SOME DISCOVERIES CHANGE THE WAY WE SEE.

SOME IMPERATIVES DEMAND A DIFFERENT LENS.

SOME INSTITUTIONS LOOK FOR PEOPLE WHO SEE THE WORLD DIFFERENTLY.

HOWARD HUGHES MEDICAL INSTITUTE
2009 ANNUAL REPORT

SEEING DIFFERENTLY

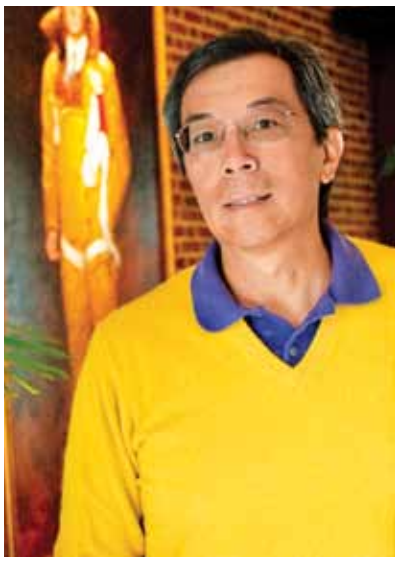
Consider this a year for "seeing differently" at the Howard Hughes Medical Institute: a year marked by a change in leadership, luminous and illuminating science, compelling new programs, and productive reflection prompted by turmoil in the broad economy. Even HHMI's annual report will be presented in a fresh light.

This year, for the first time, we are publishing the full report online. This approach saves paper (good) and makes the most of technology to present information about the Institute in greater depth (even better). Please visit: **www.hhmi.org/annualreport2009**

During more than 20 years as a Hughes investigator at the University of California, Berkeley, I have had a front-row seat that has enabled me to watch the Institute's leadership in action. I saw the great successes achieved by Purnell W. Choppin, who served as HHMI's president for 13 years, in the development of our scientific and educational programs. Indeed, my own work as a scientist benefited directly from this expansive period in HHMI's history. Later, I observed the beautiful changes made by Thomas R. Cech, who became president in 2000, as he refined the Institute's research activities and brought new vigor to our support for science education.

Since becoming HHMI's president in April, I can tell you that the change in perspective—from a ground-floor lab at Berkeley to a second-floor aerie overlooking the Institute's spacious campus—is both thrilling and humbling. Each has a terrific view. But now, in collaboration with a talented staff and with the guidance of the Institute's Trustees, I have the opportunity to see this extraordinary organization in every dimension and all its complexity. Thankfully, there's room for me to make a contribution, particularly with regard to our international presence. I have always viewed HHMI as a global enterprise and, with the help of the scientific staff and our advisors, we will consider new programs and focus on the development of the KwaZulu-Natal Research Institute for Tuberculosis and HIV in South Africa.

We do so in the face of challenging times. Although our investments performed well on a relative basis, the economic downturn means that Hughes has less money to support programmatic activities. As a matter of prudence, we have reduced spending in all areas and made operational changes; the future may require further adjustments. Yet our



capacity to achieve is still so great that we must place the emphasis where it belongs: What must we do? What imperatives demand a different lens, a new way of thinking? These are the questions—and the opportunities—that will propel HHMI in new directions.

Robert Tjian, President

TEN BIG STORIES

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WHEN THE BRAIN'S WIRING FAILS

Welcome to the 2009 Annual Report of the Howard Hughes Medical Institute. Notice anything different? This document provides only a snapshot of our activities for the year. For the complete picture—as well as interviews, interactive features, and research highlights—visit our website: www.hhmi.org/annualreport2009 We hope you enjoy the experience; let us know what you think.

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.

01 TJIAN TAKES THE HELM

Longtime HHMI investigator and distinguished biochemist Robert Tjian became HHMI's president on April 1, 2009, succeeding Thomas R. Cech, who served as president for nine years and has returned to full-time research at the University of Colorado at Boulder. During three decades on the faculty of the University of California, Berkeley, Tjian made major contributions to the understanding of how genes work. He continues to conduct research at labs in Berkeley and at HHMI's Janelia Farm Research Campus.

02 TSIEN RECEIVES NOBEL PRIZE

By co-opting the proteins that make some jellyfish glow, HHMI investigator Roger Y. Tsien and others have provided an invaluable set of tools for visualizing cells and their components. Tsien, a professor at the University of California, San Diego, shared the 2008 Nobel Prize in Chemistry for the discovery and development of green fluorescent proteins (GFPs) with Osamu Shimomura of the Marine Biological Laboratory and Martin Chalfie of Columbia University.

03 K-RITH BREAKS NEW GROUND

Together with the University of KwaZulu-Natal in Durban, South Africa, HHMI this year initiated a world-class research facility focused on the deadly intersection of drug-resistant tuberculosis and HIV in South Africa. The KwaZulu-Natal Research Institute for Tuberculosis and HIV (K-RITH), located on the campus of the Nelson R. Mandela School of Medicine, represents a commitment of some $60 million over the next 10 years.

04 EARLY CAREER HONORS

Fresh perspective is a precious commodity in science. And this year, HHMI identified 50 early career scientists whose provocative and promising research holds the potential to transform our understanding of biological phenomena—from how microbial communities interact to the complex relationships between thousands of proteins.

05 NEW TRAINING FOR FUTURE DOCS

A report issued by an expert committee convened by the Association of American Medical Colleges and HHMI has, for the first time, defined scientific competencies for future physicians. The committee argued that a shift in focus away from rigid course requirements toward an evolving set of competencies would encourage the development of innovative and interdisciplinary science curricula.

06 GENES HELP CANCER SPREAD

Understanding how cancer spreads from one location to another in the body could be key to future treatments.

Left page 01: Barbara Ries 02: Paul Fetters 03: Paul Fetters 05: skd2842902sdc/Stockbyte 06: Mark Mahaney 07: Zack Seckler/AP ©HHMI 08: Matt Kalinowski 09: Agapito Sanchez, Alexis Bywater 10: Andy Kuno/PR Newswire, ©HHMI *Right page* Illustration: Josh Cochran *From the President* Tjian: James Kegley

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Joan Massagué of Memorial Sloan-Kettering Cancer Center and colleagues identified 17 genes that help breast cancers spread to the brain by implanting tumor cells from advanced breast cancer into mice and then isolating tumor cells from the mice whose cancer spread to the brain.

07 KEEPING MICROBES MUM

Bonnie L. Bassler of Princeton University showed that shutting down the lines of communication between bacteria might be an effective way to prevent microbes from attacking their hosts. Medicines that interrupt communication between bacteria could be less likely than traditional antibiotics to spur the development of drug-resistant bacteria.

08 A BETTER MEMORY-BOOSTING DRUG

When DNA in the brain unwinds from its tightly coiled configuration, a mind is primed for learning. Drugs that promote this relaxation by blocking a class of DNA-packaging proteins enhance memory in mice but can cause side effects. Li-Huei Tsai of the Massachusetts Institute of Technology identified a single DNA-packaging protein that could be the target of safer, more specific drugs.

09 GENE NETWORK BUOYS CANCER

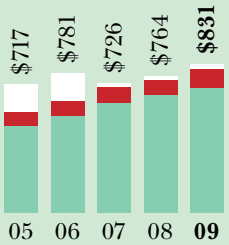
In independent studies, D. Gary Gilliland of Brigham and Women's Hospital (now senior vice president at Merck Research Laboratories) and Stephen J. Elledge (also of BWH) used RNA interference technology to turn off genes in cancer cells and see which genes affected the cancer's survival. The work suggests new ways to attack cancer by targeting a largely hidden network of normal genes that cancer cells rely on for survival.

10 WHEN THE BRAIN'S WIRING FAILS

In patients with multiple sclerosis (MS), immune cells attack the sheaths of myelin that protect the fibrous extensions of nerve cells. New research by David H. Rowitch of the University of California, San Francisco, indicated that MS impairs the body's natural mechanism for repairing myelin: Although precursors to the repair cells are present, they never mature enough to do their jobs. As a result, damage accumulates and the myelin sheath erodes.

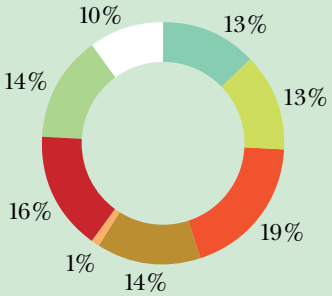
The Howard Hughes Medical Institute is the nation's largest private supporter of academic biomedical research. Classified as a medical research organization by the Internal Revenue Service, the Institute is required to spend at least 3.5 percent of its endowment each year on direct medical research activities 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, 2009, the endowment was approximately $14.0 billion.

DISBURSEMENTS
($ in millions)



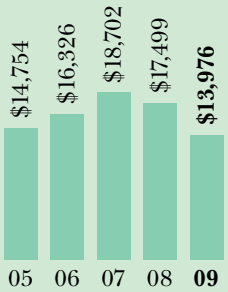
Lab construction
Grants and special programs
Scientific research

ENDOWMENT ALLOCATIONS
($ in millions)



Domestic equity
Bonds
Private equity
Hedged equity
Market neutral arbitrage
Distressed and credit sensitive
International equity
Real assets

ENDOWMENT
($ in millions)



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