Testimony of Clifford V. Harding, M.D., Ph.D. on behalf of
The American Association of Immunologists (AAI),
Submitted to the Senate Appropriations Subcommittee on Labor, Health and Human Services, Education, and Related Agencies,
Regarding the Fiscal Year (FY) 2016 Budget for the National Institutes of Health
April 1, 2015

The American Association of Immunologists (AAI), the world's largest professional society of research scientists and physicians who study the immune system, respectfully submits this testimony regarding fiscal year (FY) 2016 appropriations for the National Institutes of Health (NIH). ***AAI recommends an appropriation of at least $32 billion for NIH for FY 2016*** to fund important ongoing research, strengthen the biomedical research enterprise, and ensure that the most talented scientists, trainees, and students are able to pursue careers in biomedical research in the United States.

NIH's Essential Role in Advancing Biomedical Research

As the nation's main funding agency for biomedical and behavioral research, NIH supports the work of "more than 300,000 researchers at more than 2,500 universities, medical schools, and other research institutions in every state and around the world." [1] More than 80% of the NIH budget is awarded to these scientists through nearly 50,000 competitive grants; about 10% of the NIH budget supports the work of the almost 6,000 government researchers who work in NIH laboratories or at the NIH Clinical Center.[2] NIH funding is a vitally important economic engine in the communities and states where these researchers work; in FY 2012, NIH-funded research supported an estimated 402,000 jobs across the United States." [3]

NIH also provides crucial scientific leadership to the entire biomedical research enterprise, both within and beyond our borders. Advancing basic research from bench to bedside requires extensive collaboration among scientists from academia, government,[4] and industry; all depend on NIH personnel and policies to guide and facilitate their efforts in this enormous, complicated, and high-stakes endeavor. In fact, the biotechnology and pharmaceutical industries rely heavily on NIH's investment in basic biomedical research; it is often this research that industry uses or further explores to develop new drugs and medical devices.[5]

Erosion of NIH Budget Slows Research and Threatens U.S. Preeminence

Although NIH funds most biomedical research in the United States, its purchasing power has been dramatically reduced by inadequate budgets that have been further eroded by inflation.[6] In FY 2015, NIH's purchasing power is 22% lower than it was in FY 2003, when the five-year NIH budget doubling period ended.[7] This reduced purchasing power enables NIH to fund only ~ 16.8% of grant applications submitted, a steep decline from the ~32.4% it funded when its budget was robust.[8] This loss is not only a barrier to advancing crucially important research, it is also devastating to those who are currently engaged in - or considering - a career in biomedical research. Researchers around the country are closing labs, losing jobs, and in some cases, moving overseas, where support for biomedical research is rapidly growing.[9] Many who do stay in the U.S. are engaged in an unrelenting and time consuming search for funding, when they should be conducting research and mentoring the nation's future researchers, doctors, inventors and innovators. Most importantly of all, we will never know what research has not been pursued - or how many potential treatments and cures have not been discovered - because of inadequate funding.

The Immune System: Essential to our Health, Crucial to our Future

The importance of the immune system to human and animal health cannot be overstated, and has even been noted in Congress. In response to testimony by Dr. Anthony Fauci, Director of the National Institute of Allergy and Infectious Diseases, Senator Richard Shelby (R-AL), a senior member of the Senate Labor, Health and Human Services, Education, and Related Agencies Appropriations Subcommittee, correctly observed that "immunology kind of transcends it all." [10]

As the body's primary defense against viruses, bacteria, and parasites, the immune system protects its host from a wide range of diseases and disorders. When it is operating properly, the immune system can provide powerful protection against many illnesses, including cancer, Alzheimer's disease, and cardiovascular disease. When it underperforms, it can leave the body vulnerable to infections, such as influenza, HIV/AIDS, tuberculosis, malaria, and the common cold. The immune system can also become overactive and attack normal organs and tissues, causing autoimmune diseases including allergy, asthma, inflammatory bowel disease, lupus, multiple sclerosis, rheumatoid arthritis, and type 1 diabetes.

Immunologists are on the front lines, working to harness the immune system to protect people and animals from chronic and acute diseases and disorders, as well as from natural or man-made infectious organisms (including Ebola, plague, smallpox and anthrax) that could be used for bioterrorism.

Recent Immunological Advances: Providing Hope for Today - and Tomorrow

1. Ebola Outbreak: Finding a Vaccine to Save Lives

The 2014 Ebola virus outbreak in West Africa is the largest in recorded history. Due to the historically low incidence of infection, development of anti-Ebola therapeutics and vaccines had not been a priority for public health officials or pharmaceutical companies. However, ongoing investments in biomedical research by the federal government, including NIH and the Department of Defense, have led to the development of several promising vaccine candidates, two of which are now being administered through clinical trials in the outbreak region and may well aid in preventing this deadly disease.[11] Although pharmaceutical companies are now involved in the manufacture of these vaccine candidates and other potential therapies, it is federal taxpayer dollars that funded the research that is the cornerstone of the current Ebola virus response.[12] Ongoing biomedical research in areas like Ebola and other emerging infectious diseases, where the public health benefit outweighs the potential commercial benefit, depends heavily on federal dollars.

2. A New Way to Stop HIV … and Other Infections and Diseases?

Researchers have recently discovered that Clustered Regularly Interspaced Short Palindromic Repeats (CRISPR) systems - immune mechanisms used by bacteria to defend themselves from virus infection - present a novel therapeutic tool for immunologists, enabling them to successfully disrupt HIV replication, stop the growth of human cervical cancer cells and kill antibiotic-resistant bacteria.[13] Immunologists are also exploring the use of CRISPR to repair defective genes in stem cells, which may treat diseases like sickle cell anemia and immune deficiencies.[14]

3. Cancer Immunotherapies: Real Results in the Fight Against Cancer

Lauded by *Science* magazine in 2013 as "The Science Breakthrough of the Year," the genetic engineering of a cancer patient's T cells (immune cells) to kill the patient's own cancer cells, a procedure known as immunotherapy, continues to advance.[15] At NIH funded medical centers, scientists and doctors are observing a significant regression of blood cancers (non-solid tumors) in both children and adults.[16] This therapy, which the FDA granted Breakthrough Therapy designation in July 2014 (which can expedite

approval of a therapeutic based on clear clinical efficacy), is poised to be used for even more difficult-to-treat solid tumor cancers, and is helping to inform ongoing clinical trials in breast, lung, prostate and brain cancer.[17] The success of these therapies has also attracted the investment of pharmaceutical companies and has led to the development of several new T cell therapy-focused biotechnology companies, illustrating how investment in NIH funded research creates opportunity - and jobs - in the private sector.

4. New Therapeutic Provides Real Hope for Autoimmune Treatment

In January 2015, the FDA approved the first of a new and highly effective class of treatments for psoriasis, a serious autoimmune skin disease.[18] The new treatment inhibits IL-17 signaling, a process which initiates inflammation and which was first discovered by NIH funded researchers in 2005.[19] This treatment has proven effective in Phase II clinical trials, with more than 70% of psoriasis patients showing over 75% clearance of disease, and nearly half showing 100% clearance of disease.[20] Clinical trials targeting similar aspects of this pathway are yielding promising results and may offer hope to those suffering from other autoimmune diseases, including ankylosing spondylitis, rheumatoid arthritis, and multiple sclerosis.[21]

Conclusion

AAI greatly appreciates the strong bipartisan support for NIH and biomedical research that has been expressed by the members and staff of the subcommittee. In order to support important ongoing research, fund a reasonable number of outstanding new grant applications, and restore NIH funding to a level that can sustain a robust and dynamic biomedical research enterprise in the United States, AAI urges the subcommittee to provide NIH with an appropriation of *at least $32 billion* for FY 2016.

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[1] http://www.nih.gov/about/budget.htm. NIH funds also support the work of non-scientist technical personnel.

[2] Ibid.

[3] http://nih.gov/about/impact/economy.htm.

[4] AAI opposes a federal policy that limits government scientists' ability to attend privately sponsored scientific meetings and conferences (see http://www.hhs.gov/travel/policies/2012_policy_manual.pdf) and believes that "the rules have had an unintended and deleterious effect … [and] made government scientists feel cut off from the rest of the scientific community, wreaked havoc with their ability to fulfill professional commitments, and undermined the morale of some of the government's finest minds." *Testimony (Amended) of Lauren G. Gross, J.D., on behalf of The American Association of Immunologists (AAI), Submitted to the Senate Homeland Security and Governmental Affairs Committee for the Hearing Record of January 14, 2014: "Examining Conference and Travel Spending Across the Federal Government"* (http://aai.org/Public_Affairs/Docs/2014/AAI_Testimony_to_Senate_HSGAC_01142014.pdf)

[5] "[NIH] … annual research funding… is the most important source of discoveries in the health sciences that ultimately leads to the development of important new therapeutics …." Statement of Roger Perlmutter, Ph.D., Executive Vice President, Research & Development, Amgen, June 15, 2005 http://www.rdmag.com/articles/2005/06/managing-rapid-biotech-growth

[6] "In 12 of the past 13 years, NIH funding has either been cut or has failed to outpace rising costs." Federation of American Societies for Experimental Biology, Funding Trends, 2015. http://www.faseb.org/Portals/2/PDFs/opa/2015/2.10.15%20NIH%20Funding%20Cuts%202-pager.pdf?pdf=2.10.15%20NIH%20Funding%20Cuts%202-pager

[7] Johnson, Judith A., "NIH Funding: FY1994-FY2016," Congressional Research Service, R43341, pp. 2-3 (2015). Measured in constant 2012 dollars. Excludes funding from the American Recovery and Reinvestment Act (ARRA).

[8] Research Project Grant Award Rate ("the likelihood of an individual application submission getting funded"). Rockey, Sally, "Comparing Success Rates, Award Rates, and Funding Rates," *Rock Talk,* March 5, 2014. RPG success rates ("the number of awards made divided by the sum of the applications reviewed that fiscal year where revisions submitted in the same fiscal year are collapsed and counted as one application") have also decreased drastically, from 32.4% to 18.1%. See http://nexus.od.nih.gov/all/2014/03/05/comparing-success-award-funding-rates/.

[9] Moses, H., *et al.* The Anatomy of Medical Research: US and International Comparisons. *JAMA* 313, 174-189 (2015). Losing our best and brightest to burgeoning overseas interest and investment in biomedical research is neither specious nor unrealistic: after adjusting for inflation. According to Moses *et al.*, while U.S. funding for biomedical and health services research increased at a rate of 6 percent per year from 1994-2004, it decreased to just 0.8 percent annually from 2004-2012.

[10] NIH FY 2015 Budget Request: hearing before the Senate Appropriations Committee Subcommittee on Labor, Health and Human Services, Education, and Related Agencies, April 2, 2014, 113th Congress, second session (Comments of Senator Richard Shelby)

[11] Ledgerwood, J. E. *et al.* Chimpanzee Adenovirus Vector Ebola Vaccine -Preliminary Report. *N. Engl. J. Med.* 0, null (0).

[12] Wong, G., *et al.* Intranasal immunization with an adenovirus vaccine protects guinea pigs from Ebola virus transmission by infected animals. *Antiviral Res.* 116, 17–19 (2015); Stanley, D. A. *et al.* Chimpanzee adenovirus vaccine generates acute and durable protective immunity against ebolavirus challenge. *Nat. Med.* 20, 1126–1129 (2014).

[13] Hu, W. *et al.* RNA-directed gene editing specifically eradicates latent and prevents new HIV-1 infection. *Proc. Natl. Acad. Sci.* U. S. A. 111, 11461–11466 (2014); Kennedy, E. M. *et al.* Inactivation of the human papillomavirus E6 or E7 gene in cervical carcinoma cells by using a bacterial CRISPR/Cas RNA-guided endonuclease. *J. Virol.* 88, 11965–11972 (2014); Citorik, R. J., *et al.* Sequence-specific antimicrobials using efficiently delivered RNA-guided nucleases. *Nat. Biotechnol.* 32, 1141–1145 (2014).

[14] Huang, X. *et al.* Production of gene-corrected adult beta globin protein in human erythrocytes differentiated from patient iPSCs after genome editing of the sickle point mutation. *Stem Cells* (2015). doi:10.1002/stem.1969

[15] Couzin-Frankel, J. Cancer Immunotherapy. *Science* 342, 1432–1433 (2013).

[16] Maude, S. L. *et al.* Chimeric antigen receptor T cells for sustained remissions in leukemia. *N. Engl. J. Med.* 371, 1507–1517 (2014).

[17] Kakarla, S. & Gottschalk, S. CAR T Cells for Solid Tumors: Armed and Ready to Go? *Cancer J.* 20, 151–155 (2014)

[18] Press Announcements > FDA approves new psoriasis drug Cosentyx. at http://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm430969.htm

[19] Langrish, C. L. *et al.* IL-23 drives a pathogenic T cell population that induces autoimmune inflammation. *J. Exp. Med.* 201, 233–240 (2005).

[20] Gaffen, S. L., *et al.,* The IL-23-IL-17 immune axis: from mechanisms to therapeutic testing. *Nat. Rev. Immunol.* 14, 585–600 (2014).

[21] Novartis AIN457 (secukinumab) meets primary endpoint in two Phase III studies in ankylosing spondylitis, a debilitating joint condition of the spine. at http://www.novartis.com/newsroom/media-releases/en/2014/1864939.shtml