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Baltimore, Maryland**

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Introduction

Mr. Chairman and members of the Committee, thank you very much for inviting me to testify today at this important hearing. I am Robert Siliciano, and I am a member of the Department of Molecular Biology and Genetics at the Johns Hopkins University School of Medicine.

Let me start by commending you, Mr. Chairman and Senator Specter, for your efforts and foresight in doubling the National Institutes of Health (NIH) research budget between 1998 and 2003. Many of the amazing advances in health care treatment today are the result of federal investment in research identifying early indicators and causes of diseases. I am convinced we are on the cusp of a dramatic transformation in health care, which is a direct result of the nation's investments in health science discovery and cures. My fellow researchers on the panel and I are pleased to be here today to tell you about this transformation.

On behalf of myself and all my colleagues at Johns Hopkins, I would like to recognize the persistence of many on this committee for your ceaseless support of NIH's work. I would also take this opportunity to invite you to visit our campus in Baltimore to see for yourselves the exciting work that my colleagues and I - not to mention our students - engage in every day. You will find no more persuasive argument for the value of investing in research than witnessing innovation firsthand.

NIH Support for My Work on HIV/AIDS

Early in the AIDS epidemic, an AIDS patient could expect to enter hospice care within a few years after the diagnosis. However, significant research developments in the area of “Highly Active Anti-Retroviral Therapy,” or HAART – that combination of drugs commonly referred to as the “AIDS cocktail” has led to increasing the survival rate of those diagnosed with HIV. This therapy involves a variety of drugs that attack the virus at different stages of its life cycle, thus reducing its ability to replicate itself in healthy cells. HAART combines drugs that were developed during some of the first stages of AIDS research. By 1990, monotherapy – treatment using one nucleoside analog – was showing some promise, but debate persisted in the research community as to which of this class of drugs were the most useful. In 1995, studies showed that treatment with simultaneous use of two nucleoside analogs would prove more effective in prolonging life. By 1997, combination therapy had expanded to include protease inhibitors and non-nucleoside reverse transcriptase inhibitors, both classes of drugs that attack HIV as it attempts to insinuate itself into healthy cells.

The result of HAART has been the transformation of AIDS from a disease that meant rapid and certain death to a chronic condition that can now be managed over a patient’s lifetime. When widespread use of HAART began in the mid 1990s, U.S. mortality rates immediately plummeted – from nearly 41,000 in 1995 to 17,000 in 1997. HAART even proved effective for patients who had already reached the terminal stages of the disease; many were able to leave hospice care and return to relatively normal lives.

For the more than 40 million people infected with HIV, the best current hope for avoiding the fatal consequences of the infection lies in treatment with HAART. The benefits of HAART in reducing mortality are clear, but major questions remain about how best to use HAART and how to make it available to all who need it.

Our work has shown that current HAART regimens cannot cure the infection in most patients because the virus persists in a very stable latent reservoir in resting memory CD4⁺ T cells (cells that control the activities of all of the other cells). Because HAART is not curative, treatment of

HIV infection is a lifelong challenge. Most infected individuals will ultimately have to depend upon HAART to avoid fatal immunodeficiency. Problems of drug resistance and drug toxicity make this an alarming prospect.

My lab is interested in understanding viral persistence and in applying basic studies of viral dynamics in HIV infection to optimizing antiretroviral therapy. Our work on viral persistence began in 1994, with the idea that the capacity of HIV to establish a state of silent or latent infection at the level of individual cells might provide a mechanism for viral persistence in the face of immune responses and antiretroviral therapy. We hypothesized that HIV might capitalize on an extremely fundamental aspect of the immune system, immunologic memory, to ensure its persistence in the host.

At any given time, most of the lymphocytes in the body are in a resting state. When a lymphocyte encounters a bacterial or viral protein that it is programmed to recognize, it becomes activated and begins to proliferate, generating effector cells that eliminate the invading microorganism. Most of these effector cells die, but some survive and return to a resting state as memory cells. These cells persist indefinitely, allowing effective responses to future challenges with the relevant microorganism.

HIV preferentially infects activated CD4⁺ T lymphocytes, inserting its genetic information into the genome of the host cells and directing the production of new virus particles in a process that usually leads to the death of the infected cells. However, a small subset of the activated CD4⁺ T cells that are infected with HIV survive long enough to revert back to a resting memory state. Because the expression of HIV genes depends on host transcription factors induced in activated T cells, viral gene expression is automatically extinguished when these cells return to a quiescent state. The result is a stably integrated but transcriptionally silent form of the HIV genome in a memory T cell, a cell whose function it is to survive for years in a quiescent state. Upon subsequent re-exposure to the relevant microorganism, the latently infected cell is reactivated and becomes competent for HIV gene expression and virus production. Over the past several years, we have been able to demonstrate the presence and persistence of latently infected resting memory CD4⁺ T cells with integrated HIV DNA in infected individuals. The cells are present

only at low frequencies, reflecting the fact that most productively infected CD4⁺ T cells die before they can revert back to a resting memory state. Particularly important is whether this small reservoir of latent virus persists in patients on HAART. In the years following the advent of HAART, which began in the mid-1990s, there was considerable optimism that virus eradication might be possible with prolonged treatment, based on analysis of the rapid decay of plasma virus to undetectable levels following the initiation of HAART.

We have shown, however, that the frequency of latently infected cells does not decrease even in patients on HAART who have had suppression of viremia to undetectable levels for as long as seven years. As a result of this discovery in 1999, the overall approach to the treatment of HIV infection has significantly changed. In particular, it became more conservative. Patients were no longer started on therapy as soon as they were diagnosed. Initiation of therapy was delayed until later stages of disease, since there was no hope of eradication. This work raised the possibility that the virus could persist indefinitely in all patients on HAART, leading many investigators to question the wisdom of beginning aggressive therapy with the goal of eradicating the infection, particularly in light of the substantial long-term toxicities of HAART regimens.

Several additional findings add to the seriousness of the problem presented by the latent reservoir. We have shown that this reservoir is a permanent archive for drug-resistant viruses that are generated by inadequate treatment. Once drug-resistant viruses have entered the reservoir, they persist there indefinitely, permanently restricting the patient's therapeutic options. The problem of stored drug-resistance mutations is particularly severe in the case of perinatally infected children, who face a lifetime of treatment.

In 2000, we demonstrated the presence and persistence of this latent reservoir in these children. In addition, we have demonstrated that latency operates at the transcriptional level. Latently infected cells carry integrated HIV DNA but contain little translatable HIV RNA. Unfortunately, the last hope for detecting and targeting latently infected cells was that the cells might be expressing low levels of particular viral proteins, allowing recognition by immune effector mechanisms. It now appears that we may be dealing with a completely silent form of latent

infection that will be difficult to target with antiretroviral drugs or HIV-specific immune responses. These findings apply not only to children but to all HIV patients.

In 2001, we became interested in understanding the nature of the low-level virus production that continues in patients on HAART whose plasma virus levels are below the limit of detection of standard assays. We have developed methods for cloning and characterizing the extremely low levels of plasma virus that are present in such patients. We have shown that this virus is generally archival in nature, is devoid of new drug-resistance mutations, and may be derived from the activation of latently infected cells. Most importantly, we do not see evidence for the continued evolution of drug resistance in most patients on suppressive HAART regimens. This provides a counterpoint to our disheartening findings on the stability of the latent reservoir. Although current HAART regimens cannot produce eradication because of the extraordinary stability of the latent reservoir, they can largely halt virus evolution, affording patients the possibility of lifelong suppression of viremia if the problem of drug toxicity can be overcome.

It is important to point out that despite the spectacular advances that have been made in anti-retroviral therapy - at least 3 million years of life have been saved in United States alone - the definitive study that would allow us to determine when exactly treatments should commence may not be funded because of insufficient funds for vaccine and treatment trials. An unfortunate tension exists due to this competition for diminishing NIH dollars.

It is also worth pointing out that the discoveries our community of researchers have made extend well beyond HIV. What we have learned from studies of HIV can be applied to other viruses. For example, we have learned how to measure the amount of virus in the blood. This knowledge, which has provided us with a real-time measure of the amount of viral replication in a patient, along with the importance of utilizing it to treat viruses such as influenza and Hepatitis B and C, has revolutionized the success of these treatments.

In the future, we hope to address several critical questions related to the molecular mechanism of HIV latency and the clinical implications of this form of viral persistence. We are interested in whether it will ever be possible to eliminate this reservoir. Furthermore, we hope to translate our

findings on mechanisms of viral persistence into new approaches for optimizing antiretroviral therapy. The correct choice of a HAART regimen is literally a matter of life and death for many patients, and we feel basic studies of viral persistence can be applied to improving decisions about how and when antiretroviral therapy should be given. Over the years, this research has received nearly \$7 million in support from the NIH.

I want to emphasize that many labs would like to pursue the problem of how to eliminate the latent reservoir, but everyone I know has had to scale back research efforts because of flat NIH budgets. In my own lab we are now finding it difficult to take on new staff and begin new projects. Typically, in the past, I would spend about 30 percent of my time applying for grants; now about 60 percent of my time is spent preparing applications. Furthermore, some prominent investigators are getting out of research. Few scientists want to tackle high-risk problems like this because research of this type is more difficult to fund. In fact, a very good colleague of mine has made a major discovery on a unique group of patients who control HIV without medication. He has not been able to get funding even though the potential savings is more than \$14,000 annually per patient. Additionally, a mentor of mine, and one of the most respected people in the field, is thinking of getting out of research because he has no funding.

Federal Investment in Research is a Critical Component of Our Nation's Competitiveness

The United States has long been the world leader in scientific discovery, thanks largely to government policies that encourage innovation, improve education, and facilitate the transfer of knowledge from the laboratory to the marketplace. Today we face serious threats to this preeminence. Other nations bring to the table strong educational systems, focused government policies, and low-cost workers.

Basic research is essential to our ability to meet this challenge. William R. Brody, president of The Johns Hopkins University and co-chair of a national committee on competitiveness, puts it this way: "Knowledge drives innovation. Innovation drives productivity. Productivity drives economic growth." Our ability to compete in the global economy depends, first and foremost, on our ability to continue making new discoveries. The more we learn about how things work - the

principles of basic biology, chemistry, physics, and mathematics - the more opportunity we have to put that knowledge to work. When we know more, we can use that knowledge to make our world better, to build new businesses, devise new products, and to improve our standard of living.

America's most innovative industries are built on decades of basic research, research that had no discernable practical application at the time it was undertaken. For example, the highly theoretical world of quantum mechanics spawned the semiconductor industry and the information revolution. Johns Hopkins scientists thinking about the principle of physics, called the Doppler effect, used it to invent what became today's Global Positioning System. Two Johns Hopkins biologists shared a Nobel Prize in 1978 for using restriction enzymes to cut DNA into fragments that created today's thriving biotechnology industry, which is based on genetics.

In the United States, funding basic research has long been a governmental function. Why? Because it takes a long time to do it, because there is always a risk that any single project will come to nothing, and because it is difficult to capture an immediate return on investment for an idea that has not yet been developed to the stage of a marketable invention.

Despite a societal consensus that basic research is a government responsibility, U.S. federal research and development spending, as a percentage of Gross Domestic Product (GDP), peaked *40 years ago* in 1965, at just below 2 percent of GDP. In the past 40 years, that percentage has diminished by more than half, to about 0.8 percent of GDP. Overall R&D spending, especially in basic sciences, continues to decline. We must reverse this trend now, by strengthening the nation's commitment to science related federal agencies and departments.

The investments in biomedical research being made by rising economic powers such as China are increasing. While China lacks a central institution like the NIH to oversee its national investment in biomedical research, its National Science and Technology Plan for 2006-2020 emphasizes a long-range strategy to raise its biomedical research to world-class standards. This is being supported by a pledge to raise R&D spending from 1.3 percent of GDP in 2005 to 2.5 percent by 2020 (*Science* 9 March, 2007: Vol. 315. no. 5817).

If we look to one promising field of the future - that of nanotech - overall government spending globally grew by 10 percent to \$6.4 billion in 2006. According to a report released by Lux Research, the U.S. came out on top, with \$1.78 billion, followed by Japan and Germany. But China actually ranks second when purchasing power parity is considered. China's funding is the equivalent of \$906 million. (*UPI* 9 March, 2007). In this sector, like so many others, China will compete.

The life sciences research funded by the NIH is a key component of our overall national science agenda. For example, Johns Hopkins University is the nation's leading recipient of federal research grants. In FY2005, our researchers attracted nearly \$1.3 billion in federal R&D funding and \$1.4 billion in overall R&D funding, a category in which Johns Hopkins has led all U.S. institutions for 27 consecutive years. This support enables us to improve medical care worldwide, advance human knowledge, and train new generations of innovative researchers.

Investment in research universities like Johns Hopkins yields tangible economic benefits as well. In 2006, Johns Hopkins researchers filed more than 420 U.S. patent applications, received 79 U.S. patents, and licensed 72 technologies for commercial development. Some of these inventions will be commercialized by Maryland companies. Already, there are at least 19 existing Maryland-based start-ups bringing Johns Hopkins technology to market. That is a tremendous amount of knowledge made available to American business and the American public for an incalculable range of benefits.

While the President and Congress have embraced the notion that funding for basic research in the physical sciences is essential to strengthening America's competitive standing in the world, and Johns Hopkins certainly recognizes and appreciates the significant investments included in the FY2007 Continuing Resolution, we remain concerned that funding for biomedical research has not kept pace with this commitment. Aggressive, stable, and sustained federal spending on the NIH and biomedical research must be understood and embraced as a critical component of America's competitiveness.

Justification of NIH Funding

On January 15, 2007, President Bush signed the National Institutes of Health Reform Act of 2006. While the law calls for a 6% increase for FY2007 and an 8% increase for FY2008, the reality is that this funding commitment has not fully materialized. For FY2006, the NIH budget was cut in both nominal and real terms. For FY2007, the NIH received a modest yet important increase of approximately \$620 million. We are very grateful that this Congress chose to single out the NIH, along with several other science agencies, to be among the few areas of federal spending to receive increases. We recognize that budgets are tight and we see this as a critical statement of Congress' desire to strengthen and preserve the scientific enterprise in this country. Despite this increase, however, FY2007 marks the fourth year in a row, when adjusting for inflation, that NIH funding has been cut.

At Johns Hopkins, we have annually led the nation in NIH research dollars and we have seen a marked decline in grants awarded to our School of Medicine. Fewer projects are being funded and NIH support of on-going investigations is being cut. Recent figures suggest that the number of grants and overall funding levels have declined. In FY2002, the average funding level per grant was \$142,210 for the School of Medicine. By FY2006, the funding level dropped nearly \$50,000 per grant to \$92,683, a decline of 34.8 percent. Hardest hit are America's young researchers. I fear that we may lose a generation of enthusiastic, inquisitive scientists if they conclude that NIH grants are out of reach.

Flat Funding Threatens Our Young Investigators

One of the first and earliest victims of declining NIH funding has been the young investigator. You have heard today, and often over the past several years, from Dr. Zerhouni regarding NIH's concern that we are potentially sacrificing an entire generation of young scientists. The Director's concern is real and very serious.

Quite simply, we have to do more to support and encourage our young investigators. Most ideas that turn into Noble Prizes come from investigators before they reach the age of 40. As a country, then, shouldn't we be supporting these scientists when they are in their professional prime? Unfortunately, the statistics tell an entirely different story. In the case of initial R01/R29 awards, between 1970 and 2004, the average age by which an investigator with a Ph.D gains his or her first award has gone from 34.3 years of age to 41.7. In the case of MDs, during this same period, that age has gone from 36.7 years to 43.3 (*AAMC* 12 July, 2006). With diminished NIH funding, our young scientists are witnessing firsthand the decline in overall success rates for grant applications. In 1998, the first year of the doubling, overall success rates were about 31 percent for grant submissions. For 2007, the success rate is projected to drop to only about 19 percent. Left unaddressed, there is no question that the current decline in NIH funding places an entire generation of young scientists at risk.

Even at my own institution, where we have many of the best and brightest among the current generation of young scientists, we are seeing many of these men and women unable to gain funding support. Without sustainable and predictable increases in NIH funding, this nation is at risk of losing an entire generation of scientists.

Research Impacts Health Care Costs

When advocates for increasing biomedical research funding meet with members of Congress and their staff, they are often asked: "What have we to show for the money that NIH has received in the past?" As we think about this question, it is important to recognize that the pace of biomedical research and science in general is often slow and unpredictable. It may be years before we can point to specific therapies or new medical devices that can trace their origins to recently funded efforts. But the simple answer is: We have a great deal to show!

Here are three powerful examples - there are, of course, many more - of what Johns Hopkins scientists have accomplished in terms of improving healthcare and reducing costs, thanks to NIH support.

Detection of Vision Problems of Diabetics

Diabetes is the leading cause of blindness in adults, with 12,000 to 24,000 new cases each year. Early identification of retina disease is critical to stave off vision loss, especially for the 10 million diabetics who are 60 years or older, most of them on Medicare or Medicaid. Yet more than half of all diabetics fail to get an annual eye exam as recommended by the American Diabetes Association. To address this dilemma, Dr. Ran Zeimer, director of the Ophthalmic Physics Laboratory at the Johns Hopkins Wilmer Eye Institute, came up with a novel solution after more than a decade of research: Why not develop an easy-to-use digital camera that tests for retinopathy when diabetics visit their primary care physicians for check-ups?

Thanks to NIH support, Dr. Zeimer perfected an instrument called the DigiScope. The DigiScope takes images of the retina in just minutes as patients sit in front of an automated camera and look at a series of blinking lights. These images are then transmitted via the Internet to a reading center for expert interpretation. More than 20,000 individuals not under the care of an ophthalmologist have been screened to date in the offices of primary care physicians. Those with vision-threatening disease have been identified and referred to eye specialists. In most cases, diabetics without complications are spared visits to an ophthalmologist, while Medicare and Medicaid are spared an expense.

Advances in Treatment for Sickle Cell Patients.

Thanks to continuous NIH grants extending back to 1982, Drs. George Dover and Samuel Charache of Johns Hopkins spent their careers fighting sickle cell disease – a miserable, inherited illness in which sickle-shaped red blood cells get stuck in narrow channels and block blood flow to tissue and vital organs. Patients with sickle cell disease – 72,000 in the United States – suffer frequent bouts of fatigue and shortness of breath, joint and body organ pains that turn excruciating and lead to frequent hospitalizations. The pneumonia-like conditions, chest pains, and fever can be life-threatening. Until fairly recently, early death was the norm, with life expectancy for a sickle cell patient projected to be only 20 to 30 years.

In the 1990s, Drs. Dover, Charache, and their Hopkins research team found that a cancer drug (hydroxyurea) did remarkable things for sickle cell sufferers. A 1995 NIH-supported multi-center study proved that hydroxyurea therapy dramatically reduces the frequency and severity of painful episodes, hospitalizations and transfusions. In a 2003 study, daily doses led to 30 percent fewer hospital days, 58 percent fewer transfusions, and a 40 percent reduction in deaths. Today, hydroxyurea therapy is recommended for adults and adolescents with moderate-to-severe recurrent pain. As a result, the life expectancy for sickle cell patients has doubled.

There have been financial benefits, too. According to another NIH-sponsored study, hydroxyurea therapy saves the U.S. health care system \$5,210 per sickle cell patient per year. With 72,000 Americans suffering from sickle cell disease, the potential annual savings is more than \$375 million annually.

Faster Diagnoses in Emergency Rooms

With the existing threat of bioterrorism, it is crucial to find ways to swiftly identify patients in hospital emergency rooms who have biochemical pathogens or life-threatening infectious diseases, such as meningitis, sepsis, and bacterial endocarditis (an infection of the inner lining of the heart or heart valves). Current testing methods are time-consuming and usually lead to delays in diagnosing and treating these diseases. The current blood and culture tests for some diseases can take 24 hours or more.

Dr. Richard E. Rothman of the Johns Hopkins Department of Emergency Medicine is working on novel ways to identify quickly multiple blood-borne and pulmonary infectious diseases and bioterrorism pathogens. His patented molecular diagnostic tests involve both exhaled breath and body fluids. Early experiments have shown that these new diagnostic tools can detect 25 common bacterial infections and five categories of bioterrorism agents in fewer than 4 hours. Faster response times are expected as the diagnostic tools are fine-tuned.

Conclusion

Thank you for your efforts to strengthen America's biomedical research community. Johns Hopkins stands ready to support you in this important endeavor. I invite you and your staff to visit our campuses, explore our facilities, and meet our researchers who are taking the lead in these vital fields.