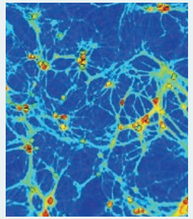

Shine That Light Over Here

Scientists at HHMI's Janelia Farm Research Campus have created a kind of molecular flashlight, GCaMP6, that tracks brain activity by lighting up when calcium is released during nerve cell signaling. This ultrasensitive tool allows scientists to image large groups of neurons as well as tiny cellular compartments with better resolution than previously possible. Janelia researchers work in small, interdisciplinary teams to advance brain research and imaging technologies.

Janelia Group Leaders
Loren Looger, Karel Svoboda, Vivek Jayaraman, and Rex Kerr
GENIE Project
Janelia Farm Research Campus

Wheat Gene Fends Off Deadly Rust

Wheat is one of the world's most important food crops—and perennially under attack by pathogens such as stem rust. Scientists have battled stem rust for decades by developing resistant wheat varieties that later become challenged as the fungus evolves. Now, HHMI-GBMF Investigator Jorge Dubcovsky has identified a wild wheat gene, *Sr35*, that elicits a strong immune response against a current, virulent form of stem rust. Breeding *Sr35* into commercial wheat may provide a powerful defense in the war against this pathogen.

HHMI-GBMF Investigator
Jorge Dubcovsky
University of California, Davis

In Support of STEM

Fewer than half the students who enter college intending to major in science, technology, engineering, or math (STEM) stick with it. HHMI is working to change that. We recently invited more than 200 U.S. research universities to apply for $65 million in science education grants to be distributed in 2014 as 35 awards of up to $2.5 million each. Our goal is to transform introductory courses by inspiring and equipping students to persist in STEM disciplines.

President's Letter

People say ideas are a dime a dozen—and it can seem that way today, in our information-rich world. But a big idea, well executed, remains something rare and special.

For 60 years, HHMI has empowered scientists to continually push the frontiers of biomedical research. We believe in big ideas. Our researchers are using the best new molecular tools to reveal brain activity, disease genetics, basic cellular activity, and more, in ways that transform our understanding of how biology works. In the classroom, our educators are matching this creativity with their own bold experiments in biology instruction, seeking to spark the next generation of scientists.

To back them up, we're thinking big, too. Over the past year, we selected 27 new HHMI investigators, announced $65 million in science education grants, and pledged $22.5 million over five years to the National Math and Science Initiative. In addition to funding, we're providing free films for the classroom, and tools and software for any interested researchers to use. Our goal is to share resources and promote excellence at a scale that has meaningful and sustained impact across a wide swath of the science community.

And we're not alone. HHMI is increasingly partnering with other funders to support basic science. With the Gordon and Betty Moore Foundation, we have supported leading plant scientists and will open a new, advanced imaging center for visiting scientists at our Janelia Farm Research Campus in the coming year. HHMI is also part of a new collaboration, the Science Philanthropy Alliance, that seeks to increase basic research funding at universities and research organizations across the United States.

As we look ahead in 2014, we're working hard to make the next big idea possible. Please join us.

Robert Tjian, President

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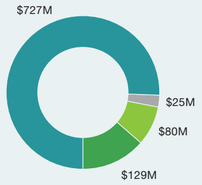
Financials

The Howard Hughes Medical Institute is the nation's largest private supporter of academic biomedical research. As a medical research organization, the Institute spends at least 3.5 percent of its endowment each year on research activities and related overhead, excluding grants and investment management expenses. At the close of fiscal year 2013, the Institute had $16.9 billion in diversified net assets, an increase of $1.1 billion from the previous fiscal year's end. Since 2004, the Institute has provided over $7 billion in direct support for research and science education.

Disbursements (FY 2013)



- U.S. Scientific Research & Lab Construction
- International Research
- Science Education
- Administration & Interest Expense

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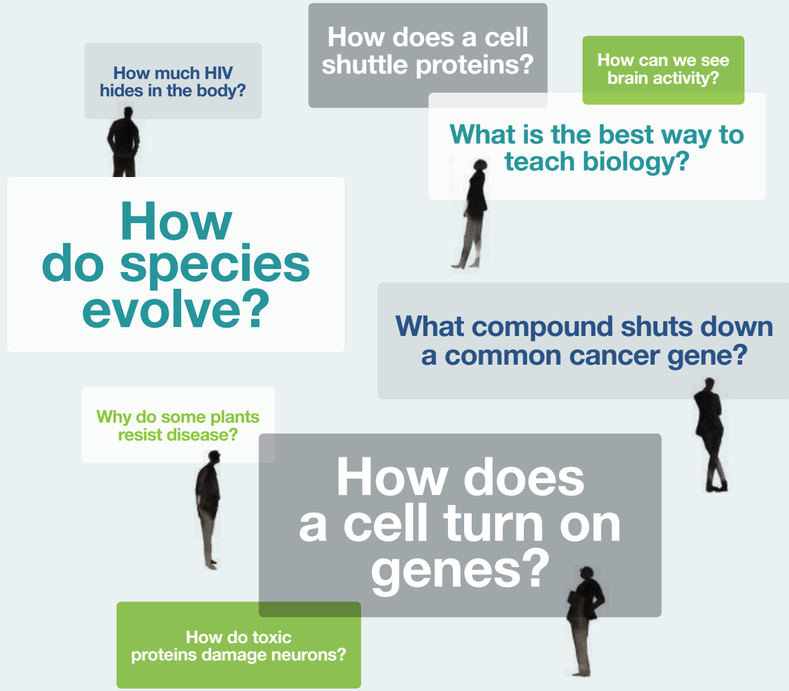
What's the Big Idea?



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Big Ideas, Big Questions

HHMI scientists are explorers. They take risks, pushing the frontiers of basic research. Our researchers are leaders in their fields—and sometimes even launch new fields. With similar drive, our educators cast off old paradigms in search of what works to inspire the next generation of scientists. It all begins with questions—and often, a big idea.

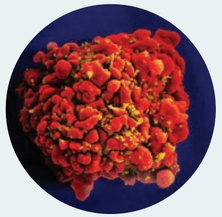
Cancer Gene Caught in a Bind

For more than 30 years, the *K-Ras* gene has been at the top of the drug design target list. A mutant form of the gene is commonly implicated in human cancers but has been considered "undruggable." In a major advance, HHMI Investigator Kevan Shokat and his lab group have identified a "pocket," or binding site, in the K-Ras protein and designed a chemical compound that fits inside. The new inhibitor halts the activity of mutant K-Ras, yet leaves the normal protein untouched. This research could ultimately lead to molecularly targeted cancer therapies.

HHMI Investigator
Kevan Shokat
University of California, San Francisco

Can UTeach? Training Grows

American students continue falling behind in the essential subjects of math and science. Fighting this trend, the National Math and Science Initiative works to significantly improve the number and quality of new K-12 teachers in the United States. In a White House briefing held in March, HHMI committed to invest $22.5 million over five years to expand the Initiative's UTeach Program to an additional 10 research universities. These schools will graduate students who both major in math or science and are qualified to teach it.



Sizing Up HIV in the Body

How to quantify latent virus in HIV patients has been an important outstanding question in the field. HHMI Investigator Robert Siliciano led a team of scientists in a sobering discovery: the amount of HIV lying dormant in a patient's body may be up to 60 times larger than previous estimates. The finding further complicates efforts to cure HIV/AIDS, as a significant percentage of these silent viruses can be reactivated once antiviral therapies are stopped. For researchers, the target just got bigger.

HHMI Investigator
Robert Siliciano
The Johns Hopkins University

Team Targets Ataxia

Like Alzheimer's disease, the lesser known spinocerebellar ataxia type 1 (SCA1) wreaks havoc in the brain as toxic proteins accumulate inside neurons. In SCA1, the toxic protein is ataxin-1. With support from an HHMI Collaborative Innovation Award, HHMI Investigator Huda Zoghbi assembled a team with diverse expertise to examine how hundreds of different genes affect ataxin-1 levels in neurons. The search led them to a single signaling pathway: RAS-MAPK-MSK1. Inhibiting the pathway in mice engineered to mimic the human disease reduced neurodegeneration in the animals, suggesting the team is on the right track.

HHMI Investigator
Huda Zoghbi
Baylor College of Medicine

Nobel for Cell Traffic Discoveries

HHMI Investigators Randy Schekman of the University of California, Berkeley, and Thomas Südhof of Stanford University, along with Yale University's James Rothman, won the 2013 Nobel Prize in Physiology or Medicine for their discoveries detailing how molecules are ferried within and between cells. The three scientists each made major contributions toward solving the mystery of how a cell organizes its transport system to release insulin into the blood and move chemicals across the brain, among other biological activities.

Understanding Heart Defects

Every year, thousands of babies are born with severely malformed hearts. HHMI Investigators Richard Lifton and Christine Seidman are leading research efforts to explain why. They have found that about 10 percent of severe congenital heart defects are not inherited, but instead are caused by spontaneous mutations in the developing heart. The researchers found mutations in a variety of genes, many of them concentrated in a pathway that regulates key developmental steps.

HHMI Investigator
Richard Lifton
Yale University

HHMI Investigator
Christine Seidman
Brigham and Women's Hospital

Coming Soon to a Classroom Near You

Few high school students have probed the mysteries of evolution in the Galapagos or wrestled with the structure of DNA, but now they can—through films. HHMI recently added four new short science documentaries to its free classroom offerings. Three of the films are part of *The Origin of Species* series, which follows naturalists traveling the world to understand how species form. The fourth film, part of a new series called *Great Discoveries in Science*, traces the quest to solve the structure of DNA. Each film comes with an extensive set of classroom materials, from hands-on activities to virtual labs.

Innovators Named HHMI Investigators

In May, HHMI selected 27 of the nation's top biomedical researchers to become Investigators. This new crop of HHMI scientists will receive $150 million, collectively, over the next five years to push the leading edge of basic research, asking hard questions and following unexpected discoveries. They join about 320 current HHMI investigators at more than 70 universities, institutes, and other organizations nationwide. By investing in people, not projects, HHMI aims to advance science through its flexible support of talented individuals.

How to Turn Genes On? Step by Step

A human's 20,000 or so genes exist within a vast jumble of DNA. To work properly, each gene must be activated at the right time and place. Researchers know that a group of proteins assemble into a "pre-initiation complex" that triggers this process, but the exact molecular mechanisms have remained elusive. Using cryoelectron microscopy, Eva Nogales' team captured first ever images of this cellular machinery, illustrating the stepwise assembly of this protein complex in structural detail.

HHMI Investigator
Eva Nogales
University of California, Berkeley