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HHMI Expands Support of New Physician Scientists

Each year United States medical schools graduate thousands of newly-minted physicians. Yet only a small number of these physicians pursue careers in academic research. The reasons for this outcome are many, but two in particular rank at the top of the list every year: Lack of financial support and insufficient time for research.

Long a supporter of physician-scientists, the Howard Hughes Medical Institute (HHMI) has decided to focus expanded resources on a cadre of physicians who demonstrated an early interest in research by taking time off from medical school to spend a year or more in the lab. Each year, alumni of the HHMI-National Institutes of Health Research Scholars Program and the HHMI Research Training Fellowships for Medical Students are invited to apply for Early Career Awards as they begin their careers as physician-scientists. This year, HHMI has increased the number, size, and duration the grants.

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"Physician-scientists are uniquely positioned to translate research discoveries into direct benefits for patients," said Peter J. Bruns, vice president for grants and special programs at HHMI. "The research these talented young scientists are doing has the potential to have a tremendous impact on public health."

With its newest group of awardees, the Institute is investing \$7.5 million to help ensure that promising physician-scientists have the resources they need to launch their careers. The 20 awardees selected this year will receive

\$375,000 over a five-year period. When the Institute announced its first early-career awards in 2006, 13 grantees received \$150,000, awarded over a three-year period.

The funds must be used for direct research expenses and are meant to provide resources during a critical time for scientists: once they have completed their mentored training and are working toward establishing and obtaining funding for their own laboratories. The recipients' institutions must agree to let the young physician-scientists, who are in tenure-track positions, spend at least 70 percent of their time doing research.

“These awards support young investigators at a very precarious point in their academic careers,” said William Galey, program director for HHMI's graduate education and medical research training programs. “It's a time when they have to make a decision as to how much science they will do. It's not easy to go back and do science once you've started down the clinical path, so it's really important to get a good solid footing early in your career. These awards help protect physician-scientists from the demands of clinical service, and allow them the time and funds to do science.”

Applications were reviewed by a panel of leading physician-scientists. In evaluating each applicant's ability and promise for a research career, the panel considered the quality and quantity of formal research training, the commitment of the applicant's research institution, the quality of the research environment, the applicant's commitment to pursuing a biomedical research career, and the quality of the proposed research plan.

The early-career awards complement several other HHMI programs that aim to encourage individuals with medical training to pursue research careers. The Research Scholars Program makes it possible for medical and dental students from around the country to spend a year living and working at the NIH, while the Medical Fellows Program enables students to conduct research at other institutions.

The Institute also supports physician-scientists through its investigator program, which gives outstanding, creative scientists the freedom and support to pursue innovative research. As many as 15 additional physician-scientists are expected to be named HHMI investigators in the fall of 2007.

The new awardees are:

Nicholas Boulis, M.D. Emory University School of Medicine Atlanta, GA
Medical Fellows Program Alumnus To modulate neuronal function to treat disorders such as pain, spasticity, and epilepsy, surgeons must implant electrodes in the brain. Boulis, a neurosurgeon, is working to develop more

precise alternatives. He is striving to create methods to manipulate neural activity by delivering genes directly to neurons. Boulis is currently developing viral vectors that deliver genes to motor neurons to control spasticity.

Katherine Crew, M.D. Columbia University College of Physicians and Surgeons New York, NY Research Scholars Program Alumna Recent research suggests that vitamin D may influence the development of breast cancer. Crew plans to evaluate whether high doses of vitamin D can reduce breast density - an important predictor of breast cancer risk - in women who are at elevated risk for the disease. The results of her study may be valuable in designing a larger clinical trial to evaluate vitamin D's effectiveness in preventing breast cancer.

Sarah Fortune, M.D. Harvard University School of Public Health Boston, MA Medical Fellows Program Alumna Fortune studies the protein secretion system ESX-1, which is required for *Mycobacterium tuberculosis* to infect its host. Her HHMI award will allow her to test the hypothesis that the bacteria that cause tuberculosis release their virulence factors into a host cell, thereby allowing the bacteria to co-opt the infected host. Her research will focus on characterizing the genes that contribute to tuberculosis infection through this secretion system, with the long-term aim of helping to reveal how pathogens manipulate their hosts.

Paul J. Galardy, M.D. Mayo Clinic Rochester, MN Research Scholars Program Alumnus Cells use the protein ubiquitin to tag proteins and modify their function, change their location, or direct them towards degradation. This system regulates several important cellular processes, including cell division—a key part of tumor development. Galardy intends to study how changes in the enzymes that remove ubiquitin tags can influence tumor growth, with the ultimate goal of generating new drug targets for childhood cancers.

Aram Hezel, M.D. (*2006 awardee) Massachusetts General Hospital Boston, MA Medical Fellows Program Alumnus Hezel is investigating how inhibiting a signaling pathway known as TGF-beta can affect the growth and metastasis of pancreatic tumors. Using animal models and human cancer cells, he will evaluate molecules that interfere with the TGF-beta pathway and their specific effects on cells. He also plans to develop methods to assess the pathway's activity in patients with metastatic disease, to identify which patients are the best candidates for treatment with TGF-beta inhibitors.

Farouc Jaffer, M.D., Ph.D. Massachusetts General Hospital Boston, MA Research Scholars Program Alumnus Activation of the transcription factor PPAR-gamma may reduce the inflammation associated with atherosclerosis, the narrowing of arteries caused by excessive buildup of fatty substances. Using in vivo molecular magnetic resonance imaging and optical imaging technology, Jaffer will investigate how PPAR-gamma activation affects the immune cells and specific molecules that contribute to inflammation.

Eric Johannsen, M.D. Brigham and Women's Hospital Boston, MA Medical Fellows Program Alumnus Epstein-Barr herpesvirus (EBV) rarely replicates in cells in which it has established an infection. Instead, EBV expresses proteins that cause cells to divide, increasing the number of EBV infected cells and occasionally causing cancer. Anti-herpesvirus drugs, which target viral replication, are of no clinical value in treating EBV-associated malignancies. Johannsen's research provides evidence that LF2, a protein produced by the virus, is responsible for inhibition of EBV replication in cells. Further studies of LF2 could help explain the mechanism by which LF2 blocks Epstein-Barr virus replication and identify drugable targets in EBV-infected cells.

Aarif Khakoo, M.D. University of Texas-MD Anderson Cancer Center Houston, TX Medical Fellows Program Alumnus Khakoo, a cardiologist, will pursue research based on the clinical observation that some patients receiving the cancer drugs sunitinib and imatinib develop heart disease. Sunitinib and imatinib impair tumor growth by blocking the effects of proteins that help tumor cells divide and promote the growth of blood vessels that nourish these tumors. Khakoo plans to follow up on this clinical observation by investigating the possibility that one of these proteins, PDGFR, helps the heart communicate with arteries into which it pumps blood.

Nerissa Ko, M.D. University of California, San Francisco, School of Medicine San Francisco, CA Research Scholars Program Alumna Ko, a neurologist, plans to investigate the causes of cerebral vasospasm, a narrowing of a blood vessel in the brain that is a common and often fatal complication of subarachnoid haemorrhage. Ko will focus on how variations in the gene for endothelial nitric oxide synthase, an enzyme that synthesizes nitric oxide in blood vessels, affect blood flow and clinical outcomes in patients. The ultimate goals of Ko's research are to help clinicians predict which patients are at risk and to identify targets for new therapies.

Ross Levine, M.D. Memorial Sloan-Kettering Cancer Center New York, NY Medical Fellows Program Alumnus Levine studies myeloproliferative diseases, blood disorders caused by an overproduction of blood cells in the bone marrow. In the lab of HHMI investigator Gary Gilliland at Brigham and Women's Hospital, he helped identify a single point mutation on a gene known as *JAK2* that can be blamed for three different leukemia-like diseases. Not all patients with myeloproliferative diseases, however, have this mutation. Levine plans to search for other mutations that might have similar effects, with the goal of better understanding how these diseases develop and identifying potential targets of new therapies.

Emanuel Maverakis, M.D. University of California Davis School of Medicine Davis, CA Medical Fellows Program Alumnus Autoimmune diseases like rheumatoid arthritis, multiple sclerosis, and lupus are caused when the immune system attacks the body's "self" proteins. Maverakis studies how these self-reactive pathogenic T-cell responses are initiated, driven, and controlled. He is designing new technologies to study these

autoreactive T cells inside the body. He is also screening novel molecules for their ability to inhibit the immune system, with the ultimate goal of finding new pathways to control pathogenic immune responses. For example, he has found that a fragment of the protein fibrinogen, which participates in blood clotting and wound healing, can counteract autoimmune diseases in animal models.

Sridhar Ramaswamy, M.D. Massachusetts General Hospital Cancer Center Boston, MA Research Scholars Program Alumnus Ramaswamy will investigate how mesenchymal cells - which develop from the middle layer of an embryo and are found in most human tumors -- influence tumor growth and development. He wants to create mesenchymal cell lines with different genetic profiles and monitor their effects on the growth, survival, and differentiation of human epithelial cancers. The results of his studies should provide new information about the signals these cells emit that drive cancer progression. Ramaswamy intends to apply information from this study towards a better understanding of how cancer spreads.

Vicente Resto, M.D., Ph.D. University of Texas Medical Branch Galveston, TX Medical Fellows Program Alumnus Tumors that spread from their original sites to lymph nodes are often more aggressive and least responsive to therapy. Resto is investigating how head and neck tumors metastasize to lymph nodes. He will focus on identifying glycoproteins on the surface of tumor cells that interact with proteins on lymphocytes (cells found in the lymph nodes), and then determine whether expression of these glycoproteins correlates with lymph node metastasis and clinical outcomes in patients.

Manish Sagar, M.D. Brigham and Women's Hospital Boston, MA Research Scholars Program Alumnus Sagar is working to develop a live virus vector for treatment against HIV infection. The hepatitis GB-C virus is not known to cause disease in humans, and can stay in the body for a long period of time after infection. Previous studies have shown that AIDS develops more slowly in HIV seropositive patients who are simultaneously infected with the GB-C virus. Before Sagar explores the possibility of a GB-C virus-directed AIDS vaccine, he will attempt to better understand the pathophysiology of GBV-C such as identifying the host cell receptor or receptors that GBV-C uses to enter the body.

Sean Savitz, M.D. Beth Israel Deaconess Medical Center Boston, MA Medical Fellows Program Alumnus The chemical necrostatin inhibits necrosis, such as occurs in the brain during a stroke. Savitz is working to develop necrostatin as a therapy for stroke and in combination with the only approved agent for stroke, tissue plasminogen activator. His goal is to develop a therapy that will protect patients from brain cell death after they suffer a stroke. These studies will be done using animal models, including animals with diabetes and hypertension, common conditions in stroke patients.

Costi Sifri, M.D. University of Virginia Health Sciences Center
Charlottesville, VA Research Scholars Program Alumnus The roundworm *C. elegans* is susceptible to many of the same pathogens that infect humans. Sifri is taking advantage of this fact to study pathogenesis and immunity using the worm as model organism to study staph infection. Using RNA interference - a method of shutting off specific genes with small bits of RNA - he will search for genes that control infection with *Staphylococcus aureus*, with the expectation that related genes may be involved in controlling staph infection in humans.

Jonathan Stiber, M.D. Duke University Medical Center Durham, NC
Research Scholars Program Alumnus Stiber is investigating how a protein called Homer influences muscle function. The protein regulates channels in muscle cells that are activated by mechanical stretch. By better understanding Homer's role in converting mechanical forces into biochemical changes inside cells, Stiber hopes to aid the development of new treatments for cardiac hypertrophy, cardiomyopathies, and muscular dystrophy.

Charlotte Sumner, M.D. Johns Hopkins University School of Medicine
Baltimore, MD Research Scholars Program Alumna The inherited motor neuron disease spinal muscular atrophy (SMA) results from deficiency of a widely expressed protein called survival motor neuron (SMN) protein. Sumner's research suggests that intrinsic abnormalities in the development of muscle contribute substantially to the pathogenesis of SMA. To further investigate this possibility, Sumner will evaluate different stages of myogenesis in cells that lack SMN, test whether reintroducing the protein to muscle cells will improve the condition of mice with SMA, and explore the potential benefits of muscle-directed therapy in animal models.

Matthew Walter, M.D. Washington University School of Medicine St. Louis, MO Research Scholars Program Alumnus Myelodysplastic syndromes are blood disorders that result from blood cells failing to develop properly. Scientists have narrowed down a region within chromosome 5 that is critical in the disorder, but they have not yet identified the specific genes involved. Walter intends to characterize and identify all of the genes within this region that contribute to myelodysplastic syndromes.

Rebekah White, M.D. Duke University Durham, NC Medical Fellows Program Alumna White wants to find out whether interfering with a protein known as angiopoietin-2, which helps regulate the growth and stability of blood vessels, can alter tumors' sensitivity to radiation therapy. White and her colleagues have designed an RNA ligand that specifically inhibits angiopoietin-2, and will test its effects on human pancreatic tumors, both with and without radiation.

Allan Wu, M.D. University of California, Los Angeles David Geffen School of Medicine Los Angeles, CA Research Scholars Program Alumnus Wu wants to understand how the brain balances the body's needs for speed and accuracy as it controls movement. Using functional magnetic resonance

imaging, he will evaluate brain activity in two selected brain regions thought to govern distinct aspects of motor control. He will also study how stimulating these regions, using the non-invasive technique of transcranial magnetic stimulation, can alter motor behavior. Wu hopes that a better understanding of how the brain controls movement will be a foundation for designing interventions for Parkinson's disease and other movement disorders.