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Background on Patient-Oriented Researchers Selected in the 2002 Competition

In 2002, the Howard Hughes Medical Institute (HHMI) completed its first competition dedicated to physician-scientists who conduct patient-oriented research. In that competition, 12 new HHMI investigators were selected from among 138 nominees. HHMI physician-scientists selected in the 2002 competition have identified new drug targets, developed new therapeutic agents, and improved our understanding of the genetic basis of disease.

Listed below are brief summaries of the research carried out by the 12 patient-oriented researchers selected by HHMI in 2002:

Robert B. Darnell, M.D., Ph.D. The Rockefeller University Darnell studies degenerative brain disorders that are provoked by the body's immune response to certain cancers. This work has permitted him to unravel how a factor in the brain regulates alternative splicing—which allows a single gene to give rise to multiple proteins—to influence synaptic function.

Brian J. Druker, M.D. Oregon Health and Science University Druker's search for a molecule that would block an enzyme that promotes chronic myelogenous leukemia (CML) and gastrointestinal stromal tumors led to the identification of the compound STI-571, commonly known as Gleevec. Druker played a key role in shepherding the drug through clinical trials in patients. Druker is now studying why some patients with CML develop resistance to Gleevec and why most patients on the drug have minute levels of cancer that linger after treatment ends.

Todd R. Golub, M.D. Dana-Farber Cancer Institute Golub and colleagues are developing new diagnostic tests for childhood leukemia. They are devising strategies for diagnosing the disease and predicting responses to cancer therapy based on gene activity present in tumor samples. Last year, Golub worked with HHMI investigators H. Robert Horvitz and Tyler Jacks to show that tiny RNA molecules known as microRNAs can serve as a powerful diagnostic tool for cancer.

Katherine A. High, M.D. The Children's Hospital of Philadelphia High studies the molecular basis of blood clotting and has showed that gene therapy can achieve long-term improvement in dogs with hemophilia. High's

team has developed a virus to deliver the gene for factor IX, critical for blood clotting, to patients with severe hemophilia B. She is currently exploring ways to modulate a patient's immune response long enough for the virus to deliver the gene safely to a patient's cells.

Helen H. Hobbs, M.D. University of Texas Southwestern Medical Center at Dallas Hobbs is defining the genetic factors responsible for differences in blood cholesterol levels. Her discovery and characterization of genetic defects causing both high and low levels of cholesterol has led to the identification of new drug targets for the treatment of high cholesterol. Hobbs is also principal investigator for the Dallas Heart Study, which looks for behavioral, environmental, metabolic, and genetic risk factors for cardiovascular disease in a population of 3,000 individuals in the Dallas metro area.

Brendan H. Lee, M.D., Ph.D. Baylor College of Medicine Linking studies on mammalian tissue and organ development with clinical research in patients with skeletal malformations, Lee hopes to understand the consequences of gene mutations on craniofacial/limb development. His recent work has identified a gene responsible for some cases of brittle bone disease. Lee and colleagues are also investigating gene-nutrient interactions which can lead to brain damage and death in patients who have disorders in the urea cycle.

Emmanuel J. Mignot, M.D., Ph.D. Stanford University School of Medicine Mignot and his colleagues are studying sleep disorders, focusing primarily on narcolepsy, which causes those afflicted to fall into a deep sleep with little or no warning. Their goal is to discover the cause of sleep disorders so they can design ways to treat them, not just their symptoms. He is investigating whether narcolepsy is exacerbated by an autoimmune response against specific cells in the brain.

Charles L. Sawyers, M.D. University of California, Los Angeles Sawyers collaborated with Brian Druker to design and conduct the clinical trials of STI-571 (Gleevec) for treatment of chronic myelogenous leukemia (CML). His work demonstrating the molecular basis for resistance to Gleevec aided the identification and development of a new drug, dasatinib (Sprycel), which was granted accelerated approval by the Food and Drug Administration in 2006 for the treatment of patients with resistance or intolerance to prior CML treatment. Sawyers continues to search for new therapeutic targets for treatment of prostate cancer and a form of brain cancer called glioblastoma.

Robert F. Siliciano, M.D., Ph.D. The Johns Hopkins University School of Medicine Siliciano is searching for ways to prevent or treat human immunodeficiency virus (HIV) infection. He and colleagues have shown that HIV-1 can persist in a silent form, even in patients who are being treated with an effective antiretroviral therapy. Siliciano hopes to understand the molecular mechanisms that cause this viral persistence, and thereby design a means to eradicate the virus.

Edwin M. Stone, M.D., Ph.D. University of Iowa Roy J. and Lucille A. Carver College of Medicine Stone collaborated with HHMI investigator Val Sheffield to identify the chromosomal location of genes that cause 14 different eye diseases. He continues to focus on finding and characterizing genes that contribute to macular degeneration, glaucoma, and photoreceptor degeneration. In an effort to bring genetic discoveries to the clinic as rapidly as possible, Stone and his colleagues at the University of Iowa created the first international center for molecular diagnosis of eye diseases.

Bruce D. Walker, M.D. Harvard Medical School, Massachusetts General Hospital Walker's group is studying people who live with human immunodeficiency virus (HIV) infection without developing AIDS, even though they have not been treated with antiviral drugs. By learning how the immune system of these individuals is able to fend off the virus, researchers may be able to use that knowledge to boost immunity in patients with AIDS. Working primarily with well-defined patient populations in the United States and South Africa, Walker is focusing on speeding translation of research advances to the clinical setting.

Christopher A. Walsh, M.D., Ph.D. Harvard Medical School, Beth Israel Deaconess Medical Center Walsh's lab is interested in the genes that control the development and function of the human cerebral cortex. Walsh collaborates with clinical geneticists and pediatric neurologists around the world to improve diagnosis of childhood brain disorders. His work has identified some of the genes thought to influence the size of the human brain.