
Every day, HHMI supports the pursuit of knowledge and the application of that knowledge to benefit humanity. We have structured the Institute—physically, programmatically, philosophically—to empower the world’s finest scientists and educators. These individuals are also architects of discovery: shaping their laboratories and classrooms, guiding their teams, and conceiving the pioneering experiments that lead to innovations of lasting consequence.

HOWARD HUGHES MEDICAL INSTITUTE 2010 ANNUAL REPORT

ARCHITECTS OF DISCOVERY

FROM THE PRESIDENT



Forty-nine years separated identification of the “Philadelphia chromosome” in patients with chronic myelogenous leukemia from the 2009 Lasker Award ceremony honoring three scientists for their work in developing drugs that target the protein produced by the aberrant gene. The time span illustrates the complexity of transforming fundamental biological knowledge—acquired in many labs over many years—into therapies that are safe and effective. And this is a success story, due in part to research by Lasker awardees (and HHMI investigators) Brian Druker and Charles Sawyers.

The Howard Hughes Medical Institute, founded shortly before Peter Nowell and David Hungerford named the chromosomal abnormality, is dedicated to discovery research in the biological sciences. We believe knowledge generated in our laboratories will someday benefit humanity and have created enabling structures that provide our scientists with the long-term freedom needed for big research challenges.

This year’s annual report theme—“Architects of Discovery”—speaks to that enabling

framework, which is taking literal form in the construction of a laboratory building to house the KwaZulu-Natal Research Institute for Tuberculosis and HIV (K-RITH) in Durban, South Africa. Our 10-year commitment to K-RITH recognizes that solutions to human needs demand patience and time.

Patience and urgency are twin poles that define a scientist’s life, as HHMI investigator Jim Allison well knows. Influenced by the loss of family members to cancer, he focused on immunology to find more effective treatments. This year, a drug built on a key discovery made in Allison’s lab in the 1990s became the basis for a promising treatment for late-stage melanoma. It also validates a novel approach for boosting the immune response to tumor cells.

X-ray crystallographer Tom Steitz has patiently characterized complex biological molecules, and the ribosome—a vast molecular machine that generates the proteins needed for cell function—was an irresistible target. In 2009, he shared a Nobel Prize for achieving that goal. (HHMI investigator Jack Szostak was also honored for illuminating the

processes that protect chromosomal tips during replication.) More than bragging rights were at stake in tackling such a complex structure: many antibiotics work by shutting down bacterial ribosomes. New drugs are desperately needed, and novel antibiotics based on Steitz’s discoveries are now in development; two of the newest have the potential to treat drug-resistant infections like tuberculosis. We await the outcome of further studies with the opposite of patience.

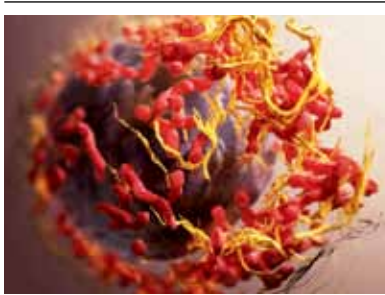
Yet it’s perhaps no accident that, for 13 years, HHMI benefited from the leadership of an historian trained to take the long view: Hanna Holborn Gray, a Renaissance scholar and academic leader. As Trustee Chair, she demanded the best thinking on the Institute’s behalf, balancing today’s urgent need with the patience to enable discovery for decades to come. Thank you, Mrs. Gray.

A handwritten signature in black ink, appearing to read "Robert Tjian". The signature is fluid and cursive, with a large initial "R" and "T".

Robert Tjian, President

10 BIG STORIES

Welcome to the 2010 Annual Report of the Howard Hughes Medical Institute. This document provides a snapshot of our activities for the year. For a detailed picture—including interviews, interactive features, and a deeper look at many of the stories presented here—visit the full report online: www.hhmi.org/annualreport2010. We'd love to hear what you think.



01

New Melanoma Drug Shows Promise

For the first time, a drug was shown in a clinical trial to extend the lives of patients with stage III and IV melanoma. Called ipilimumab, the drug liberates the immune system from a molecule that usually reins it in, leaving T cells free to do an important job: attack tumors. Research by HHMI investigator Jim Allison set the

foundation for the drug's development 15 years ago when, at the University of California, Berkeley, he discovered the molecule and found a way to shut it down.



02

Transforming Science Education at All Levels

There's no substitute for first-hand discovery. That's the

essential philosophy behind a new cycle of science education grants, totaling \$70 million, that will allow 50 universities across the country to test innovative ways of teaching science to undergraduate and precollege students. Another \$9 million in grants will support 13 leading research scientists who are committed to making science more engaging to undergraduates.



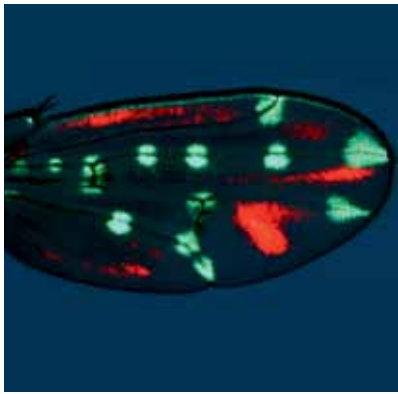
03

Schmoke Elected Chairman of the HHMI Trustees

Kurt L. Schmoke, dean of the Howard University School of Law, was elected chairman of the Trustees of HHMI. A distinguished attorney and respected advisor to a number of educational and other organizations, Schmoke has dedicated much of his life to public service. In addition to academia, his career has included private practice, a domestic policy position in the Carter White House, and three

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.

terms as mayor of Baltimore, MD, where he focused on improving the city's school system and economic development. Schmoke succeeds Hanna H. Gray, president emeritus of the University of Chicago, who will continue to serve as a Trustee.



04

Evolution's Art

The rainbow of colors and patterns that decorate the animal kingdom remains one of nature's most awesome mysteries. With two papers that describe the evolution of spots and color changes in fruit flies, Sean B. Carroll strengthened the notion that evolution tends to tinker with existing genetic machinery to arrive at new patterns and forms. Carroll, an HHMI investigator at the University of Wisconsin–Madison, has spent his career studying the genetic underpinnings of evolution and development, identifying the molecular mechanisms that lead to new traits and species. He is also an award-winning author and educator; in 2010, he was named vice president for science education at HHMI, succeeding Peter J. Bruns.



05

Our Biased Genes

With support from an HHMI Collaborative Innovation Award, HHMI investigator Catherine Dulac and a team of researchers revealed how genetic contributions from mom or dad affect an offspring's behavior. The ambitious new analysis in mice demonstrated that for more than 1,300 genes active in the brain, there is a significant bias as to which copy is active—the one inherited from the mother or the one that came from the father.



06

The Molecular Origins of a Rare Eye Disorder

After a search across five continents for children with a rare eye movement disorder, a large international team of collaborators led by

HHMI investigator Elizabeth C. Engle identified the condition's genetic cause. Children with the inherited disease, called congenital fibrosis of the extraocular muscle type 3, have drooping eyelids and cannot move their eyes fully. Once Engle, of Children's Hospital Boston, and her colleagues identified 29 families with the disorder, they were able to link it to a gene encoding a protein that helps neurons navigate a developing nervous system and connect with the appropriate cells.



07

Bishai Named Head of New TB-HIV Institute

Physician and renowned tuberculosis researcher William R. Bishai was named the first full-time director of the KwaZulu-Natal Research Institute for Tuberculosis and HIV (K-RITH), a collaboration between HHMI and the University of KwaZulu-Natal in Durban, South Africa. At the Johns Hopkins University, Bishai's research has focused on understanding how the tuberculosis bacillus is so successful at infecting humans. His first priority as K-RITH director will be to recruit an international cadre of

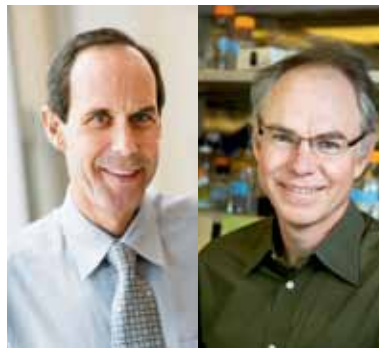
scientists and clinicians with the long-term goal of controlling the devastating coepidemic of tuberculosis and HIV.



08

Nobels Honor Szostak, Steitz

HHMI investigators Thomas A. Steitz and Jack W. Szostak were awarded Nobel Prizes in 2009. Steitz, of Yale University, shared the Chemistry award with Venkatraman Ramakrishnan of the Medical Research Council Laboratory of Molecular Biology and Ada E. Yonath of the Weizmann Institute of Science for research that showed, with x-ray crystallography and a host of other techniques, what the ribosome looks like and how it functions at the atomic level. Szostak, of Massachusetts General Hospital and Harvard Medical School, shared the Physiology or Medicine prize with Elizabeth Blackburn of the University of California, San Francisco, and Carol Greider of the Johns Hopkins University School of Medicine, for discovering how chromosomes are protected by telomeres and the enzyme telomerase. The work has revealed how organisms rely on telomerase to protect their genome from degradation.



09

Druker, Sawyers Receive Lasker Award

Decades of deeply collaborative work that no single lab could have accomplished alone led to development of the first treatment that selectively targets an enzyme that causes cancer. In 2009, the three lead researchers received the Lasker-DeBakey Clinical Medical Research Award. Presented to HHMI investigator Charles L. Sawyers of Memorial Sloan-Kettering Cancer Center, HHMI investigator Brian J. Druker of Oregon Health & Science University, and Nicholas B. Lydon, formerly of Novartis, the award recognized their development of novel drugs for chronic myeloid leukemia,

work that revolutionized treatment of the once-incurable disease.



10

Genetic Stutter Can Lead to ALS

Starting with two simple experimental systems—yeast and flies—HHMI investigator Nancy M. Bonini and colleagues discovered one of the most common genetic risk factors identified to date for the neurodegenerative disease amyotrophic lateral sclerosis (ALS), also known as Lou Gehrig's disease. In about 5 percent of ALS patients, a genetic stutter produces too many copies of a short segment of DNA in a gene called *ataxin-2*, the University of Pennsylvania team found. The mutation appears to contribute to the protein clumping that interferes with the normal function of motor neurons.

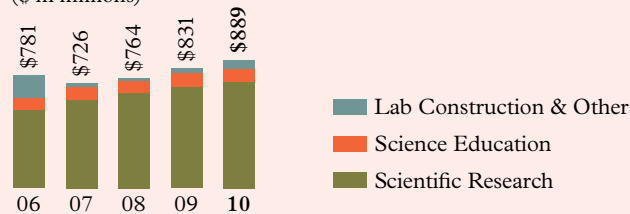
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REPORT, PLEASE VISIT:
[WWW.HHMI.ORG/
ANNUALREPORT2010](http://WWW.HHMI.ORG/ANNUALREPORT2010)**

FINANCIAL HIGHLIGHTS

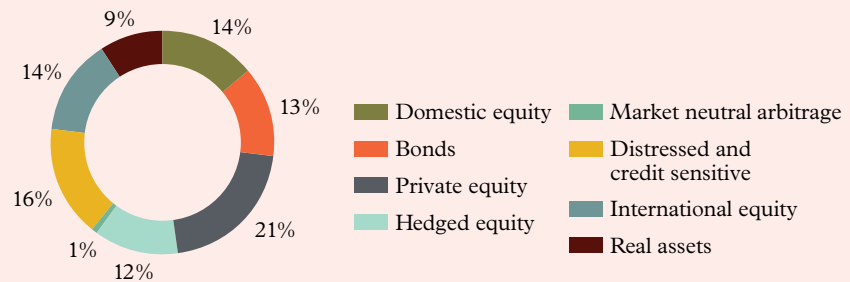
The Howard Hughes Medical Institute is the nation's largest private supporter of academic biomedical research. Classified as a medical research organization by the Internal Revenue Service, the Institute is required to spend at least 3.5 percent of its endowment each year on direct medical research activities and related overhead, exclusive of

grants and investment management 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 maintain its purchasing power and will fund the Institute's research and grants programs in perpetuity. On August 31, 2010, the endowment was approximately \$14.8 billion.

Disbursements
(\$ in millions)



Endowment Allocations



Endowment
(\$ in millions)

