outdated electrical system.

New Janelia Scientists

At the end of 2008, the Janelia Farm Research Campus has grown to include 27 resident scientists. Three new scientists set up their labs this year.

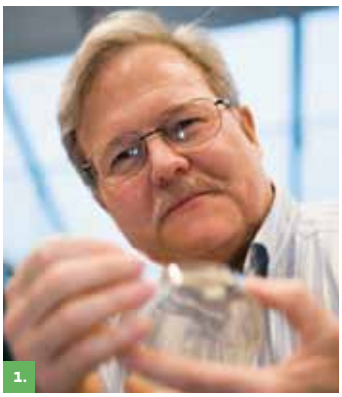
S.E. Roian Egnor, a fellow, wants to understand how neurons control animal behavior in complex, unpredictable environments. Although real-world complexity is often absent in laboratory settings, Egnor is working to re-create some of it. She is allowing mice to live and socialize in large groups and seeking out strains for study that are most like their wild counterparts. She is studying vocalization and other behaviors in these mice.

Group leader Mats G.L. Gustafsson is creating light microscopy techniques that enable scientists to see and track biological structures far smaller than those that can be viewed with traditional light microscopes. Although the wavelength of light limits the spatial resolution of most optical microscopy techniques, Gustafsson is devising ways to overcome those restrictions.

Luke Lavis, a fellow, uses organic chemistry to add new, more powerful fluorescent dyes to the selection currently available to biologists. His goal is to develop probes that can be turned on and off with stimuli such as light and enzymes as well as dyes that can be used to visualize structures and processes inside living organisms.

Students at Janelia Farm

This summer, 12 undergraduates from colleges and universities in the United States and the United Kingdom spent 10 weeks immersed in the culture of research at Janelia Farm. Selected from more than 100 applicants, the students carried out independent research projects in Janelia Farm labs, with group leaders and fellows serving as mentors. Janelia Undergraduate Scholars worked on developing genetic tools to allow scientists to visualize signaling in specific subpopulations of neurons; learning how flies use visual cues to know when to turn during flight; and testing a method to implant electrodes into the mouse brain to measure neuronal activity without disrupting behavior.



1. **Visiting Janelia**
Dan Bogenhagen, SUNY Stony Brook, visits Janelia Farm to use super-resolution imaging techniques developed in Eric Betzig's lab to study mechanisms of nucleoid replication in mitochondria.

Visiting Scientists

The collaborative nature of Janelia Farm extends well beyond its glass walls into the international research community. New connections were made, ideas exchanged, and knowledge and skills shared as a steady stream of scientists visited Janelia Farm from around the world in 2008. Some gathered for a few days for a conference to discuss the latest developments in fields such as bioimaging and neural circuits; others stayed longer to collaborate with Janelia scientists and take advantage of the campus's resources. Twenty-four scientists—from Germany, France, Spain, Canada, Portugal, and the United States—participated in Janelia Farm's Visitor Program in 2008, staying for up to two years. Among their studies were investigations into aggression in fruit flies and the application of integrated circuit design techniques to study the brain.

Nationwide Science Education Experiment Begins

Fortified by hands-on workshops held this summer at the Janelia Farm Research Campus, faculty and teaching assistants at 12 colleges and universities have begun teaching a genomics course created through HHMI's Science Education Alliance (SEA).

SEA aims to elevate U.S. science education from cookbook-based experiments to hands-on, inquiry-based learning. The new course, which utilizes SEA-produced materials, allows students to do real research in a classroom setting by finding, sequencing, and labeling bacterial viruses, known as phages. "The phage genomics course is the beginning of the transformation that the Science Education Alliance hopes to bring to science education," says HHMI's Tuajuanda C. Jordan, a biochemist and the director of SEA.

SEA is already recruiting more schools to expand the program next year, to reach 36 participating institutions in three years.

Through two seminars, SEA promoted hands-on science education to a broader audience, as well. *Genomics: Opportunities, Tools, and Challenges* gave educators an overview of current and future techniques for biology education. A *Quantitative Biology* workshop brought together college math and biology professors to figure out the best way to make students ready for a more integrated future.

1. **Holiday Lectures**
Bruce D. Walker and Bisola O. Ojikutu speak with D.C. area high school students.

AIDS Lectures Educate, Inspire Students

Students from around the Washington, D.C., area and across the country learned about the hurdles facing physicians, scientists, and others on the front lines of the global AIDS epidemic in the 2007 Holiday Lectures on Science.

AIDS: Evolution of an Epidemic was presented by HHMI investigator Bruce D. Walker, a leading AIDS researcher and clinician at Harvard Medical School and Massachusetts General Hospital, and Bisola O. Ojikutu, an infectious disease specialist at Massachusetts General Hospital and director of the Office of International Programs in Harvard Medical School's Division of AIDS.

One hundred eighty high school attendees—and 2,100 students across the United States watching by same-day webcast—learned about the genesis of HIV and the AIDS epidemic; the virus's life cycle, its evolution, and its effect on the immune system; and the disease's impact on society, including drug distribution and vaccine development. Both physicians shared their experiences treating HIV/AIDS patients in Boston and South Africa's KwaZulu-Natal Province, which has among the highest HIV/AIDS prevalence rates in the world. HIV-positive people from both continents described how they became infected with HIV and their battles with treatment and discrimination. The students were captivated when a nurse administered a real-time HIV blood test to both Ojikutu and an HIV-positive activist from South Africa. HHMI's Educational Resources department created a DVD of the lectures with extra animations for classroom use. More than 13,600 copies of *AIDS: Evolution of an Epidemic* have been distributed to teachers and students across the country. It is available free at www.hhmi.org/catalog/.

Students Awarded Gilliam Fellowships

"A doctor can help one person at a time, but a researcher can help 10,000 people with a single discovery." This sentiment, expressed by new Gilliam fellow Daniel Gilmer, is echoed by several of the students awarded the 2008 Gilliam Fellowship for Advanced Study. The award, for promising students from groups traditionally underrepresented in the sciences, pays for up to five years of study toward a Ph.D. in the sciences wherever the student chooses to attend graduate school. The winners are former participants in HHMI's Exceptional Research Opportunities (EXROP) program, which places underrepresented students in the labs of HHMI investigators. *The 2008 awardees are:*

Silvia Caballero

Until she worked on HIV/AIDS in the lab of HHMI investigator Bruce Walker, Caballero didn't know that researchers could so directly help patients. Now this Peru native who moved to the United States at age 16 wants to pursue a doctoral degree in immunology or virology to develop a new generation of treatments and bring them to patients.

Lee "Shoa" Clarke

As a child of a struggling single mother, Clarke dreamed of becoming a physician to help people in need. But his college premed classes were missing one subject he loves: math. Now Clarke is bringing the two pursuits together in an M.D./Ph.D. program, where he hopes to combine computer-based research with genetics.

Alejandra Figueroa-Clarevega

Figueroa-Clarevega grew up in rural Honduras, where she volunteered with the international medical brigades who treated local children. Those early experiences, combined with a stint at the Pan American Health Organization, sealed her focus: to pursue research at the intersection of public health, genetics, and infectious diseases, especially neglected diseases such as river blindness.

Daniel Gilmer

After years volunteering close to his home outside Orlando, Florida, and doing missionary work in Kenya, Zimbabwe, and South Africa, Gilmer thought the best way to combine community service and science was to be a medical doctor. But several in-lab experiences convinced Gilmer he can do more good as a scientist. So this Howard University graduate dropped plans for medical school and will pursue a Ph.D.

Bertrade (Betty) Mbom

Mbom had a hard time in her first year at Carnegie Mellon University. But rather than complain, Mbom, whose parents immigrated from Cameroon, created a program at the school to help other students from traditionally underrepresented groups cope during their first years in college. She is taking that same assertiveness to science, with plans to get a Ph.D. in biology and then become a professor.

Physician-Scientists Encouraged by Early Career Awards

Nineteen promising physician-scientists at 14 academic medical centers have received Early Career Physician-Scientists awards to pursue research that brings science and medicine together. These young physicians will receive $375,000 over five years to help them develop their research programs during this vulnerable time in their careers. 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, also known as the Cloister Program. Their research is focused on important problems in cancer, heart disease, asthma, diabetes, kidney disease, and HIV infection.

Research Highlights

1. **Death Signal**
Triggering cancer cells' own suicide bomb.

2. **Pared-Down Cell**
Protocells consist of only genetic material surrounded by a fatty acid membrane.

The Tick-Tock of the Bacterial Circadian Clock

Researchers discovered how a bacterial circadian clock keeps time using only three interacting proteins. The cellular equivalent of this clock's pendulum and timing gear is so rugged that it can keep precise time for weeks, even after its components have been isolated from bacteria and placed in a test tube.

Erin K. O'Shea, ***Harvard University***

Stress Boosts Learning

Emotional encounters supercharge learning in a way that indelibly imprints those experiences in memory. HHMI researchers have shown that the stress hormone norepinephrine boosts learning by strengthening connections between neurons.

Richard L. Huganir, ***The Johns Hopkins University School of Medicine***

Smac-ing Lung Cancer to Death

HHMI scientists developed a small molecule that turns the TNFα survival signal of cancer cells into a death signal. The molecule mimics the activity of Smac, a protein that triggers the suicide of some types of cancer cells. The new compound may be useful as a targeted treatment for lung and other cancers.

Xiaodong Wang, ***University of Texas Southwestern Medical Center at Dallas***

New Studies Illuminate the Computational Power of Single Neurons

Using light to activate individual neurons in mice, scientists found that relatively few neurons need to be activated to drive perceptions and behavior and that signal strength in one neuron influences signal strength in neighboring neurons. This discovery demonstrates that even short bursts of activity in a few neurons can influence learning and decision-making.

Karel Svoboda, ***Janelia Farm Research Campus***

Plants Can Sense Midnight

Plants "know" when the clock strikes midnight. New HHMI research shows that midnight is crucial to plants because it marks the start of tasks such as growth and protein synthesis, which are typically neglected during the day.

Joanne Chory, ***Salk Institute for Biological Studies***

From Millions of Points of Light to Detailed 3-D Images

Recent advances in fluorescence microscopy let scientists peer inside cells with far better clarity than that achieved with traditional optical imaging techniques. HHMI researchers developed new imaging technology that permits them to see the complete 3-D architecture of many of the tiniest structures of cells.
Xiaowei Zhuang, ***Harvard University***

Genome-Wide Survey Nets Key Melanoma Gene

A newly discovered protein helps determine whether a pigment-producing skin cell that grows too fast becomes a benign mole or a deadly melanoma. This natural defense mechanism against cancer could help researchers design new therapies for melanoma.
Michael R. Green, ***University of Massachusetts Medical School***

Malaria Parasite Makes High-Speed Dash to Liver

Malaria parasites duck in and out of cells to evade the body's immune system on their way to invading the liver, according to an HHMI international research scholar. The pursuit starts earlier than once thought—right after the mosquito injects the parasite through the skin. Previous studies indicated that the chase began only after the parasites reached the liver.
Robert Ménard, ***Institut Pasteur, Paris***

A New Drug for Three Kinds of Leukemia

Three years after discovering a genetic mutation that causes a trio of leukemias, HHMI researchers helped move a new leukemia drug into clinical trials. The three leukemias, polycythemia vera, essential thrombocytosis, and primary myelofibrosis, affect about 80,000 to 100,000 people in the United States. The drug is now in phase 1 clinical trials at several cancer centers in the United States.
D. Gary Gilliland, ***Brigham and Women's Hospital***

Human Genome Is More Complex than Expected

The first high-resolution maps of several human genomes are helping researchers understand how humans differ from each other. A large team of scientists compared the genomes of eight people—of African, Asian, or Western European descent—with a reference human genome. From individual to individual, they found substantial structural variations, many more than 6,000 base pairs long.
Evan E. Eichler, ***University of Washington***

Model Protocell Created in the Lab

Simple protocells are thought to have given rise to Earth's earliest life forms. HHMI scientists created model protocells in the lab and demonstrated how they might have taken up the nutrients that propelled their growth.
Jack K. Szostak, ***Massachusetts General Hospital***

Mutant Mouse Mimics Human Bone Cancer

A new mouse model will allow researchers to investigate the genetic underpinnings of osteosarcoma, the most common form of bone cancer. The disease, which usually affects adolescents and young adults, results from the unregulated growth of the cells that form bone matrix. This animal model offers opportunities to develop new therapeutic approaches to counter the fast-spreading cancer.
Stuart H. Orkin, ***Children's Hospital Boston***

1. **330 Vertebrae**
Snake embryos form from head to tail.

1.

How the Snake Got Its Vertebrae

Thirty-three vertebrae enable the human spine to twist and bend, whereas a snake's slither requires more than 300 vertebrae. Both species' spines are formed when cells in a developing embryo pinch off into a string of identical segments, which will later sprout blood vessels, peripheral nerves, and muscle. HHMI researchers discovered how cells know when to stop this process to ensure that each animal ends up with the appropriate number of vertebrae.

Olivier Pourquié, ***Stowers Institute for Medical Research***

New Flu Treatments May Come from Fruit Fly Study

The influenza virus easily mutates to develop resistance to therapies that target the virus directly. To identify genes and proteins within the host that aid viral infection, HHMI scientists infected fruit fly cells with modified influenza virus and found 100 or more host cell genes that the virus relies on for infection. The researchers hope these new targets will offer improved treatment possibilities by more stably suppressing the virus and leaving it unable to quickly evolve resistance.

Paul Ahlquist, ***University of Wisconsin–Madison***

Help for Children Who Can't Fight Infection

HHMI international researchers discovered a genetic flaw in a critical immune system gene that leaves children vulnerable to meningitis. Children with defective or missing copies of the *MYD88* gene were prone to infections with *Streptococcus* pneumonia even though they could fight off infections by other bacteria. The MyD88 protein controls many of the most important immune system receptors involved in fighting microorganisms.

Jean-Laurent Casanova, ***Necker Hospital for Sick Children, Paris***

Honors and Awards

1. **Ana Belén Elgoyhen**
2. **Thomas M. Jessell**
3. **Robert J. Lefkowitz**

Druker Wins Keio Prize

HHMI investigator Brian J. Druker of Oregon Health & Science University won the 2007 Keio Medical Science Prize from Keio University in Tokyo, Japan, together with Hiroaki Mitsuya of Kumamoto University and the U.S. National Cancer Institute. Given annually, the ¥20 million (about $183,000) prize awards outstanding achievements in medical and life sciences. Druker was recognized for his development of Gleevec, the first drug to target the genetic defects of a particular cancer, chronic myelogenous leukemia.

Elgoyhen Receives L'Oréal-UNESCO Award

HHMI international research scholar Ana Belén Elgoyhen of the Institute for Research on Genetic Engineering and Molecular Biology, CONICET, in Buenos Aires, Argentina, won the 2008 L'Oréal-UNESCO Award for Women in Science for Latin America. The $100,000 prize, awarded annually, recognizes five outstanding women researchers worldwide.

Hynes Awarded E.B. Wilson Medal

The 2007 E.B. Wilson Medal went to HHMI investigator Richard O. Hynes, Massachusetts Institute of Technology, for his work on how cells adhere to one another. The medal, the highest science honor of the American Society for Cell Biology, is awarded for lifetime contributions to cell biology.

Jessell Receives Kavli Prize

HHMI investigator Thomas M. Jessell of Columbia University received the first annual Kavli Prize in Neuroscience for his research on how neural cells assemble into circuits. He shares the $1 million prize with Pasko Rakic of Yale University and Sten Grillner of the Karolinska Institute. This new prize comes from the Norwegian Academy of Science and Letters, the Kavli Foundation, and the Norwegian Ministry of Education and Research.

National Academies Book Award Goes to Kandel

Eric R. Kandel, an HHMI investigator at the Columbia University College of Physicians and Surgeons, won the 2007 Best Book Award from the National Academies for *In Search of Memory: The Emergence of a New Science of Mind*. The book blends a personal memoir with an explanation of the science of memory.

National Medal of Science Awarded to Lefkowitz

President George W. Bush bestowed Robert J. Lefkowitz with the nation's highest award for science. Lefkowitz, an HHMI investigator at Duke University Medical Center, received the 2008 National Medal of Science. Lefkowitz studies G protein–coupled receptors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1. **Nahum Sonenberg**
2. **Joan A. Steitz**
3. **Angelika Amon**
4. **Todd R. Golub**
5. **Gregory J. Hannon**


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involved in fundamental processes such as pain tolerance, glucose metabolism, and the regulation of heart rate and blood pressure.

Lifton Receives Wiley Prize

HHMI investigator Richard P. Lifton of Yale University School of Medicine received the 2008 Wiley Prize in Biomedical Sciences. Awarded by the Wiley Foundation, the annual $35,000 prize recognizes a scientist whose contributions have opened new fields of research or advanced new concepts within biomedicine. Lifton was chosen for his discovery of the genes that cause many forms of high and low blood pressure in humans.

Sonenberg Wins Gairdner Award

Nahum Sonenberg, an HHMI international research scholar at McGill University, received a 2008 Gairdner International Award. These annual awards recognize outstanding discoveries and contributions to medical science. Sonenberg, who received $30,000, studies how cells control protein synthesis.

Gruber Prize Goes to Spradling

Allan C. Spradling, an HHMI investigator at the Carnegie Institution of Washington, won the 2008 Gruber Genetics Prize of $500,000 from the Peter and Patricia Gruber Foundation for his contributions to fruit fly genomics.

Steitz Shares Albany Prize

HHMI investigator Joan A. Steitz of the Yale University School of Medicine and Elizabeth H. Blackburn of the University of California, San Francisco, were the first two women to receive the Albany Medical Center Prize in Medicine and Biomedical Research. The $500,000 prize, awarded annually since 2001, honors innovative biomedical research. Steitz discovered and defined the function of small nuclear ribonucleoproteins—complexes of RNA and proteins involved in splicing introns from RNA strands.

Tuschl Awarded Delbrück Medal

HHMI investigator Thomas Tuschl, of The Rockefeller University in New York, received the 2007 Max Delbrück Medal, from the Max Delbrück Center for Molecular Medicine in Berlin, for his development of RNA interference—a technique that helps scientists investigate the function of individual genes. Tuschl was also honored with the 2008 Ernst Jung Prize for Medicine, an annual award from the Hamburg-based Jung Foundation for Science and Research that recognizes young medical researchers.

Three Investigators Receive Paul Marks Prize

Three HHMI investigators were honored with the 2007 Paul Marks Prize for Cancer Research. Named for Paul A. Marks, president emeritus


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of Memorial Sloan-Kettering Cancer Center, the biennial prize aims to recognize significant contributions to the field of cancer research made by young investigators. The winners were Angelika Amon, of the Massachusetts Institute of Technology, who studies the effects of chromosome segregation in cancer cell growth; Todd R. Golub, of the Dana-Farber Cancer Institute, who employs microarrays in order to better classify subtypes of cancer; and Gregory J. Hannon, of Cold Spring Harbor Laboratory, who studies the role of RNA interference in cancer initiation and progression.

Seven Elected to National Academy of Sciences

Four HHMI investigators, an HHMI professor, and two members of HHMI advisory boards were elected to the National Academy of Sciences in April 2008. They were among 72 new members and 18 foreign associates elected in recognition of their distinguished and continuing achievements in original research. The investigators are Michael J. Bevan, University of Washington School of Medicine; Gail Mandel, Oregon Health & Science University; David J. Mangelsdorf, University of Texas Southwestern Medical Center at Dallas; and Gary Struhl, Columbia University College of Physicians and Surgeons. The HHMI professor is Jasper Rine, University of California, Berkeley. Michael R. Botchan, a member of the HHMI medical advisory board, and Janet Rossant, a member of the HHMI scientific review board, were also elected.

Seven Elected to Institute of Medicine

In October 2007, six HHMI investigators and one HHMI international research scholar were elected members of the National Academy of Sciences' Institute of Medicine. The investigators are James P. Allison, Memorial Sloan-Kettering Cancer Center, New York; Katherine A. High, The Children's Hospital of Philadelphia; William G. Kaelin Jr., Dana-Farber Cancer Institute, Boston; Louis J. Ptáček, University of California, San Francisco; Matthew P. Scott, Stanford University School of Medicine; and Thomas C. Südhof, University of Texas Southwestern Medical Center at Dallas (now at Stanford University). HHMI international research scholar Peter St George-Hyslop is at University of Toronto.

Two HHMI Professors Elected to National Academy of Engineering

HHMI professors Rebecca Richards-Kortum, Rice University, and David Walt, Tufts University, were elected in February 2008 to the National Academy of Engineering.

American Academy of Arts and Sciences Elects 14

Eight HHMI investigators, three HHMI professors, one Trustee, and two members of the Institute's advisory boards are among the 190 new fellows and 22 foreign honorary members elected to the American Academy of Arts and Sciences in April 2008. The investigators are Linda B. Buck, Fred Hutchinson Cancer Research Center; Lawrence S.B. Goldstein, University of California, San Diego; John Kuriyan, University of California, Berkeley; Stephen G. Lisberger, University of California, San Francisco; Craig C. Mello, University of Massachusetts Medical School; Norbert Perrimon, Harvard Medical School; Louis J. Ptáček, University of California, San Francisco; and Leonard I. Zon, Children's Hospital Boston. The professors are Utpal Banerjee, University of California, Los Angeles; Jasper Rine, University of California, Berkeley; and Huntington F. Willard, Duke University. Also elected were HHMI Trustee James A. Baker, scientific review board member Mary Beckerle, and medical advisory board member Bruce W. Stillman.

Richard Gordon Darman

Richard Gordon Darman, a financial executive with a distinguished career in public service and a Trustee of the Howard Hughes Medical Institute, died January 25, 2008, in Washington, D.C. He was 64.

Darman was elected a Trustee in 2005, serving as chairman of the Audit and Compensation Committee and as a member of the Finance Committee. Armed with a powerful intellect and irrepressible humor, he made his mark at HHMI—often by asking a deceptively simple question that generated lively discussion.

Throughout his tenure in the federal government, Darman played key roles in the development of tax, spending, and economic policies. He served four presidents, holding positions in the White House, the Office of Management and Budget, and six cabinet departments. As deputy treasury secretary during the Reagan Administration, Darman received the Treasury's highest award—the Alexander Hamilton medal—for his contributions to the 1986 Tax Reform Act and two international monetary policy accords.

Darman joined The Carlyle Group, a global private equity firm, in 1993 as a partner. He was also chairman of the board of AES Corp., an international power company. Darman served as a trustee of several publicly traded mutual fund groups and as chairman of the board of the Smithsonian National Museum of American History. A graduate of Harvard College and the Harvard Business School, Darman wrote widely about public policy and politics.

Jeremy R. Knowles

Jeremy R. Knowles, a Trustee of the Howard Hughes Medical Institute for nearly a decade, died April 3, 2008, in Cambridge, Massachusetts. He was 72.

An accomplished chemist whose research traversed the boundaries of chemistry and biochemistry, Knowles was known for his luminous intelligence, penetrating judgment, elegant speech, and refined wit. He was a towering figure at Harvard University, whose faculty he joined in 1974 as professor of chemistry. He served as dean of the Faculty of Arts and Sciences from 1991 to 2002, reprising the role from 2006 to 2007.

Knowles helped shape the vision of the Institute's science education programs and chaired a Trustee subcommittee that served as an important sounding board for new initiatives. That interest reflected his own commitment to teaching; Knowles delighted in returning to the classroom upon stepping down as dean.

Born in England, Knowles served as an officer in the Royal Air Force before reading chemistry at Balliol College at Oxford University. He received his B.A. in 1959 and his D.Phil. in 1961.

Through his research, Knowles made lasting contributions to understanding the chemistry of enzyme action. In addition to many honors and awards, he was elected a fellow of the Royal Society in 1977 and a foreign associate of the National Academy of Sciences in 1988.

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University of Wisconsin–Madison
Paul Ahlquist, Ph.D.
Sean B. Carroll, Ph.D.
Edwin R. Chapman, Ph.D.
Judith Kimble, Ph.D.

Howard Hughes Medical Institute investigators conduct research in Institute laboratories at host institutions nationwide in concert with associated hospitals and medical schools.

For information on HHMI investigators active after August 31, 2008, visit www.hhmi.org.

Janelia Farm Research Campus

September 1, 2007 – August 31, 2008

Eric Betzig, Ph.D.
Group Leader

Sydney Brenner, D.Phil.
Senior Fellow

Dmitri B. Chklovskii, Ph.D.
Group Leader

Joshua T. Dudman, Ph.D.
Fellow

Sean R. Eddy, Ph.D.
Group Leader

S.E. Roian Egnor, Ph.D.
Fellow

Mats G.L. Gustafsson, Ph.D.
Group Leader

Harald F. Hess, Ph.D.
Director, Applied Physics and Instrumentation Group

Vivek Jayaraman, Ph.D.
Fellow

Alla Y. Karpova, Ph.D.
Group Leader

Rex A. Kerr, Ph.D.
Fellow

Luke Lavis, Ph.D.
Fellow

Anthony Leonardo, Ph.D.
Group Leader

Loren L. Looger, Ph.D.
Group Leader

Jeffrey C. Magee, Ph.D.
Group Leader

Eugene W. Myers, Ph.D.
Group Leader

Hanchuan Peng, Ph.D.
Senior Computer Scientist

Michael B. Reiser, Ph.D.
Fellow

Lynn M. Riddiford, Ph.D.
Senior Fellow

Dmitry Rinberg, Ph.D.
Fellow

Elena Rivas, Ph.D.
Fellow

Charles V. Shank, Ph.D.
Senior Fellow

Julie H. Simpson, Ph.D.
Group Leader

Scott M. Sternson, Ph.D.
Group Leader

Karel Svoboda, Ph.D.
Group Leader

James W. Truman, Ph.D.
Group Leader

For information on Janelia Farm researchers active after August 31, 2008, visit www.hhmi.org/janelia.

Medical Advisory Board

September 1, 2007 – August 31, 2008

Michael R. Botchan, Ph.D.
Richard and Rhoda Goldman Distinguished Professor of Biochemistry
Co-Chair of the Department of Molecular and Cell Biology
University of California, Berkeley
(Effective January 1, 2008)

Gerald R. Fink, Ph.D.
Herman and Margaret Sokol Professor
Whitehead Institute for Biomedical Research
Massachusetts Institute of Technology

J. Larry Jameson, M.D., Ph.D.
Vice President for Medical Affairs and Lewis Landsberg Dean
Northwestern University, Feinberg School of Medicine

Rowena G. Matthews, Ph.D.
G. Robert Greenberg Professor Emeritus of Biological Chemistry and Research Professor Emeritus
Life Sciences Institute
University of Michigan
(Effective January 1, 2008)

Gregory A. Petsko, D.Phil.
Gyula and Katica Tauber Professor of Biochemistry and Chemistry and Chair
Department of Biochemistry
Brandeis University
Adjunct Professor
Department of Neurology and Center for Neurologic Diseases
Harvard Medical School and Brigham & Women's Hospital
(Through December 31, 2007)

Joan V. Ruderman, Ph.D.
Marion V. Nelson Professor of Cell Biology
Department of Cell Biology
Harvard Medical School

Carla J. Shatz, Ph.D.
Director, Bio-X
Professor of Biology and Neurobiology
James H. Clark Center
Stanford University

Bruce Stillman, Ph.D., F.R.S.
President
Cold Spring Harbor Laboratory

Lubert Stryer, M.D.
Mrs. George A. Winzer Professor of Cell Biology, Emeritus
Stanford University School of Medicine

Craig B. Thompson, M.D.
Chair
Director
Abramson Cancer Center
University of Pennsylvania

Scientific Review Board

September 1, 2007 – August 31, 2008

Wolfhard Almers, Ph.D.
Senior Scientist
Vollum Institute
Oregon Health and Science University

Michael Ashburner, F.R.S.
Professor of Biology
Department of Genetics
University of Cambridge

Mary Beckerle, Ph.D.
Ralph E. and Willa T. Main
Presidential Professor
Executive Director
Huntsman Cancer Institute
University of Utah
(Effective January 1, 2008)

Stephen J. Benkovic, Ph.D.
Evan Pugh Professor and
Eberly Chair in Chemistry
The Pennsylvania State University
(Effective January 1, 2008)

Michael R. Botchan, Ph.D.
Richard and Rhoda Goldman
Distinguished Professor of Biochemistry
Co-Chair of the Department
of Molecular and Cell Biology
University of California, Berkeley
(Through December 31, 2007)

Kathryn Calame, Ph.D.
Professor Emerita of Microbiology and
Biochemistry & Molecular Biophysics
Columbia University College
of Physicians and Surgeons

William A. Catterall, Ph.D.
Professor and Chair
Department of Pharmacology
University of Washington
School of Medicine
(Effective January 1, 2008)

Sara A. Courtneidge, Ph.D.
Professor and Director
Tumor Microenvironment Program
Director of Academic Affairs
Burnham Institute for Medical Research
(Effective January 1, 2008)

Jorge E. Galán, Ph.D.
Lucille P. Markey Professor of
Microbiology
Chairman
Section of Microbial Pathogenesis
Yale School of Medicine

Richard H. Goodman, M.D., Ph.D.
Director, Vollum Institute
Oregon Health and Science University
(Effective January 1, 2008)

Margaret K. Hostetter, M.D.
Jean McLean Wallace Professor and
Chair
Department of Pediatrics
Professor of Microbial Pathogenesis
Yale School of Medicine
(Effective January 1, 2008)

Richard D. Kolodner, Ph.D.
Member
Ludwig Institute for Cancer Research,
San Diego Branch
Professor of Medicine
University of California, San Diego,
School of Medicine
Executive Director for Laboratory
Science and Technology
Ludwig Institute for Cancer Research,
New York

Lynn Landmesser, Ph.D.
Garvin Professor and Chair
Department of Neurosciences
Case Western Reserve University
School of Medicine

Michael A. Marletta, Ph.D.
Aldo DeBenedictis Distinguished
Professor of Chemistry
Professor of Biochemistry
and Molecular Biology
University of California, Berkeley
(Effective January 1, 2008)

Gail R. Martin, Ph.D.
Professor and Vice-Chair,
Department of Anatomy
University of California, San Francisco
(Effective January 1, 2008)

Diane Mathis, Ph.D.
Head, Section on Immunology
and Immunogenetics
Joslin Diabetes Center
Professor of Medicine
Harvard Medical School

Keith Moffat, Ph.D.
Louis Block Professor, Department of Biochemistry and Molecular Biology
Deputy Provost for Research
The University of Chicago

W. James Nelson, Ph.D.
Rudy J. and Daphne Donohue Munzer Professor
Department of Biology and of Molecular and Cellular Physiology
The Bio-X Program
Stanford University

Roger A. Nicoll, M.D.
Professor
Department of Cellular and Molecular Pharmacology
University of California, San Francisco, School of Medicine
(Through December 31, 2007)

Eric N. Olson, Ph.D.
Professor and Chairman
Department of Molecular Biology
University of Texas Southwestern Medical Center at Dallas

James W. Patrick, Ph.D.
Professor of Neuroscience
Baylor College of Medicine

Gregory A. Petsko, D.Phil.
Gyula and Katica Tauber Professor of Biochemistry and Chemistry and Chair
Department of Biochemistry
Brandeis University
Adjunct Professor
Department of Neurology and Center for Neurologic Diseases
Harvard Medical School and Brigham & Women's Hospital
(Effective January 1, 2008)

Janet Rossant, Ph.D.
University Professor of Molecular Genetics and of Obstetrics and Gynecology
University of Toronto
Chief of Research
The Hospital for Sick Children, Toronto

Joshua R. Sanes, Ph.D.
Professor of Molecular and Cellular Biology
Paul J. Finnegan Family Director, Center for Brain Science
Harvard University

Robert T. Sauer, Ph.D.
Salvador E. Luria Professor
Department of Biology
Massachusetts Institute of Technology

David W. Tank, Ph.D.
Henry L. Hillman Professor
Department of Molecular Biology
Co-Director
Princeton Neuroscience Institute
Princeton University

David C. Van Essen, Ph.D.
Edison Professor and Head
Department of Anatomy and Neurobiology
Washington University School of Medicine

Christopher T. Walsh, Ph.D.
Hamilton Kuhn Professor
Department of Biological Chemistry and Molecular Pharmacology
Harvard Medical School

Huntington F. Willard, Ph.D.
Director, Institute for Genome Sciences & Policy
Nanaline H. Duke Professor of Genome Sciences
Duke University
(Effective January 1, 2008)

Janelia Farm Research Campus Advisory Committee

September 1, 2007 – August 31, 2008

Winfried Denk, Ph.D.
Director
Department of Biomedical Optics
Max Planck Institute for Medical Research

Joseph L. Goldstein, M.D.
Regental Professor and Chairman
Department of Molecular Genetics
University of Texas Southwestern Medical Center at Dallas

Gerald M. Rubin, Ph.D.
Chair
Vice President and Director,
Janelia Farm Research Campus
Howard Hughes Medical Institute

Carla J. Shatz, Ph.D.
Director, Bio-X
Professor of Biology and Neurobiology
James H. Clark Center
Stanford University

Maxine Singer, Ph.D.
President Emerita
Carnegie Institution of Washington
Senior Scientific Advisor
Carnegie Academy for Science Education

Lubert Stryer, M.D.
Mrs. George A. Winzer Professor
of Cell Biology, Emeritus
Stanford University School of Medicine

David W. Tank, Ph.D.
Henry L. Hillman Professor
Department of Molecular Biology
Co-Director, Princeton Neuroscience Institute
Princeton University

Shirley M. Tilghman, Ph.D.
President
Princeton University

Bioethics Advisory Board

September 1, 2007 – August 31, 2008

Patricia A. King, J.D.
Carmack Waterhouse Professor of Law, Medicine, Ethics, and Public Policy
Georgetown Law School
Georgetown University

Jonathan D. Moreno, Ph.D.
David and Lyn Silfen University Professor and Professor of Medical Ethics and of History and Sociology of Science
Center for Bioethics
University of Pennsylvania

Harriet S. Rabb, J.D.
Vice President and General Counsel
The Rockefeller University

Harold T. Shapiro, Ph.D.
President Emeritus and Professor of Economics and Public Affairs
Princeton University

Laurie Zoloth, Ph.D.
Chair
Professor of Medical Humanities and Bioethics and of Religion
Director of Center for Bioethics, Science and Society
Northwestern University, Feinberg School of Medicine

Fellowships & Grants

September 1, 2007 – August 31, 2008

Graduate and Medical Education Programs

Research Training Fellowships for Medical Students

Initial Awards: First Year of Research

Shaka Bahadu
Weill Cornell Medical College

Hasani Baharanyi
Yale School of Medicine
(Harvard Medical School)*

Kristopher Bosse
University of Pennsylvania
School of Medicine

Lior Braunstein
Harvard Medical School

Rebekah Browning
Ohio State University College
of Medicine and Public Health

Ann Cai
Harvard Medical School

Justin Chan
Mount Sinai School of Medicine

Jennifer Chen
Johns Hopkins University
School of Medicine
(Stanford University
School of Medicine)*

Rex Cheng
Duke University School of Medicine
(University of California, San Francisco,
School of Medicine)*

Hao Jun Chong
University of California,
San Francisco, School of Medicine

Lisa Chu
University of California,
San Francisco, School of Medicine

Raul Clavijo
University of California,
San Francisco, School of Medicine
(Stanford University
School of Medicine)*

Justin Cohen
Yale School of Medicine

Mackenzie Cook
Duke University School of Medicine
(University of Wisconsin School of
Medicine and Public Health)*

Agnieszka Czechowicz
Stanford University
School of Medicine

Neil Desai
Yale School of Medicine

Susan Emmett
Duke University School of Medicine

Lauren Frazer
University of Pittsburgh
School of Medicine

Michael Galvez
Stanford University
School of Medicine

Matthew Goldstein
Stanford University
School of Medicine

Divakar Gupta
Duke University School of Medicine

Mohamad Halawi
Duke University School of Medicine

Seunggu Han
University of California,
San Francisco, School of Medicine

Asaff Harel
University of Pittsburgh
School of Medicine

Le He
Case Western Reserve University
School of Medicine

Karim Helmy
University of Medicine and Dentistry
of New Jersey–New Jersey Medical
School (Memorial Sloan-Kettering
Cancer Center)*

Heidi Hillesland
University of New Mexico
School of Medicine

Susan Hiniker
University of Michigan Medical School

* A fellowship institution affiliation other than the medical school is indicated in parentheses.

Suejy Hobson
David Geffen School of Medicine
at UCLA

Michael Hodavance
Duke University School of Medicine

Jennifer Hong
Stanford University
School of Medicine

Jeffrey Hsu
David Geffen School of Medicine
at UCLA

Ryan Huss
Stanford University
School of Medicine

Timothy Johnson
Emory University
School of Medicine

Michelle Jonelis
University of California,
San Francisco, School of Medicine
(University of California,
San Diego, School of Medicine)*

Amit Khera
University of Pennsylvania
School of Medicine

Thomas Kosztowski
Johns Hopkins University
School of Medicine

Carson Lam
Northwestern University,
The Feinberg School of Medicine

John Lewis
Duke University School of Medicine

Christopher Liu
Baylor College of Medicine

Gene Ma
Stanford University
School of Medicine

Allan Mabardy
University of Massachusetts
Medical School

Kimberley Mak
Harvard Medical School
(Memorial Sloan-Kettering
Cancer Center)*

Priya Malik
Cleveland Clinic
Lerner College of Medicine of
Case Western Reserve University

Sean McEvoy
Yale School of Medicine

Justin Mendel
Emory University
School of Medicine

Yasha Modi
Yale School of Medicine

Nikhil Nayak
Yale School of Medicine

Paul Nuyujukian
Stanford University
School of Medicine

Sarina Pasricha
Northwestern University
The Feinberg School of Medicine

Jeremy Pearl
Stanford University
School of Medicine

David Perlmutter
University of Rochester
School of Medicine and Dentistry

Rebecca Pomerantz
University of Pittsburgh
School of Medicine

Makeda Robinson
Stanford University
School of Medicine

Karl Staser
Indiana University
School of Medicine

Rosalyn Sulyanto
Harvard University
School of Dental Medicine

Tina Tailor
Duke University School of Medicine

Corinne Taraska
University of Washington
School of Medicine

Patrick Varley
New York University
School of Medicine

Matthew Vestal
Yale School of Medicine

Guadalupe Villarreal
Harvard Medical School

Joshua Weiner
Yale School of Medicine
(Harvard Medical School)*

Kari Wellnitz
University of Texas
Health Science Center at Houston

Emily Williams
University of Pennsylvania
School of Medicine

Sima Yazdani
Duke University School of Medicine

Hasan Zaidi
Johns Hopkins University
School of Medicine

Zachary Zumsteg
David Geffen School of Medicine
at UCLA

Corinna Zygourakis
Harvard Medical School

Continued Awards:
Second Year of Research

David Caretto
University of California,
San Francisco, School of Medicine

Mark Chao
Stanford University
School of Medicine

Craig Giacomini
Stanford University
School of Medicine

Maya Kasowski
Yale School of Medicine

Steven Minear
Stanford University
School of Medicine

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

HHMI-NIH Research Scholars†

Shila Azodi
Texas Tech University
Health Sciences Center
School of Medicine

Amar Bansal
New York University
School of Medicine

Ayush Batra
Cleveland Clinic
Lerner College of Medicine of
Case Western Reserve University

Steven Beaudry‡
West Virginia School of
Osteopathic Medicine

Kevin Blaine
Cleveland Clinic
Lerner College of Medicine of
Case Western Reserve University

Patrick Blake
Cleveland Clinic
Lerner College of Medicine of
Case Western Reserve University

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

Ian Buchanan
Warren Alpert Medical School
of Brown University

Marianne Castillo
University of Medicine and Dentistry of
New Jersey–New Jersey Medical School

Jessica Chang
Duke University School of Medicine

* A fellowship institution affiliation other than the medical school is indicated in parentheses.
† This program is administered through Grants & Special Programs but is budgeted as a research operation.
‡ Second year in program as an advanced scholar.

Rachel Chard
Oregon Health & Science University
School of Medicine

Jenny Chen
Indiana University
School of Medicine

Audree Condren
University of Oklahoma
College of Medicine

Jeremiah Davis
George Washington University
School of Medicine and Health Sciences

Chibawanye Ene‡
Indiana University
School of Medicine

Natasha Fewkes
Oregon Health & Science University
School of Medicine

Cedar Fowler
Tufts University School of Medicine

Rachel Giese
University of Texas
Health Science Center at San Antonio
School of Medicine

Joshua Gordon‡
David Geffen School of Medicine
at UCLA

Lillian Guenther
State University of New York
Downstate Medical Center
College of Medicine

Jason Hawkes
University of Utah
School of Medicine

Caitlin Hicks
Cleveland Clinic
Lerner College of Medicine of
Case Western Reserve University
(Deferring until 2009)

Brett Jagger‡
Indiana University School
of Medicine

Guy Jones
University of Medicine and Dentistry of
New Jersey–New Jersey Medical School

Samantha Jordan
Tufts University
School of Dental Medicine

Anusha Kalbasi
David Geffen School of Medicine
at UCLA

Wee-Tin Kao
State University of New York
at Stony Brook
Health Sciences Center
School of Medicine

Amelia Keaton
University of South Carolina
School of Medicine

Steve Khachi
Des Moines University
College of Osteopathic Medicine

Angela Lee
Harvard Medical School

Elise Meoli‡
University of Rochester
School of Medicine and Dentistry

Derek Narendra‡
University of Michigan Medical School

Rell Parker
University of California, Davis,
School of Veterinary Medicine

Justin Poling
Vanderbilt University
School of Medicine

Matthew Reilley
Dartmouth Medical School

Paul Romesser
Boston University
School of Medicine

Sarah Rusk
Case Western Reserve University
School of Medicine

Alex Ryder
Vanderbilt University
School of Medicine

Michelle Samuel
University of Pennsylvania
School of Veterinary Medicine

Logan Schneider
University of Florida
College of Medicine

Abigail Shearin
University of Pennsylvania
School of Veterinary Medicine

Hubert Shih
David Geffen School of Medicine
at UCLA

Scott Steward-Tharp‡
University of Iowa College of Dentistry

Jayesh Thawani
University of Michigan Medical School

Mari Tokita
Warren Alpert Medical
School of Brown University

Jessica Valdez
University of New Mexico
School of Medicine

Dean Wang
Cleveland Clinic
Lerner College of Medicine of
Case Western Reserve University

Frederick Wang
Yale School of Medicine

Jered Wendte
Oklahoma State University
Center for Veterinary Health Sciences

Caroline Yeager
Duke University School of Medicine

James H. Gilliam Jr. Fellowships for Advanced Study

Silvia G. Caballero
City University of New York,
Hunter College*
(Deferring fellowship)

Lee Shoa Long Clarke
Stanford University

Alejandra Figueroa-Clarevega
Washington University in
St. Louis*
(Deferring fellowship)

Daniel B. Gilmer
Rockefeller University

Bertrade C. Mbom
Stanford University

Physician-Scientist Early Career Awards

Yvonne Chan, M.D.
University of Pittsburgh
School of Medicine

John Chang, M.D.
University of Pennsylvania
School of Medicine

Hyung Chun, M.D.
Stanford University
School of Medicine

Todd Fehniger, M.D., Ph.D.
Washington University
School of Medicine

Matthew Freedman, M.D.
Dana-Farber Cancer Institute

Timothy Graham, M.D.
Beth Israel Deaconess Medical Center

Ari Green, M.D.
University of California,
San Francisco, School of Medicine

Fred Hsieh, M.D.
Cleveland Clinic Foundation

Hanlee Ji, M.D.
Stanford University
School of Medicine

Regina LaRocque, M.D.
Massachusetts General Hospital

Eduardo Mendez, M.D.
University of Washington
Medical Center

Goutham Narla, M.D., Ph.D.
Mount Sinai School of Medicine

‡ Second year in program as an advanced scholar.
* Undergraduate Institution.

Mark Onaitis, M.D.
Duke University School of Medicine

Tipu Puri, M.D., Ph.D.
University of Chicago,
Division of Biological Sciences and
Pritzker School of Medicine

Benjamin Purow, M.D.
University of Virginia
School of Medicine

Joshua Roffman, M.D.
Harvard Medical School

Allan Tsung, M.D.
University of Pittsburgh
School of Medicine

Arun Venkatesan, M.D., Ph.D.
Johns Hopkins University
School of Medicine

Paul Yu, M.D., Ph.D.
Harvard Medical School

Other Graduate Science Education Awards

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

Undergraduate Science Education Program

Baccalaureate and Master's Degree Institutions

Amherst College
Amherst, Massachusetts
$1,300,000

Barnard College
New York, New York
$1,500,000

Bowdoin College
Brunswick, Maine
$1,100,000

Bryn Mawr College
Bryn Mawr, Pennsylvania
$1,200,000

California State University–Fullerton
Fullerton, California
$1,200,000

Calvin College
Grand Rapids, Michigan
$1,100,000

Carleton College
Northfield, Minnesota
$1,500,000

City University of New York, Hunter College
New York, New York
$1,400,000

Colby College
Waterville, Maine
$1,000,000

Colgate University
Hamilton, New York
$1,200,000

College of Charleston
Charleston, South Carolina
$1,500,000

College of Wooster
Wooster, Ohio
$1,000,000

Davidson College
Davidson, North Carolina
$1,500,000

Drew University
Madison, New Jersey
$1,100,000

Franklin & Marshall College
Lancaster, Pennsylvania
$1,300,000

Furman University
Greenville, South Carolina
$1,200,000

Georgetown College
Georgetown, Kentucky
$1,300,000

Gonzaga University
Spokane, Washington
$1,200,000

Grinnell College
Grinnell, Iowa
$1,200,000

Gustavus Adolphus College
Saint Peter, Minnesota
$1,000,000

Hampton University
Hampton, Virginia
$1,200,000

Harvey Mudd College
Claremont, California
$1,500,000

Haverford College
Haverford, Pennsylvania
$1,400,000

Hope College
Holland, Michigan
$1,400,000

Kalamazoo College
Kalamazoo, Michigan
$1,000,000

Lewis and Clark College
Portland, Oregon
$1,300,000

Morehouse College
Atlanta, Georgia
$1,400,000

Mount Holyoke College
South Hadley, Massachusetts
$1,500,000

North Carolina Central University
Durham, North Carolina
$900,000

Oakwood College
Huntsville, Alabama
$1,200,000

Occidental College
Los Angeles, California
$1,400,000

Saint Joseph's University
Philadelphia, Pennsylvania
$1,000,000

San Jose State University
San Jose, California
$1,300,000

Smith College
Northampton, Massachusetts
$1,300,000

Spelman College
Atlanta, Georgia
$1,400,000

Swarthmore College
Swarthmore, Pennsylvania
$1,600,000

Trinity University
San Antonio, Texas
$1,500,000

University of Louisiana at Monroe
Monroe, Louisiana
$700,000

University of Puerto Rico–Mayaguez
Mayaguez, Puerto Rico
$1,400,000

University of Richmond
Richmond, Virginia
$1,400,000

University of Texas–Pan American
Edinburg, Texas
$1,200,000

Vassar College
Poughkeepsie, New York
$1,500,000

Washington and Jefferson College
Washington, Pennsylvania
$1,000,000

Washington and Lee University
Lexington, Virginia
$1,300,000

Wellesley College
Wellesley, Massachusetts
$1,200,000

Wesleyan University
Middletown, Connecticut
$1,400,000

Whitman College
Walla Walla, Washington
$800,000

Wilkes University
Wilkes-Barre, Pennsylvania
$1,000,000

HHMI's Exceptional Research Opportunities Program (EXROP)

Jarrad Aguirre
Yale University

Julian Artunduaga
University of Maryland,
College Park

Erwin Cabrera
University of Maryland,
Baltimore County

Angela Castellanos
Stanford University

Lesley Chapman
Duke University

Sarah De Leo
Louisiana State University
and A & M College

Ryan Dosumu-Johnson
University of California, Los Angeles

Omer Durak
California Institute of Technology

Mariam El-Ashmawy
Arizona State University

Melody Esmaeili
University of California, Berkeley

Jason Espinoza
University of Arizona

Terry Felton
Xavier University of Louisiana

Marty Fernandez
University of Florida

Christopher Ferreira
University of Massachusetts

Jeremy Flores
University of Texas at Austin

Philia Gau
Cornell University

Deric Griffin
Louisiana State University and
A & M College

Shuo Han
Massachusetts Institute
of Technology

Akil Jackson
Morehouse College

Sarah Jackson
Trinity University

Pouya Jamshidi
University of California, San Diego

Melissa Kemp
Williams College

Espoir Kyubwa
University of California, San Diego

Luis Lazaro
Rice University

Kristen Lessl
University of Michigan–Ann Arbor

Yendi Linares
Emory University

Sylvester Marshall III
Washington University

Janielle Maynard
Howard University

Carlo Mejia
University of California, Riverside

Christina Moore
University of California, Berkeley

Brittney Newby
Florida A & M University

Kathy Ngo
University of California,
Los Angeles

Jacqueline Nkuebe
Harvard University

Ugochi Nwosu
Harvard University

Casandra Panea
Yale University

Jude Phillip
City University of New York,
City College

Dami Phillips
Carnegie Mellon University

Christopher Pina
University of California, Davis

Cindy Puente
City University of New York,
Hunter College

Jacqueline Ramirez
College of William and Mary

Erica Rangel
University of Colorado at Boulder

Brandon Roane
Duke University

Karen Rodriguez
University of Colorado at Boulder

Damaris Rosado
University of Texas at El Paso

Stephanie Rosales
Columbia University

Cristine Santiago
University of Puerto Rico–Cayey

Krystal St. Julien
University of Washington

Daisha Steadman
Georgia State University

Cindy Thomas
State University of New York
at Stony Brook

Valerie Vassor
Swarthmore College

Gabriel Walton
University of Miami

Sarah Whiteside
Massachusetts Institute
of Technology

Patrick Williams
University of Pittsburgh

Ramone Williams
Emory University

Anna Zelaya
California State Polytechnic
University–Pomona

Other Undergraduate Science Education Awards

Grinnell College
Grinnell, Iowa
Grant: Survey of Undergraduate Research Experiences and Classroom Undergraduate Research Experiences
$240,000

University of Wisconsin–Madison
Madison, Wisconsin
Grant: Summer Institute on Undergraduate Education in Biology
$150,000

Precollege Science Education Program

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; Student Research; Curriculum Development; and College Scholarships‡‡
$1,000,000

College Scholarships

Amanda Victoria Below
Stone Bridge High School

Nhat-Minh Le Bui
Heritage High School

Maria Elizabeth Chopivsky
Loudoun County High School

Justin Michael Cook
Dominion High School

Mikaela Anita Finnegan
Heritage High School

Bethany Lynn Hansberger
Park View High School

Patricia Diane Hicks
Loudoun Valley High School

Lisa Huynh
Park View High School

Sonnya Keunju Im
Briar Woods High School

Kevin Isa Izadpanah
Potomac Falls High School

Lesley Anne Luginbill
Briar Woods High School

Andrew James Mann
Broad Run High School

Chesney Sarah Oravec
Stone Bridge High School

Gurleen Pahal
Potomac Falls High School

Premkumar Periyasamy
Broad Run High School

Mickinjit S. Sahni
Freedom High School

Sanam Shahid
Freedom High School

Kevin Matthias Shea II
Loudoun Valley High School

Elizabeth Sara Stevens
Loudoun County High School

Emily Louise Wilson
Dominion High School

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

Other Precollege Science Education Awards

Institute for Systems Biology
Seattle, Washington
Grant: Building Parent Partnerships in Science Education
$25,000

University of Mississippi School of Medicine
Jackson, Mississippi
Grant: A Muse of Fire: Stimulating Student Inquiry with Red Imported Fire Ants
$50,000

International Program

Courses

Federal University of Minas Gerais
Belo Horizonte, Brazil
$150,000

University of Rijeka
Rijeka, Croatia
$150,000

Other International Grants

Institute of Biotechnology, National Autonomous University of Mexico
Cuernavaca, Mexico
Grant: Frontiers in Genomics Program
$20,000

Educational Resources

American Society for Cell Biology
Bethesda, Maryland
Grant: *CBE-Life Sciences Education*
$400,000

WGBH Educational Foundation
Boston, Massachusetts
Grant: NOVA scienceNOW
$4,500,000

Office of Grants and Special Programs

HHMI Investigator Education Grants

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

Catherine Dulac, Ph.D.
Harvard University
Grant: Equipment for use in research-based course in experimental and cellular biology
$150,000

Other Awards

Albert Einstein College of Medicine
Bronx, New York
Grant: To support the work of Jacqueline Achkar, M.D.
$88,457

Albert Einstein College of Medicine
Bronx, New York
Grant: To support the work of Sarita Shah, M.D., M.P.H.
$57,557

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

Brigham & Women's Hospital
Boston, Massachusetts
Grant: To support the work of D. Branch Moody, M.D.
$90,000

Edendale Hospital, KwaZulu-Natal
Peitermaritzburg, South Africa
Grant: To support the work of Douglas Wilson, M.B.Ch.B.
$81,000

Harvard University School of Public Health
Boston, Massachusetts
Grant: To support the work of Sarah Fortune, M.D.
$89,492

Harvard University School of Public Health
Boston, Massachusetts
Grant: To support the work of Eric Rubin, M.D., Ph.D.
$89,492

Massachusetts General Hospital
Boston, Massachusetts
Grant: To support the work of Marcus Altfeld, M.D., Ph.D.
$119,520

University of KwaZulu-Natal
Durban, South Africa
Grant: To support the work of Prashini Moodley, M.B.Ch.B., M.Med., Ph.D.
$81,000

University of KwaZulu-Natal
Durban, South Africa
Grant: To support the work of Yunus Moosa, M.B.Ch.B., Ph.D.
$81,000

University of KwaZulu-Natal
Durban, South Africa
Grant: To support the work of Thumbi Ndung'u, B.V.M., Ph.D.
$81,000

University of KwaZulu-Natal
Durban, South Africa
Grant: To support the work of Alexander Pym, M.D.
$162,000

University of Pittsburgh
Pittsburgh, Pennsylvania
Grant: To support the work of Graham Hatfull, Ph.D.
$90,000

Yale University
New Haven, Connecticut
Grant: Course in Durban, South Africa
$30,000

HHMI Awards

United Way of Loudoun County and Other Community Organizations in Loudoun County
Leesburg, Virginia
$39,028

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

Finance & Investments

September 1, 2007 – August 31, 2008

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 fiscal year on August 31, 2008, the endowment was $17.5 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 exclusive of grants and investment management expenses.

Disbursements in Fiscal Year 2008

Disbursements during the fiscal year totaled $764 million: $658 million for scientific research including operations at the Janelia Farm Research Campus; $83 million for grants for science education and international research scholars, and $23 million to expand the HHMI headquarters campus and to purchase equipment for the Janelia Farm Research Campus. Over the past five years, disbursements by the Institute totaled approximately $3.6 billion.

Scientific Research

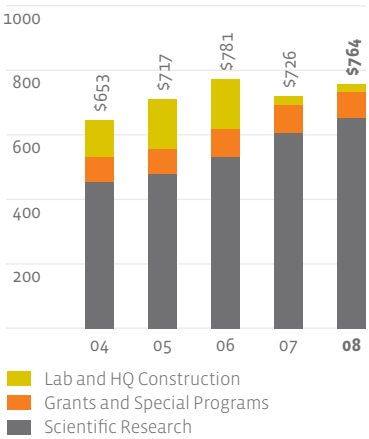
Research activities are conducted principally at Institute laboratories at medical centers, teaching hospitals, and universities in the United States by investigators who hold faculty appointments at the host institutions. These individuals, together with their support staffs, are HHMI employees and are compensated directly by the Institute. Investigators may spend up to 25 percent of their time on teaching, administration, and other activities that benefit their institutions. At the end of fiscal year 2008, the Institute supported 335 investigators at 66 academic medical centers.

As of August 31, 2008, the Institute's investment in laboratory space, equipment, and other property amounted to greater than $1.4 billion, with a current replacement value of approximately $1.8 billion.

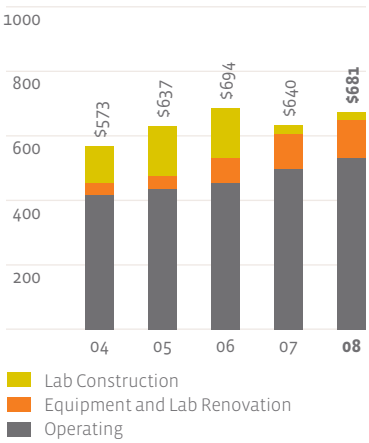
Janelia Farm Research Campus

The Janelia Farm Research Campus, situated on a 689-acre site along the Potomac River in Ashburn, Virginia, just outside Washington,

Disbursements
($ in millions)



Scientific Research
($ in millions)



D.C., 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 of the project was more than $500 million. In its first two years of operation, expenditures at Janelia Farm totaled approximately $163 million. In fiscal year 2008, expenditures at Janelia Farm totaled $96 million, of which $22 million represented personnel expenditures and approximately $47 million was for equipment and for completing construction of specialized research facilities. When Janelia Farm is at full capacity, which is expected to occur by the end of fiscal year 2012, it will house a permanent research staff of about 250—including 25 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 $83 million to support the activities of 585 grantees in 29 countries during fiscal year 2008.

Endowment

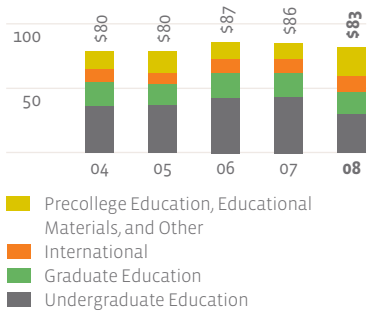
The Institute's endowment is managed under the direction of its Vice President and Chief Investment Officer. Approximately 78 percent of the endowment is invested by external fund managers; the remainder is internally managed. External managers are used to manage virtually all asset classes, including public equities and alternative investments, including hedge funds and private equities.

At the close of fiscal year 2008, the endowment value was $17.5 billion, a decrease of $1.2 billion from the end of fiscal year 2007. The endowment return for fiscal year 2008 was negative 2.01 percent.

The composition of the Institute's endowment by investment category on August 31, 2008, is reflected in the graph at right.

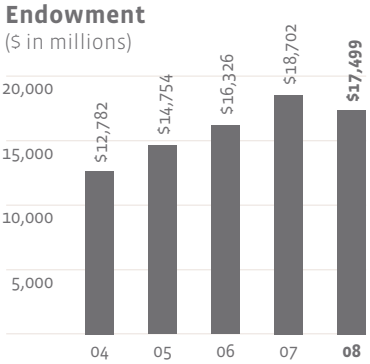
Grants and Special Programs

($ in millions)

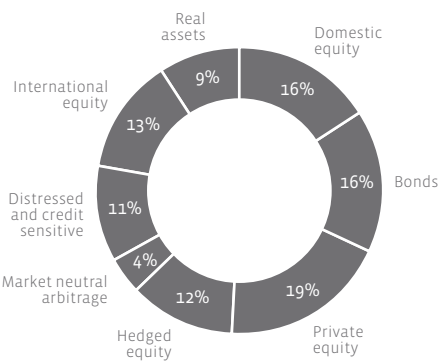


Endowment

($ in millions)



Endowment Allocations



Statement of Financial Position

August 31, 2008 and 2007
($ in millions)

	2008	2007
ASSETS		
Cash and cash equivalents	$ 202	$ 105
Investments	18,270	19,358
Investment and currency receivables, and other assets	2,259	1,416
Laboratory space, equipment, and other property—at cost, net of accumulated depreciation and amortization	836	796
Total Assets	**$ 21,567**	**$ 21,675**
LIABILITIES		
Accounts payable, accrued expenses, and obligations	203	208
Grants commitments	202	158
Investment purchases payable, repurchase obligations, short sales, and currency payables	3,047	2,049
Notes and bonds payable	700	627
Total Liabilities	**4,152**	**3,042**
Net Assets	**$ 17,415**	**$ 18,633**

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, 2008, 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 5
Cech: Bruce Weller
Page 8
Capecchi: Ramin Rahimian
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Stem cells (Capecchi): Andrew Paul Leonard/Photo Researchers, Inc.
DNA (Capecchi): Biophoto Associates/Photo Researchers, Inc.
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ES cells (Capecchi): Prof. Miodrag Stojkovic/Photo Researchers, Inc.
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Daley: M. William Lensch
Melton: Joshua Dalsimer
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Breast cancer (Massagué): David Padua/Massagué lab
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Pyle: Ruthanna Terreri
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Myers: Paul Fetters
Neuron (Myers): James Cavallini/Photo Researchers, Inc.
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Baker: Brian Smale
HIV protein (Baker): Laguna Design/Photo Researchers, Inc.
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