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HHMI Announces Selection of New Investigators Who Conduct Patient-Oriented Research



Image Title: From left (row 1): Katherine A. High, Emmanuel J. Mignot, Brendan H.L. Lee, Charles L. Sawyers; (row 2): Robert B. Darnell, Bruce D. Walker, Helen H. Hobbs, Todd R. Golub; (row 3): Robert F. Siliciano, Edwin M. Stone, Christopher A. Walsh, Brian J. Druker. - Paul Fetters

The Howard Hughes Medical Institute has selected 12 of the nation's top physician-scientists to be appointed as HHMI investigators in an innovative program to improve the translation of basic science discoveries into enhanced treatments for patients.

They will join 324 HHMI investigators across the United States, a group whose recent honors include the National Medal of Science and the Lasker Award. Earlier this month, nine HHMI investigators were elected to membership in the National Academy of Sciences.

"This group of physician-scientists has already made impressive contributions to understanding some of society's most vexing health problems, including AIDS, cardiovascular disease and cancer," said HHMI

President Thomas R. Cech. “We believe that they have the potential to continue to improve healthcare by finding new ways to translate basic science discoveries into useful therapy for patients.”

“Medical research is thriving today, primarily as a result of the powerful new tools of molecular biology that have revealed new concepts about the inner workings of the human cell,” said Joseph L. Goldstein of the University of Texas Southwestern Medical Center at Dallas and chairman of HHMI’s Medical Advisory Board. “What are crucially needed are more patient-oriented researchers with the expertise to translate and transform these molecular advances into the realities of clinical medicine. In the conquest of any disease, patient-oriented researchers are essential at every stage — from the delineation of a new syndrome, to elucidation of pathogenesis, to design and evaluation of a new drug.”

With the completion of the human genome sequence and the advent of other technological advances such as those in the area of biomedical imaging, there are new opportunities for bridging the gap between advances in basic science and clinical research. The purpose of this investigator competition was to identify researchers whose scientific work is guided by their interaction with patients or other human subjects.

Although several of the 324 current HHMI investigators are doing patient-oriented research on diseases such as colon cancer, hypertension, and hypertrophic cardiomyopathy, the majority of Hughes scientists focus on basic research directed toward understanding the genetic, molecular and cellular bases of human disease. This type of research is generally characterized as being disease-oriented rather than patient-oriented, because the research does not require significant contact with patients.

In June 2001, letters inviting nominations were sent to 119 institutions, including medical schools, research institutes, schools of public health and some independent hospitals. By September 10, 2001, the closing date for nominations, 138 nominations had been received. A review committee of distinguished biomedical scientists evaluated the nominations. Following the recommendations of the advisors, 12 physician-scientists were selected for appointment.

The Institute is a medical research organization that enters into long-term collaboration agreements with universities and other academic research organizations, where its investigators hold faculty appointments. Under these agreements, HHMI investigators, all of whom are employees of the Institute, carry out their research with considerable freedom and flexibility in HHMI laboratories located on various campuses. This model emphasizes “people, not projects” and differs from the grant-based approach used elsewhere. The Institute expects to provide initial research budgets of up to \$1 million annually for each of its new investigators, plus payments to the host institutions for laboratory space.

The Institute's biomedical research expenditures this fiscal year will total about \$450 million. In addition to conducting medical research, the Institute has a large grants program that supports science education in the United States and the research of a select group of biomedical scientists in other countries. HHMI grants will total more than \$100 million during the current fiscal year.

Established in 1953 by the aviator-industrialist for whom it is named, the Institute maintains its headquarters and conference center in Chevy Chase, Maryland, just outside Washington, D.C.

**Investigators and Research Descriptions Robert B. Darnell, M.D., Ph.D.
The Rockefeller University New York, NY**

Dr. Darnell studies paraneoplastic neurologic disorders (PNDs), which are believed to arise when tumor cells abnormally produce proteins that are usually made only in neurons. In PND patients, the immune system produces antibodies and T cells that effectively attack the patient's own tumor. But the same immune cells can also attack healthy neurons, in what is termed an autoimmune response, which can lead to neuronal degeneration in specific regions of the brain.

One of the goals of Dr. Darnell's research is to learn more about the neuronal proteins that are attacked by the immune system. Using serum from patients with PND, Dr. Darnell's research team has identified a series of genes that encode previously undiscovered neuron-specific proteins. Recent work has focused on the role that neuronal RNA binding proteins play in the brain and in disease. By studying the PND antigens, Dr. Darnell and colleagues have found that neurons are unique in the way they regulate gene expression through their processing of RNA. These findings are relevant for a number of diseases. For example, the Darnell laboratory recently discovered how the RNA binding protein associated with fragile X mental retardation might cause the range of cognitive and behavioral abnormalities characteristic of this disease.

A second goal is to understand the nature of the anti-tumor and autoimmune response, with the aim of developing new immunotherapies. By starting with the unique set of PND patients, the Darnell laboratory is working its way back toward understanding how people's immune system may normally suppress cancer as well as how autoimmune diseases, such as multiple sclerosis, arise — two pursuits that may lead to novel strategies for treating these life-threatening conditions.

**Brian J. Druker, M.D. Oregon Health and Science University Portland,
OR**

One of the most exciting recent advances in cancer treatment is the development of STI571, commonly known as Gleevec, a drug that inhibits the activity of specific proteins called tyrosine kinases that promote the formation of chronic myelogenous leukemia (CML) and gastrointestinal stromal tumors (GIST). Working from the premise that the

leukemia-cell-specific Bcr-Abl tyrosine kinase caused CML, Dr. Druker searched for a molecule that would block the action of this altered kinase without interfering with other normal kinases. His search led to scientists at Novartis, who provided a number of chemical compounds that Dr. Druker tested to see whether they blocked the activity of the wayward kinase. The studies turned up STI571, a compound that Dr. Druker played a key role in shepherding through development — from early experimental therapy to large-scale clinical trials in patients.

As the STI571 studies have shown, tyrosine kinases make excellent targets for new cancer therapies. Dr. Druker and his colleagues are continuing to study how tyrosine kinases spur cellular transformation. His group is now studying the FLT3 tyrosine kinase, which is mutated in 30 percent of patients with acute myeloid leukemia. Using the STI571 studies as a road map for drug development, Dr. Druker and his colleagues hope to design an effective FLT3 kinase inhibitor.

Todd R. Golub, M.D. Dana-Farber Cancer Institute Boston, MA

Dr. Golub is addressing clinical problems in cancer medicine by studying primary patient material at the genetic level. He and his colleagues are developing diagnostic and prognostic tests for childhood leukemia based on the cloning of genes involved in chromosome translocations; they are devising strategies for predicting responses to chemotherapy based on DNA microarray gene expression patterns; and they are exploring novel therapeutic strategies based on whole genome analyses of patient samples.

Dr. Golub and his colleagues have shown that children with acute lymphoblastic leukemia (ALL) carry a rearrangement of the *TEL* gene. They demonstrated that 27 percent of patients they studied carried a specific *TEL/AML1* fusion gene that can be used as a diagnostic marker to predict a favorable response to therapy. *TEL/AML1* testing is now being used at some medical centers to tailor individual treatment plans for patients with ALL in the hope of reducing toxicity caused by chemotherapy.

Unlike acute leukemias, most adult solid tumors are characterized by more complex gene rearrangements. Dr. Golub is now taking a number of different approaches that will yield a more accurate picture of how these tumors develop by taking a "whole genome" look at cancer. His research team is bringing the power of genomic technologies to bear on clinical dilemmas in cancer treatment, with an eye toward developing more rational approaches to treatment planning and drug development.

Katherine A. High, M.D. The Children's Hospital of Philadelphia Philadelphia, PA

For the past 16 years, Dr. High has studied the molecular basis of blood coagulation, with an emphasis on hereditary bleeding disorders. Approximately 10 years ago, she became interested in developing a gene transfer approach to the treatment of hemophilia B, a bleeding disorder caused by a deficiency of clotting factor IX. Gene therapy is a novel area of therapeutics in which the active agent is a DNA sequence rather than a protein or small molecule. The therapeutic possibilities for gene therapy are

enormous, but they have been limited by practical difficulties related to inefficient gene transfer, transient gene expression or unacceptable toxicities.

In 1999, Dr. High's research team showed that gene therapy could achieve long-term improvement in a naturally occurring hemophilia that affects dogs. Using a genetically engineered virus, called adeno-associated virus, as a vector to deliver therapeutic genes, Dr. High and her colleagues continued to improve results in the hemophilia dog model, and have recently demonstrated high-level expression of clotting factor in these animals. Concurrently, they have carried out the first studies of parenterally administered adeno-associated virus vectors in humans. These clinical studies are ongoing in patients with severe hemophilia B.

**Helen H. Hobbs, M.D. University of Texas Southwestern Medical Center
Dallas, TX**

Dr. Hobbs and her colleagues are studying how abnormalities in the processing of dietary lipids cause human diseases. Her research team is identifying the genetic factors that influence how low-density lipoprotein (LDL) and high-density lipoproteins (HDL), the two major cholesterol-carrying lipoproteins, accumulate in the blood. Many different genes and environmental factors contribute to the variations in levels of LDL and HDL. In an effort to identify genetic factors that lead to variations in lipoproteins levels, Dr. Hobbs and her colleagues have collected and characterized the plasma lipoprotein levels in over 500 families in which multiple family members have elevated plasma levels of lipoproteins. Her group has also recently identified genes that play critical roles in limiting the amount of dietary cholesterol that accumulates in the body. Dr. Hobbs is investigating why some individuals are more likely than others to develop high plasma cholesterol levels on a high cholesterol diet.

Levels of lipoprotein(a) [Lp(a)]— which at high levels can increase one's risk of developing heart disease — can differ dramatically between individuals and ethnic groups. Dr. Hobbs and her research team have shown that sequence variations in the apo(a) gene are the major determinant of plasma concentrations of Lp(a) within ethnic groups, but it is not known why individuals of African descent have about a three-fold higher mean plasma level of Lp(a) or whether high levels of Lp(a) in African-Americans are a risk factor for heart disease. Her group is examining these questions by performing family studies and by studying the relationship between plasma levels of Lp(a) and atherosclerosis in African-Americans.

As principal investigator of the Dallas Heart Disease Prevention Project, Dr. Hobbs and her colleagues are studying heart disease in a population of 3,000 randomly selected individuals who are being characterized for behavioral, environmental, metabolic and genetic risk factors for cardiovascular disease. The extensive database generated from this study will be used to identify new predictive cardiac risk factors and to explore the relationship between the metabolic syndrome X, which is characterized by obesity, insulin resistance, high triglyceride levels, high blood pressure, and heart disease.

Brendan H. L. Lee, M.D., Ph.D. Baylor College of Medicine Houston, TX

Dr. Lee is studying the developmental and biochemical pathways that regulate mammalian tissue and organ development. He is applying knowledge from these studies to the design of new diagnostic and therapeutic tools for disorders that result from abnormalities in these pathways.

In pathways that are not well understood, such as those that regulate the early development of organs, Dr. Lee and his colleagues have focused on the transcriptional networks that govern pattern formation and cell differentiation. In their studies on skeletal and kidney development, they have correlated human genetic disease phenotypes with mouse models to elucidate the regulators and targets of key transcription factors specifying unique developmental programs. These basic and translational studies in the laboratory are linked with clinical research coordinated from the Texas Children's Hospital Skeletal Dysplasia Clinic. In this environment, the multidisciplinary care of pediatric patients with skeletal malformations is closely linked with studies aimed at understanding the consequences of gene mutations on craniofacial/limb skeletal development, and at quantitation and treatment of osteopenia (less than normal amount of bone) associated with skeletal dysplasias.

Dr. Lee and his colleagues are also studying patients who have disorders in the urea cycle, which is responsible for removing ammonia that is generated by protein intake in food and by the breakdown of proteins in the body during illness. If ammonia is not cleared from the blood, it can reach toxic levels, causing brain damage and death. Since much basic information about the urea cycle is already available, Dr. Lee has attempted to translate that information into stable isotope-based metabolic protocols in patients with urea cycle defects to develop new tools to diagnose and manage the disorders. By understanding the underlying gene-nutrient interactions in these disorders, Dr. Lee and his colleagues may develop new strategies important for the nutritional management of both healthy and acutely ill children. The ultimate goal of Dr. Lee's research in this area is to translate information from these pathways into treatment, including gene replacement therapy, for urea cycle disorders.

Emmanuel J. Mignot, M.D., Ph.D. Stanford University School of Medicine Palo Alto, CA

Dr. Mignot and his colleagues are studying narcolepsy, a severe sleep disorder that usually manifests during a person's teens or early 20s. With little or no warning, a narcoleptic person feels irrepressibly sleepy and quickly falls into deep sleep.

In 1999, Dr. Mignot's research team and another group led by HHMI investigator Masashi Yanagisawa at the University of Texas Southwestern Medical Center converged on a faulty neuropeptide system that induced narcolepsy in dogs and mice. Dr. Mignot, whose group has been studying narcolepsy for more than a decade, showed that molecules, which they called hypocretins, were absent in the brain of patients with narcolepsy.

Dr. Mignot is now investigating whether narcolepsy is exacerbated by an autoimmune response against specific cells in the brain. The scientists are also studying the underlying pathophysiology of narcolepsy in two animal models, zebrafish and mice, and they are planning studies to map narcolepsy genes in humans. The studies underway in Dr. Mignot's laboratory may provide information that can improve the treatment of a number of sleep disorders that afflict humans.

Charles L. Sawyers, M.D. Jonsson Comprehensive Cancer Center David Geffen School of Medicine at the University of California, Los Angeles Los Angeles, CA

Dr. Sawyers is investigating how molecular abnormalities in leukemia and prostate cancers lead to abnormal growth and cellular transformation. The leukemia studies focus on signal transduction pathways involving the *Abl* gene. The c-Abl tyrosine kinase is involved in a chromosome translocation, which creates the *Bcr-Abl* oncogene in patients with chronic myelogenous leukemia (CML).

In collaboration with Dr. Brian Druker at Oregon Health and Science University (see above), Dr. Sawyers designed and conducted the phase I-II clinical trials of STI571 (Gleevec) for treatment of CML. Dr. Sawyers recently showed that resistance to STI571 occurs through mutation or amplification of the *Bcr-Abl* gene.

Building on the lessons learned in the development and clinical trials of STI571, Dr. Sawyers is now developing kinase inhibitor therapy for other cancers. Currently he is studying how the *PTEN* tumor suppressor gene restricts access to the Akt pathway, which regulates growth signals. When *PTEN* is mutated, the Akt pathway promotes rapid cell growth, which may lead to cancer. Since 1997, Dr. Sawyers and his colleagues have learned critical information about how PTEN and Akt interact. The studies may help identify the molecular changes that accompany a form of brain cancer called glioblastoma and prostate cancer, a disease that kills 40,000 men in the United States every year.

Robert F. Siliciano, M.D., Ph.D. The Johns Hopkins University School of Medicine Baltimore, MD

Dr. Siliciano's laboratory is searching for ways to prevent or treat HIV infection through the development of new vaccine or drug therapies. Combination drug therapy for HIV-1 infection can reduce the amount of virus in the blood to undetectable levels in many patients. However, Dr. Siliciano and his colleagues have shown that HIV-1 can persist in a silent, or latent, form in a long-lived population of memory T cells. Since this reservoir of HIV-1 decays very slowly, latent infection of these so-called memory CD4⁺ T cells provides a mechanism for lifelong persistence of HIV-1, even in patients on effective antiretroviral therapy.

A major goal of Dr. Siliciano's laboratory is to understand the mechanisms by which the latent T cell reservoir is established and maintained. This

information will aid in developing approaches for eradicating or containing the virus in CD4+ T cells. His group is also studying how drug therapy affects the evolution of HIV-1. HIV-1 can mutate rapidly to evade drug therapy, so understanding how to measure and control HIV-1 evolution may lead to improved treatment for HIV-1 infection.

Edwin M. Stone, M.D., Ph.D. University of Iowa Roy J. and Lucille A. Carver College of Medicine Iowa City, IA

Dr. Stone's research interests are in inherited eye diseases. He established the Molecular Ophthalmology Laboratory at the University of Iowa in 1987 to facilitate the diagnosis and treatment of human eye diseases. Since 1990, Dr. Stone has collaborated with HHMI investigator Dr. Val Sheffield at the University of Iowa in identifying the chromosomal location of genes that cause 14 different eye diseases and over 70 different mutations that cause a range of disease, including hereditary obesity, corneal dystrophies, vitreoretinopathy, optic neuropathy, deafness, and Pendred Syndrome.

Dr. Stone and his colleagues have also created the first international center for ophthalmic molecular diagnosis and have provided expert diagnostic assistance to physicians throughout the United State and fifteen foreign countries. The group has also initiated strategies to develop vectors for gene transfer to the eye for treatment of a variety of inherited eye diseases.

Bruce D. Walker, M.D. Harvard Medical School Massachusetts General Hospital Charlestown, MA

Dr. Walker and his colleagues are investigating the cellular immune response to human viral pathogens, particularly HIV-1, HIV-2, and hepatitis C virus. Numerous studies in mouse models of viral infection have shown that virus-specific cytotoxic T lymphocytes form a strong natural defense mechanism against viruses. Dr. Walker has been investigating the role of these cells in chronic human viral infections, and is particularly interested in translational studies to answer basic questions related to viral pathogenesis in humans.

Dr. Walker's group has focused their research efforts on persons in the earliest stages of HIV infection to determine how the immune system fights the virus during the initial encounter. In addition, they have followed a group of people who have been infected with HIV for more than two decades and yet remain well. This is a special group because their illness has not progressed despite the fact that they have never been treated with antiviral drugs. By understanding how the immune systems of these people effectively cope with the virus, the researchers hope to learn how to neutralize or kill HIV-infected cells, and how to boost immunity to viruses as a means of combating these infections.

As director of the Harvard Medical School Division of AIDS and of the Partners AIDS Research Center, Dr. Walker has actively encouraged collaboration within the AIDS research community at Harvard and abroad. He and his colleagues have initiated studies in Uganda to test candidate HIV

vaccines and have set up a fully functioning laboratory in Kampala to support these studies. Dr. Walker and his colleagues are also aiding several institutions in South Africa (Universities of Cape Town, Natal and Witwatersrand) to expand their immunology programs and to provide new opportunities for African scientists who are studying virology.

Christopher A. Walsh, M.D., Ph.D. Harvard Medical School Beth Israel Deaconess Medical Center Boston, MA

Dr. Walsh's laboratory is interested in the causes of mental retardation and epilepsy in children. Although these common conditions impact many children and their families, we know little about what causes them and in many cases lack specific diagnostic tests. Increasingly, children with mental retardation and epilepsy are being discovered to have abnormal development of the largest structure of the human brain, the cerebral cortex. The cerebral cortex, or "gray matter," is a folded sheet of neurons that forms a wrapping around the outside of the brain. Abnormal development of the cerebral cortex in humans can also result in autism, dyslexia and other learning disorders, and perhaps some psychiatric conditions as well.

By identifying the genes that are mutated in patients with disorders of brain development, Dr. Walsh and his colleagues are learning what proteins are involved, as well as where and how they function. For example, some of the gene mutations they have already identified result in brains that are too small, or abnormally patterned, or show accumulation of cortical cells in abnormal locations. The different disorders reflect the site of action and function of the genes involved, and other members of his lab study the function of these genes in normal development.

Dr. Walsh has ongoing collaborations with clinical geneticists and pediatric neurologists around the world to improve diagnosis of childhood brain disorders. His group is pioneering an "Internet Clinic," in which the clinical histories and magnetic resonance (MRI) images of patients are received via email. Dr. Walsh, a genetic counselor, neuroradiologists and other specialists then review the information. Working closely with the referring physician, Dr. Walsh and his colleagues refine the diagnosis, and in some cases work with the physician and family to obtain additional MRI images and obtain DNA samples for genetic mapping. The collaboration has led to the clinical description of more than a dozen new neurological syndromes whose genetic bases are currently being investigated.