

CATALYSTS FOR COLLABORATION
GENOMICS COMMUNICATION INNOVATION
UNDERSTANDING THE MIND IMAGING
NEUROSCIENCE COMMUNITY EDUCATION
STORYTELLING DISCOVERY CREATIVITY

Science expresses what we know about the world and pursues what we don't. HHMI catalyzes that pursuit. We help set experiments in motion, enable scientists to take on challenging questions, and spark reactions that reach beyond the laboratory and classroom to benefit humankind.

FROM THE PRESIDENT



My colleagues and I at the Howard Hughes Medical Institute deal with an inherent tension as we go about our work. We seek to catalyze innovation and creativity in biomedical research and in the teaching of science. Yet we place an equal, if not greater, value on the Institute's sustained commitment to people, programs, and entire fields of research over a period of many years.

These may seem like competing aims, but they are not. Indeed, one of HHMI's greatest strengths derives from balancing experimentation and investment in new activities with a willingness to provide patient, long-term support. The challenge comes in knowing when to step into a new area and discerning when a field has achieved sufficient maturity that HHMI can safely reduce its investment.

Structural biology is a good example. More than 20 years ago, we gave the field a jump-start by building infrastructure, supporting courses for scientists at places like the Cold Spring Harbor Laboratory, and identifying promising structural biologists, many of whom were early in their careers.

Today, structural biology is well established and our investments have yielded spectacular results. We can therefore strive to repeat this experiment with other fields of research.

Plant science is another example, albeit with a different twist. This year, in collaboration with the Gordon and Betty Moore Foundation, HHMI selected 15 outstanding scientists who work on a range of important biological questions using many different plant systems—everything from algae to tomatoes. Clearly, scientists have long understood the importance of fundamental plant research, but funding agencies have overlooked its value and potential for human health and well-being. HHMI and the Moore Foundation made an investment that we hope will accelerate a seminal, yet undernourished, field of research.

This year has been marked by fresh starts, by opportunities that enable HHMI to serve as a catalyst. We are partnering with the Wellcome Trust and the Max Planck Society to create an open access journal that puts scientists back at the heart of the publishing

enterprise. And we are stepping into another important area—science documentary filmmaking—in which we believe HHMI investments can advance science literacy in significant ways.

As a practicing scientist—and as the leader of an organization dedicated to science—I believe that change is an important part of our mandate. We are called upon to catalyze discovery and educate new generations of scientists for the benefit of humanity, writ large.

A handwritten signature in black ink, which appears to read "Robert Tjian". The signature is fluid and cursive, with a long horizontal stroke extending to the right.

ROBERT TJIAN, PRESIDENT

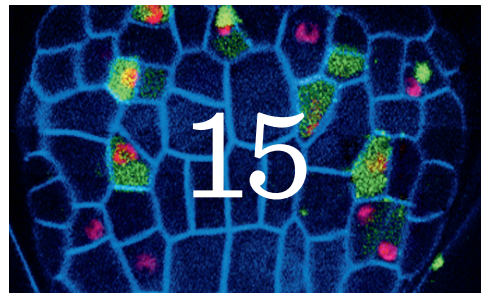
TEN BIG STORIES

Welcome to the 2011 Annual Report of the Howard Hughes Medical Institute. In this document you will find a financial summary, HHMI president Robert Tjian's annual letter, and ten big stories from the past year. For a more complete picture—including interviews, research highlights, and multimedia—please visit our companion website: www.hhmi.org/annualreport2011.

From the HHMI charter: 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.

For the full report, please visit: www.hhmi.org/annualreport2011.

One



15 New Plant Scientists

Together with the Gordon and Betty Moore Foundation (GBMF), HHMI selected 15 of the nation's most innovative plant scientists to become the first HHMI-GBMF investigators. With a combined total investment of \$75 million over five years, HHMI and GBMF formed the collaboration to begin to remedy the serious underfunding of fundamental plant science research, which holds great potential for addressing the world's pressing demands for new sources of energy, food, and medicine.

Six



Friedman Receives Lasker Award

For their research on the appetite-controlling hormone leptin, HHMI investigator Jeffrey Friedman of The Rockefeller University and Douglas Coleman of The Jackson Laboratory received the 2010 Lasker Award for Basic Medical Research. Beginning in the 1960s, Coleman performed experiments suggesting that obese mice are overweight in part because they lack a substance that helps them control their appetites. In 1994, Friedman pinpointed leptin as the mystery substance and later uncovered the hormone's role in moderating energy usage.

Two



Shutting Off Anxiety

Scientists are beginning to understand the neural circuits that underlie anxiety, the most common psychiatric disease. With the flick of a light-activated genetic switch that lets them manipulate specific neurons in the brain, HHMI investigator Karl Deisseroth of Stanford University and colleagues reduced symptoms of anxiety in laboratory mice. The experiments demonstrated that a cluster of neurons in the amygdala—an almond-shaped structure in the brain—helps control apprehension in the absence of any immediate threat.

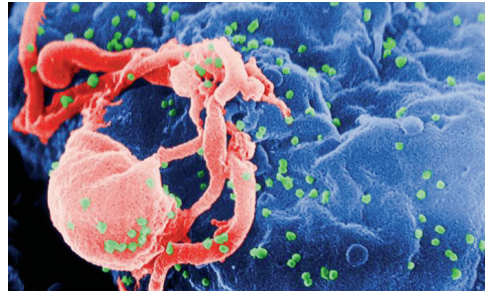
Seven



Targeting Cancer Stem Cells

Stem cells can differentiate into multiple cell types and divide in perpetuity; cancer stem cells use those characteristics to wreak havoc. HHMI investigator Elaine Fuchs of The Rockefeller University found that two signaling pathways are critical to regulating the growth of squamous cancer stem cells—which can seed tumors in the skin, head, neck, lungs, esophagus, and other tissues. Interfering with these cancer-specific pathways could lead to drugs that destroy cancer stem cells more effectively while sparing normal stem cells.

Three



What It Takes to Control HIV Naturally

The small fraction of people who are infected with HIV and can stay healthy without drugs are helping scientists learn about potential ways to fight the virus. In the first genome-wide association study of these individuals, HHMI investigator Bruce Walker of Massachusetts General Hospital identified a few amino acids that seem to predict a person's ability to keep the virus in check. The findings indicate what an effective natural immune response is and how it is induced—information that could help generate more effective vaccines and treatments.

Eight



Missing DNA Makes Us Human

Among the features that set humans apart from other animals are 510 segments of regulatory DNA that are present in other species but surprisingly missing from the human genome. David Kingsley of Stanford University School of Medicine and colleagues showed that two of the missing sequences help explain why humans lack features found in other mammals, such as sensory whiskers, but have evolved much larger brains. The loss of specific regulatory sequences likely contributed to the evolution of many unique human traits.

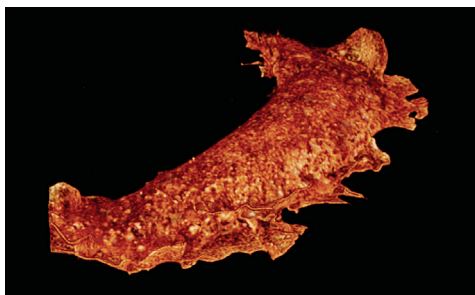
Four



New Open Access Journal

HHMI investigator Randy W. Schekman was named editor-in-chief of a new open access journal announced this year by HHMI, the Max Planck Society, and the Wellcome Trust. A distinguished cell biologist and the 14th editor of the *Proceedings of the National Academy of Sciences*, Schekman will lead the team of active scientists who will serve at the heart of the new journal's editorial operations. The first issue is expected to publish in 2012.

Five



Microscopy's New World

A technique developed by Janelia Farm group leader Eric Betzig produced striking, three-dimensional movies of living cells. The technique, called Bessel beam plane microscopy, shines thin sheets of light at the side of a cell, capturing 200 frames per second. The flat images are stitched together to create a three-dimensional photo of the cell. Time-lapse series of these images allow the scientists to watch cellular processes such as chromosomes moving apart during cell division.

Nine



RNA-DNA Differences Uncovered

It was long assumed that RNA sequences closely correspond to the DNA sequences they are made from. But when HHMI investigator Vivian Cheung of the University of Pennsylvania School of Medicine analyzed the RNA and DNA from 27 individuals, she found differences between the RNA and DNA in around 40 percent of genes. The finding suggests that unknown cellular processes are acting on RNA to generate a sequence that is not an exact replica of the DNA from which it is copied.

Ten



Documentary Film Unit Announced

Movies and television are a universal experience—and an ideal tool for sparking a passion for science among the public. This year, HHMI launched a \$60 million, five-year initiative to produce world-class science documentary films for broadcast, theatrical release, and digital distribution. Led by former National Geographic Television president Michael Rosenfeld, the new film unit will partner with producers and broadcasters around the world to tackle subjects from astronomy to evolution. A series of short films for science educators will be produced in tandem.

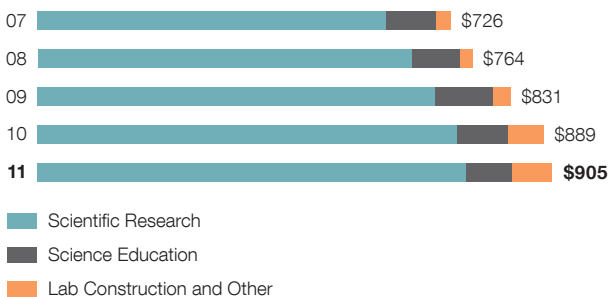
FINANCIAL HIGHLIGHTS

The Howard Hughes Medical Institute is the nation’s largest private supporter of academic biomedical research. As a medical research organization, the Institute must spend at least 3.5 percent of its endowment each year on direct medical research activities and related overhead, exclusive of grants and investment management expenses. The endowment is the Institute’s principal source of funding. The investment objective is to manage the endowment in a prudent manner that will fund the Institute’s research and grants programs in perpetuity. On August 31, 2011, the endowment was approximately \$16.1 billion.

Endowment
(\$ IN MILLIONS)



Disbursements
(\$ IN MILLIONS)



Endowment Allocations
(\$ IN MILLIONS)

