DEPARTMENT OF HEALTH AND HUMAN SERVICES NATIONAL INSTITUTES OF HEALTH

Fiscal Year 2012 Budget Request

Witness appearing before the

Senate Subcommittee on Labor-HHS-Education Appropriations

Susan B. Shurin, M.D., Acting Director National Heart, Lung, and Blood Institute

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Mr. Chairman and Members of the Committee:

I am pleased to present the President's budget request for the National Heart, Lung, and Blood Institute (NHLBI) of the National Institutes of Health (NIH). The Fiscal Year (FY) 2012 budget of \$3,147,992,000 includes an increase of \$80,903,000 over the comparable FY 2011 level of \$3,067,089,000.

The NHLBI provides global leadership for a research and education program to promote prevention and treatment of heart, lung, and blood diseases. Our vision is to enhance the health of all individuals and thereby enable them to enjoy longer and more productive lives. The Institute advances its objectives through an innovative program of excellent science that addresses urgent public health needs, capitalizes upon extraordinary opportunities, leverages strategic assets, balances and integrates basic and clinical research approaches, and calls upon the creativity, expertise, and dedication of thousands of scientists here and abroad. The American people have generously supported this work for many years, and tremendous progress has resulted.

This testimony highlights three areas of particular current emphasis: 1) Genetics and Genomics; 2) Regenerative Medicine; and 3) Translational Medicine.

GENETICS AND GENOMICS

NHLBI-funded gene-sequencing projects and genome-wide association studies have been extraordinarily productive. Scanning the genomes of more than 100,000 people from all over the world, scientists recently reported the largest set of genes yet discovered that underlie blood lipid variations known to be major risk factors for coronary heart disease. Altogether, the gene variants explain between one-quarter and one-third of the inherited portions of cholesterol and triglyceride measured in the blood. Of the variants, 59 had not been previously identified and thus provide new clues for developing effective medicines to combat heart disease. This exciting discovery follows upon similar research, reported in 2009, regarding another heart disease risk factor—hypertension. Using genomic analysis of over 29,000 participants from the Framingham Heart Study and other cohorts, an international research team identified a number of unsuspected genetic variants associated with systolic and diastolic blood pressure. Although hypertension has long been known to run in families and have a substantial genetic component, previous attempts to identify genes associated with blood pressure had met with only limited success. The new findings from both the lipid and the blood pressure studies illustrate the potential of large-scale genome-wide scans to identify genes that play roles in a complex disease of widespread public health importance.

Smaller-scale genome-wide scans are also providing valuable new information about less common disorders, such as thoracic aortic aneurysm and dissection—a condition that is often asymptomatic until an unpredictable catastrophic cardiovascular event occurs. Researchers comparing 418 patients with non-familial thoracic aneurysms to normal controls identified a number of genetic variants that appeared more frequently in the patients. Many of the variants exist in genes that are in some manner involved in contraction of smooth-muscle cells, suggesting that genetic variants governing smooth-muscle–cell function are a potential target of predictive tests that could be developed in the future.

Although genome-wide scans and sequencing have identified many genetic variations that contribute to disease risk, much more research is needed to understand the mechanisms underlying gene–disease associations. NHLBI is advancing this area by supporting a new program, *Next Generation Genetic Association Studies*, to investigate cells that have been reprogrammed into induced pluripotent stem cells to model heart, lung, and blood diseases and explore the functional consequences of genetic variation.

Another initiative, *Getting from Genes to Function in Lung Disease*, will support characterization of the function of lung-disease–associated genes and their variants that have been identified through GWAS or other genetic approaches. Multidisciplinary teams will use a variety of experimental methods and tools to elucidate the mechanisms that contribute to diseases such as asthma, chronic obstructive pulmonary disease (COPD), sarcoidosis, and idiopathic pulmonary fibrosis and thereby generate knowledge that may lead to more effective ways to prevent and treat them. In fiscal year 2012, the Institute plans to solicit research projects to study two severe and poorly understood conditions that affect the lungs: The *Genomic Research in Alpha-1 Antitrypsin Deficiency and Sarcoidosis* program will conduct state-of–the-art genomic, microbiomic, and phenotypic studies with the goals of understanding the molecular and cellular bases of the diseases, facilitating classification of sub-types, and developing new drug therapies.

Because genome-wide scans are not well suited to discovery of extremely uncommon genetic variants, the Institute is pursuing other avenues to explore the contributions of infrequent variants to both common and rare diseases. A program planned for fiscal year 2012 in collaboration with the National Human Genome Research Institute, *Life After Linkage: The Future of Family Studies*, will use data from existing family studies to identify and characterize genes, including rare variants, that influence complex diseases. The potential success of such an approach is illustrated by a recent breakthrough resulting from a collaboration between the NHLBI intramural program and the NIH Undiagnosed Diseases Program. Researchers identified the genetic cause of a rare and debilitating vascular disorder, not previously explained in the medical literature, that involves severe arterial calcification. Analysis of DNA from members of three affected families revealed that the variant is in a gene responsible for a product that protects arteries from calcifying. It is hoped that this understanding of the underlying defect will enable discovery of improved treatment for the patients.

REGENERATIVE MEDICINE

Body components can malfunction because of inherent defects, catastrophic or accumulated damage, or senescence, and chronic disease is often the result. Restoring healthy function via delivery of "replacement parts" and helping organs repair injury with functional tissue instead of scarring are high priorities of NHLBI. Recent progress gives much reason for optimism. For example, heart attacks cause permanent damage to heart muscle cells (cardiomyocytes) that renders them useless for pumping blood. Although cardiomyocytes cannot themselves be rejuvenated, NHLBI-supported scientists were able to induce other heart cells (fibroblasts) to become pluripotent stem cells that, in turn, were induced to become cells that looked and behaved much like cardiomyocytes. The finding suggests the possibility that fibroblasts—cells widely available throughout the body—could be directly reprogrammed into functional cells to treat or prevent heart failure and other adverse consequences of cell damage. Other NHLBI-supported researchers recently reported progress toward engineering lung tissue in a rat model, creating a scaffold populated with multipotent neonatal rat cells to produce a transplantable organ capable performing the fundamental lung function of gas exchange. The success of this study and others using cadaveric human lung tissue and immortalized cell lines suggests that such an approach might one day be beneficial for patients who are awaiting lung transplant.

NHLBI is making considerable investments to advance regenerative medicine research for cardiovascular, lung, and blood diseases. A collaborative solicitation with the National Institute of Biomedical Imaging and Bioengineering, *New Strategies for Growing 3D Tissues*, will support highly integrated, multidisciplinary research to improve understanding of how cells respond to their environment and how cell-communication systems that enable blood-vessel and organ development can be used to engineer 3D human cellular aggregates. *Translation of Pluripotent Stem Cell Therapy for Blood Diseases* will promote the development of technologies for translation of recent stem cell advances into treatments for sickle cell disease and other blood disorders. This new program will build upon the expertise, resources, and infrastructure of the ongoing NHLBI Progenitor Cell Biology Consortium, and it will encourage collaboration with two other Institute initiatives—Production Assistance for Cellular Therapies and the Gene Therapy Resource Program, which is slated for renewal in fiscal year 2012.

A major initiative planned for fiscal year 2012, *Consortium of Lung Repair and Regeneration: Building the Foundation*, will establish an interactive group of multidisciplinary teams to formulate and test innovative hypotheses about the mechanisms that control lung repair and regeneration. The program will seek to leverage innovative technologies such as tissue engineering, biomaterials and scaffolds, induced pluripotent stem-cell technology, cell-directed therapy, and humanized animal models that are not used widely in lung-regeneration research but are being applied to investigate regeneration and repair in other organ systems.

TRANSLATIONAL MEDICINE

NHLBI continues to place strong emphasis on translating basic science findings into better diagnostic, therapeutic, and preventive approaches and fostering their use in real-world clinical practice. A number of initiatives are supporting these efforts. For example, a program called Science Moving Towards Research Translation and Therapy (SMARTT) has been launched to facilitate transition of potential new therapies for heart, lung, and blood diseases from discovery in the lab to the testing needed to establish their safety and effectiveness in people. Pre-clinical development that is, readying products for testing in humans—is the first step in turning discoveries into cures, but the processes involved can be expensive and baffling to academic scientists. Connecting academic researchers with industry, the SMARTT program will offer help with manufacturing, pharmacology and toxicology testing, pre-clinical and early-phase clinical study design, and administrative and regulatory matters.

The Translational Research Implementation Program, or TRIP, is intended to facilitate well-designed clinical trials in heart, lung, or blood diseases to demonstrate the safety and efficacy of promising interventions that have emerged from fundamental studies. Its initial phase, which began in fiscal year 2010, supported the planning of trials; the second phase will fund the most promising of them beginning in fiscal year 2012. A second new program will provide planning grants to establish the feasibility of pivotal clinical trials with a major focus on hemoglobinopathies such as sickle cell disease and thalassemia. Another solicitation, planned for fiscal year 2012, would provide an innovative mechanism for the development of clinical trials for hemostatic and thrombotic disorders, including access to expertise in clinical trial methodology and design through existing institutional resources.

Several exceptionally promising new translational efforts in lung diseases are also under way. *Research Education in Sleep and Circadian Biology* is promoting the use of innovative educational tools and programs to accelerate the transfer of recent scientific advances and health knowledge in sleep and circadian biology into clinical and public-health practice. Renewal of a solicitation titled *Utilization of a Human Lung Tissue Resource for Vascular Research* will advance translational efforts in lung vascular disease, using previously collected biospecimens from patients with pulmonary hypertension. An initiative slated for fiscal year 2012 would support dosing and efficacy trials of promising but untested therapies for lung diseases, including agents that have already been approved for use in treating other diseases and combinations of common drugs with low toxicities, neither of which would be likely candidates for testing by industry. Such small proof-of-concept trials are vitally important for translating basic research advances into clinical research, providing a foundation for larger efficacy trials, and advancing understanding of disease processes.

Susan B. Shurin, M.D., Acting Director National Heart, Lung, and Blood Institute

Susan B. Shurin, M.D., is the Acting Director, National Heart, Lung, and Blood Institute (NHLBI). She joined NHLBI in 2006 as the Deputy Director, and has been Acting Director since December 2009. She is responsible for the scientific and administrative management of the intramural and extramural activities of the NHLBI, and oversight of the Institute's clinical research portfolio. Dr. Shurin represents NHLBI in activities across the National Institutes of Health (NIH) and the Department of Health and Human Services. NHLBI, the third largest of the 27 Institutes and Centers at NIH, has an annual budget of over \$3.1 billion, and manages a complex portfolio of basic, clinical, translational and epidemiologic research. Instituteconducted research takes place on the campus in Bethesda, MD and in Framingham, MA. The bulk of the Institute's resources are allocated to support extramural research across the US and across the globe. Dr. Shurin is engaged in multiple trans-NIH research and administrative activities, and in global health research on noncommunicable diseases.

Before joining the NHLBI, Dr. Shurin was professor of Pediatrics and Oncology at Case Western Reserve University; director of Pediatric Hematology-Oncology at Rainbow Babies and Children's Hospital; director of Pediatric Oncology at the Case Comprehensive Cancer Center; and vice president and secretary of the Corporation at Case Western Reserve University in Cleveland, Ohio. Dr. Shurin received her education and medical training at Harvard University and the Johns Hopkins University School of Medicine. Her laboratory research focused on the physiology of phagocyte function, recognition and killing of pathogens; mechanisms of hemolysis; and iron overload. She has been active in clinical research in many aspects of pediatric hematology-oncology, including participation in the Children's Cancer Group, Children's Oncology Group, multiple studies in sickle cell disease and hemostasis. She has had leadership roles in multiple professional organizations.