DEPARTMENT OF HEALTH AND HUMAN SERVICES

NATIONAL INSTITUTES OF HEALTH

Fiscal Year 2013 Budget Request

Witness appearing before the

Senate Subcommittee on Labor – HHS – Education Appropriations

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NIH's Mission

Good morning, Mr. Chairman and distinguished Members of the Subcommittee. I am Francis S. Collins, M.D., Ph.D., and I am the Director of the National Institutes of Health (NIH). I have with me Anthony S. Fauci, M.D., Director of the National Institute of Allergy and Infectious Disease; Richard J. Hodes, M.D., Director of the National Institute on Aging; Thomas R. Insel, M.D., Director of the National Institute of Mental Health (NIMH), and the Acting Director of the new National Center for Advancing Translational Sciences (NCATS); Griffin P. Rodgers, M.D., Director of the National Institute of Diabetes and Digestive and Kidney Diseases; and Harold E. Varmus, M.D., Director of the National Cancer Institute.

It is a great honor to appear before you today to present the Administration's fiscal year (FY) 2013 budget request for the NIH.

First, I would like to thank each of you for your continued support of NIH's mission to seek fundamental knowledge about the nature of living systems and to apply it in ways that enhance human health, lengthen life, and reduce suffering from illness and disability. In particular, I want to thank the Subcommittee for your support during the FY 2012 appropriations process, for the ultimate appropriation of $30.62 billion for NIH, and for the provisions that established NCATS.

As the largest supporter of biomedical research in the world, NIH has been a driving force behind decades of advances that have improved the health of people across the United States and around the world.

NIH basic research and translational advances have prompted a revolution in the diagnosis, treatment, and prevention of disease. Biomedical research funded by NIH has prevented immeasurable human suffering and has yielded economic benefits as well, thanks to U.S. citizens living longer, healthier, and more productive lives. These benefits include:

- nearly 70 percent reduction in the death rate for coronary disease and stroke in the last half century;
- effective interventions for HIV/AIDS prevention and treatment, such that an AIDS-free generation may be within our grasp;
- nearly 30 percent decline over the last three decades in the age-standardized prevalence of chronic disability among American seniors;
- 40 percent decline in infant mortality over 20 years and better treatments for premature and low-weight births that result in increased infant survival, the prevention of cerebral palsy, and better developmental outcomes; and
- more than 150 FDA-approved drugs and vaccines, or new uses of existing drugs.[1]

The Administration's FY 2013 budget request for NIH is $30.86 billion, which is the same overall program level as FY 2012. This proposed appropriation will enable us to spark innovation and invest in areas of extraordinary promise for medical science. We will also invest

[1] Stevens, A.J., *et al.*, "The Role of Public-Sector Research in the Discovery of Drugs and Vaccines." *N. Engl. J. Med*., 364: 535-41, 2011.

these resources wisely to encourage a vigorous workforce that is prepared to tackle major scientific and health challenges.

Within the Administration's FY 2013 budget, we will continue to protect and increase Research Project Grants (RPGs), NIH's fundamental funding mechanism for investigator-initiated research. NIH expects to support an estimated 9,415 new and competing RPGs in FY 2013, an increase of 672 above the estimate for FY 2012, with an average cost of about $431,000. For FY 2013, total RPGs are expected to number around 35,888.

To maximize funding for investigator-initiated grants, and to continue our support of first-time researchers, we propose to reduce budgets for non-competing RPGs by 1 percent from the FY 2012 level and to restrain growth in the average size of new awards. We will also no longer assume out-year inflationary increases for new and continuing grants. To nurture early career scientists, we will continue our efforts to ensure that the success rates for investigators submitting new R01 applications are the same whether the applicant is first-time or more experienced.

In FY 2013, we will also conduct an additional review of proposed awards to any principal investigator (PI) who already has NIH funding of $1.5 million or more in total annual costs, approximately 6 percent of PIs. This review will be conducted by each institute's advisory council. This is similar to a policy the National Institute of General Medical Sciences (NIGMS) has had since 1998, which will serve as a model for NIH. We recognize that some types of research, notably large complex clinical trials, routinely will trigger this review. We also know that some of our most productive investigators are leading significant research teams that require over $1.5 million to be sustained. This extra level of review will not be viewed as a cut-off point, but as an opportunity to apply additional scrutiny to be sure any added resources are justified by exceptional scientific promise.

Another significant change in the FY 2013 request is an 11 percent increase in the NCATS budget. The proposed budget includes an increase of $39.6 million for the Cures Acceleration Network (CAN), which received $10 million for start-up funding in FY 2012. As you know Mr. Chairman, CAN will fund initiatives to address scientific and technical challenges that impede translational research, and to advance the development of "high need cures" by accelerating the pace and reducing the time between research discovery and therapeutic treatment. In total, nearly half of the increase requested for NCATS will be used to transition programs from the Common Fund, allowing the Common Fund to support additional cross-cutting, trans-NIH programs.

I would also note that the FY 2013 NIGMS budget would decrease by $48.3 million (after comparability adjustments), primarily due to not continuing the 21 percent increase that Congress provided in FY 2012 for the Institutional Development Awards program. The budget of the Office of the Director is also cut by 1.9 percent from FY 2012 enacted, reflecting a reduced request for the National Children's Study; we will implement alternative sampling approaches that will reduce costs and still achieve the ambitious objectives of the Study.

In FY 2013, the President is also proposing to spend $80 million from the Prevention and Public Health Fund to provide additional support for Alzheimer's research as part of the National Plan to Address Alzheimer's Disease. As many as 5.1 million Americans currently suffer from Alzheimer's disease, more than 280,000 more Americans will be diagnosed with the disease this year, and nearly 800 of our fellow citizens are diagnosed every day. By the year 2030, the last baby boomer will turn 65 and 7.7 million Americans over the age of 65 will have Alzheimer's disease.[2] Today, Alzheimer's and other dementias cost the United States economy more than $180 billion a year and if no cures and therapies are found, will cost the United States $1.1 trillion annually by 2050. The $80 million of new funding will support research with a strong focus on the prevention of Alzheimer's disease, including research to identify genes that cause this disease, to develop tests for high-risk individuals, and to identify possible targets for therapeutic development.

Investing in Basic Science, Applying Knowledge to Therapies

NIH's commitment to basic research provides the foundation for understanding the underlying causes of diseases which is essential to the development of promising treatments and cures for some of our nation's most debilitating diseases and conditions. Apple Computer founder Steve Jobs has been quoted as saying: "*I think the biggest innovations of the twenty-first century will be the intersection of biology and technology."* [3] Jobs was absolutely right: today technological advances are driving science. We need look no further than the cost of DNA sequencing to see this dynamic at work. The cost curve for sequencing is dropping at a breathtaking rate; sequencing speed has increased even faster than computer processing speed. What's more, the average cost of sequencing an entire genome has fallen from about $3 billion 12 years ago, to $10 million five years ago, to about $7,700 today. Two U.S. companies have recently announced that they are manufacturing machines that will sequence an individual's genome in one day for approximately $1,000, and that the first such instruments will go on sale before year's end. Lower sequencing costs will likely revolutionize how clinicians diagnose and treat diseases and enable the research community to pursue previously unimaginable scientific questions.

NIH is the leading supporter of basic biomedical research in the world. Put plainly, if we don't fund basic research, most of this work would not get done, and it would be only a matter of time before this wellspring of new understanding and new therapies would dry up. NIH's funding for basic research is slightly over half (54 percent) of research funding, and this balance between basic and applied research has remained fairly constant over the past decade.

I also would like to address what may be a misconception about a competitive tension between basic and applied research at NIH. As our support of basic research has enabled new discoveries, NIH-funded scientists have always worked to turn the most compelling of them into medical advances. Basic discovery and the development of therapies go hand-in-hand at NIH. The two types of research have - and always will - exist together in a continuum. Today, I would like to highlight just a few areas in which basic research advances are opening up new translational opportunities.

[2] Alzheimer's Association, 2011 Alzheimer's Disease Facts and Figures, Alzheimer's & Dementia, Volume 7, Issue 2.
[3] Isaakson, Walter, Steve Jobs (New York: Simon & Schuster, 2011) 539.

Human Microbiome Project: One fascinating area of basic research is the Human Microbiome Project, an initiative supported through the NIH Common Fund. This project is giving us wonderful insights into the sweeping range of bacteria that live on and in each of us, and is expanding our knowledge about the role of these microbial communities in health and disease. Recent scientific evidence suggests that changes in the composition and activity of the human microbiome may contribute to obesity, which may provide us with new ways of addressing this serious threat to our nation's health.

Undiagnosed Diseases Program: Another recent example emphasizes the "virtuous cycle" between basic and clinical research. The NIH Clinical Center has recently established a groundbreaking program that seeks to identify the cause of illnesses that have remained unsolved by other medical practitioners. Since the program started in 2008 some 1,700 people with undiagnosed conditions have been referred to Dr. William Gahl, and more than 300 have been accepted for an initial week of consultations and testing. In the 15 to 20 percent of cases that we have successfully diagnosed, it has taken from a week to as long as two years to resolve. For example, a pair of sisters from Kentucky suffered from joint pain and mysterious calcification of the arteries in their extremities. Full evaluation and DNA sequencing led to the discovery of an entirely new genetic condition, where a previously unknown enzyme pathway in their arteries was blocked. This has led to a dramatic new understanding of how the large arteries in all of us maintain their normal health, with immediate research spinoffs in the basic and clinical arenas.

Alzheimer's Disease: NIH-supported investigators are expanding our understanding of Alzheimer's disease in ways that may open doors to new therapies. Using mice genetically engineered to make the abnormal human tau protein—a protein already identified in the brains of Alzheimer's patients—scientists found that Alzheimer's disease appears to spread through the brain in much the same way that an infection or cancer moves through the body. The abnormal tau protein started in one area of the brain in the mice and, over time, spread from cell to cell to other areas of the brain in a pattern very similar to the earliest stages of human Alzheimer's disease. The discovery of the tau pathway could influence the direction of future research and give investigators a target for drug development that might arrest Alzheimer's disease progression at very early stages when the disease is most amenable to treatment.[4]

Alzheimer's disease also stands to benefit from translational research by way of drug rescuing and repurposing. Recently, a team that included NIH-supported investigators reported that bexarotene, a drug compound originally developed for treating T-cell lymphoma (a type of skin cancer), was capable of clearing the protein beta-amyloid quickly and efficiently after only a short exposure to the compound in Alzheimer's disease mouse models. Beta-amyloid accumulates in the brain of Alzheimer's patients due to an impaired ability to clear the protein, leading to a build-up of beta-amyloid plaques and ultimately neuronal death. These findings are exciting because, in time, they could benefit patients with Alzheimer's disease. Hopes are particularly high because the drug used in the study has already been studied in humans, providing a wealth of information about dosage and toxicity.[5]

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[4] Liu L, Drouet V, Wu JW, Witter MP, Small SA, et al. (2012) Trans-Synaptic Spread of Tau Pathology In Vivo. PLoS ONE 7(2): e31302. doi:10.1371/journal.pone.0031302

[5] Cramer PE, Cirrito JR, Wesson DW, Lee CYD, Karlo JC, et al. (2012) ApoE-Directed Therapeutics Rapidly Clear β-Amyloid and Reverse Deficits in AD Mouse Models. http://www.sciencemag.org/content/early/2012/02/08/science.1217697.full.pdf

Cystic Fibrosis: In a step towards personal medicine, the FDA in January approved Kalydeco, the first drug to treat an underlying cause of cystic fibrosis. Twenty-three years ago, I co-led the team that discovered the gene responsible for cystic fibrosis (CF). Mutations in this gene cause a protein to malfunction, resulting in a sticky buildup of mucus in the lungs and digestive tract that eventually causes fatal health problems. Kalydeco, which was developed by Vertex Pharmaceuticals, counters one of these mutations, which affects about 4 percent of people with CF. Vertex is now testing the drug in combination with another new compound to target a more common mutation found in 90 percent of CF patients.

Clinical Research: National Center for Advancing Translational Sciences (NCATS)

The translation of basic biological discoveries into clinical applications is a complex process that involves a series of intricate steps. These steps range from the discovery of basic information about the causes of disease, an assessment of whether that information has the potential to lead to a clinical advance, the development and optimization of therapeutics to test in human trials and, ultimately, the application of the approved therapy, device, or diagnostic in the real world. Drugs exist for only about 250 of the more than 4,400 conditions with defined molecular causes.[6] And it takes far too long and far too much money to get a new drug into our medicine cabinets. This is an old problem that cries out for new and creative solutions.
In the past, drug development was based on a short list of a few hundred targets, but with advances in technology, we are now able to identify thousands of new potential drug targets.[7] We can also study whole pathways, organ systems or even entire organisms rather than limiting the research to a single aspect of cell biology or physiology. Technologies such as large-scale sequencing, robotic high-throughput screening, and real-time imaging modalities uncover massive amounts of data that may one day lead to new therapies to prevent, treat, and possibly cure diseases. Many of the NIH Institutes are deeply engaged in these efforts. But we face serious engineering challenges. To put it simply, the current translational science framework pursued in both the public and private sectors, largely focused on individual projects on specific diseases, has not been fully able to utilize recent scientific advances to address the bottlenecks that lead to long development times, high failure rates, and high costs. This month's issue of *Nature Reviews Drug Discovery* includes a review that demonstrates that, despite huge investments in biomedical science and technology, the number of new drugs approved per billion R&D dollars spent has been cut in half every nine years since 1950.[8] NCATS is the catalyst we need to reengineer the discovery and development process.

To tackle this problem in a science-driven way, NIH proposed the creation of NCATS with the goal to develop and test innovative tools, technologies, and approaches that will enhance the development of drugs and diagnostics for application in all human diseases. NIH has the expertise and enthusiasm to tackle this as a scientific problem. By focusing on the development of innovative new methods for conducting translational science, as opposed to developing therapeutics themselves, NCATS can enable others to bring new medical products to patients in a highly efficient, cost-effective manner. In the four months since it was established, NCATS

[6] Braun, *et al.,* "Emergence of orphan drugs in the United States: a quantitative assessment of the first 25 years." *Nature Rev. Drug Discov.* 9(521), 2010; Online Mendelian Inheritance in Man, http://www.ncbi.nlm.nih.gov/omim/.
[7] Collins, F.S., "Reengineering Translational Science: The Time is Right." *Sci. Transl. Med.*, 3(90):90cm17, 2011.
[8] Scannell JW, Blanckley A, Boldon H, & Warrington B. (2012). Diagnosing the decline in pharmaceutical R&D efficiency. Nature Reviews Drug Discovery 11, 191-200. doi:10.1038/nrd3681

has already developed three new initiatives in partnership with industry, academia, and other government agencies.

In the first, NIH is working closely with several pharmaceutical companies to develop model agreements for a new pilot program to rescue failed drugs. Pharmaceutical companies have access to promising compounds that have been shown to be safe in humans, but that did not prove effective in treating the condition for which they were intended. Researchers are now learning that a compound that is a failure for one condition may help to treat another. To capitalize on this, NCATS is developing a pilot program in partnership with industry that will seek to crowd source some of the most promising of these compounds to the brightest minds in science, an unprecedented opportunity for NIH-funded researchers and a new way to bridge academic science with industrial expertise.

Secondly, NCATS is partnering with the Defense Advanced Research Projects Agency (DARPA) to develop a chip that will mimic how humans respond to a drug. Scientists funded by NIH and DARPA will spend five years working closely with each other to place 10 diverse human tissues on a chip so that they will interact with drugs the same way that they do in living patients. By providing a better model to predict drug safety and efficacy, the most promising drug candidates can be identified more quickly and moved forward into development. The Food and Drug Administration will be heavily involved in an advisory capacity to ensure this research aligns with regulatory requirements.

In the third initiative, NCATS is working closely with industry to develop systematic ways to identify the most promising drug targets from the troves of data pouring out of basic research labs. To turn these discoveries into therapies, scientists in academia and industry need to be able to sift quickly and accurately through these data to identify the best targets. NCATS, along with industry partners, is taking the lead on developing a consortium that will strive to come up with the most streamlined ways to conduct target validation.

I want to emphasize that these and other initiatives within NCATS will provide resources and expertise to assist the basic research community in moving their discoveries to the next phase, as well as stimulate the basic research enterprise. For example, the Molecular Libraries and Imaging Program, originally implemented through the NIH Common Fund, has been successful in the development of chemical probes for basic and translational research. Many of these new probes have been, or are being, modified for use in the clinic, resulting in patent applications, licenses to pharmaceutical companies, and new therapeutic strategies.

In the months before NCATS was created by this Subcommittee, NIH engaged in an unprecedented outreach campaign to make sure that all stakeholders—including industry—had an opportunity to comment on the proposed Center. In addition to NIH's Scientific Management Review Board and Advisory Council to the Director, NIH consulted with the boards of the Pharmaceutical Research and Manufacturers of America and the Biotechnology Industry Association, the R&D heads of pharmaceutical and biotechnology companies, and the investment banking and venture capital communities. In addition, NIH held a series of workshops with pharmaceutical and biotech firms to discuss drug rescue and repurposing, and target validation.

It is important to note that NCATS' work will assist *all* of NIH's Institutes and Centers in their translational and drug development efforts. NCATS will provide NIH Institutes and Centers the tools, methodology, and infrastructure necessary to speed new approaches to therapeutic treatments. The new Center also will work with other NIH Institutes and Centers to convene workshops with industry, non-profits, and other government agencies to explore critical translational areas and innovative public-private sector partnerships.

With the FY 2013 budget, NIH will pursue efforts to streamline and shorten the pathway from discovery to health through several new and ongoing initiatives and programs.

Economic Returns and Global Competitiveness

In our knowledge-based world economy, innovation in medical research has been able to generate growth, high-quality jobs, better health, and better quality of life for all Americans. Investment in NIH continues to bring new ways to cure disease, alleviate suffering, and prevent illness. Furthermore, it generates new economic activity and employment in the communities that receive its funds. One study estimates that every dollar of NIH support returns $2.21 in goods and services in just one year, and that on average, every NIH grant creates seven high-quality jobs.

Investments in the biomedical infrastructure, in scientists' ideas, and in workforce training are essential to drive the innovation that will spur America's economic recovery and future growth. NIH serves as the foundation for the entire U.S. medical innovation sector that employs 1 million U.S. citizens, generates $84 billion in wages and salaries, and exports $90 billion in goods and services.[9] United for Medical Research has just released an updated version of their report "An Economic Engine: NIH Research, Employment, and the Future of the Medical Innovation Sector." According to UMR data, the $23.7 billion NIH spent extramurally in the U.S. in 2011 directly and indirectly supported 432,092 jobs, enabling 16 states to experience job growth of 10,000 jobs or more, and propelling $62.135 billion in new economic activity.

Thanks in large part to NIH-funded medical research, Americans are living longer, healthier, more rewarding lives. A child born today can look forward to an average life span of almost 79 years, an increase of nearly three decades over life expectancy in 1900. The economic value of these gains in average life expectancy in the United States has been estimated at $95 trillion for the period from 1970-2000.[10]

NIH funding is the foundation for long-term U.S. global competitiveness in industries such as biotechnology, medical devices, and pharmaceutical development. Around the world, many nations are following suit and beginning to ramp up their own investment in the life sciences. Global R&D spending is expected to grow by about 5.2 percent to more than $1.4 trillion in 2012.[11] India has posted double digit increases for several years, and Europe plans to

[9] Ehrlich, Dr. Everett, An Economic Engine: NIH Research, Employment and the Future of the Medical Innovation Sector, 8, *United for Medical Research* (May 2011).
[10] Murphy, K.M., & Topel, R.H. (2006). The value of health and longevity. *Journal of Political Economy, 114(5),* 871-904.
[11] Grueber, Martin, 2012 Global R&D Funding Forecast, 3, *Batelle and R&D Magazine* (Dec. 2011).

increase research spending by 40% over the next seven years. Even Vladimir Putin has announced the intention to increase support for research in Russia by 65% over the next five years. China has just announced that it will increase its investment in basic research by 26 percent in 2012.[12] To be sure, the scale of China's effort does not match ours. However, Chinese scientists are second only to the U.S. in the number of scientific manuscripts published annually, and China's intention to compete with us is obvious.

The U.S. must compete in training America's next generation to make tomorrow's health discoveries and ensure continued scientific leadership.

A Patient Story

Mr. Chairman, this morning I've described the promise that inexpensive whole-genome sequencing holds for future medical practice, the synergy between basic and translational research at NIH, and the need for NCATS. I'd like to close my testimony by telling you a story—a story about real patients—that ties my three points together.

As toddlers, twins Alexis and Noah Beery were diagnosed with a rare and devastating movement disorder, called dystonia. Although they initially responded to empirical treatment, their symptoms reappeared and worsened as they entered their teenage years. Noah developed severe tremors in his hands. Even worse, his sister Alexis began falling frequently and had frightening episodes where she couldn't breathe.

Desperate for answers, doctors at Baylor College of Medicine sequenced the twins' genomes. The result? Discovery of a never-before described genetic mutation affecting neurotransmitters in the brain. After being put on a new treatment regimen tailored to their unique genetic profile, the twins' symptoms began to improve within just two weeks. I recently saw a video of the two of them doing tricks on a trampoline. In fact, Alexis' breathing is so much better today that she's joined her school's track team. While this story centers on two teens with a rare disease, the outcome carries a message of hope for all of us. It points directly to the promise that NIH research offers the patients of today and tomorrow.[13]

In conclusion, we have never witnessed a time of greater promise for advances in medicine than right now. NIH is prepared to continue our long tradition of leading the world in the public support of biomedical research. Successful development of prevention strategies, diagnostics, and therapeutics will require bold investments in research across the spectrum from basic science to clinical trials, as well as new partnerships between the public and private sectors. With your support, we can promise continuing advances in medicine, creation of new economic opportunities, and stimulation of American global competitiveness in science, technology, and innovation.

This concludes my statement, Mr. Chairman and Members of the Subcommittee. I will be happy to answer any questions you may have.

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[12] Hvistendahl M. (2012). A Bumper Year for Chinese Science. *Science Vol. 335 no.6073 p.1156.* doi: 10.1126/science.335.6073.1156

[13] Bainbridge MN, et al. (2011). Whole-Genome Sequencing for Optimized Patient Management. *Science Translational Medicine 3, 87re3.* doi: 10.1126/scitranslmed.3002243