



# U.S. Senate Committee on Appropriations

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## **U.S. Senate Appropriations Subcommittee on Labor, Health and Human Services, Education, and Related Agencies Testimony of Stephen M. Strittmatter**

WASHINGTON, D.C. . The U.S. Senate Appropriations Labor, Health and Human Services, Education, and Related Agencies Subcommittee on Monday held a hearing to examine the proposed Fiscal 2008 budget for the National Institutes of Health. As part of that hearing, the subcommittee heard testimony from Stephen M. Strittmatter, Vincent Coates Professor of Neurology, Yale University School of Medicine. His testimony is below.

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Chairman Harkin, and Members of the committee, I thank you for the opportunity to offer my insights on the NIH budget. To be frank, my three decades in clinical Neurology and basic Neuroscience research at Yale, Harvard and Johns Hopkins have convinced me that the recently flat NIH budget is stifling creative, high-risk research endeavors.

The doubling of the NIH budget provided by Congress, and championed by many of you on this committee, laid the foundation to revolutionize the care of those suffering with nervous system diseases. However, for most types of neurological and psychiatric disease, we still face the crucial hurdle: the translation of basic molecular analysis of brain function and dysfunction into effective treatments. To leap over this translational hurdle requires the most creative and the riskiest experiments, including those that may lead to an experimental dead-end or multiple failures before achieving the one critical insight that will establish a new therapy. Regrettably, the decrease of inflation-adjusted NIH spending in recent years has produced a marked chilling effect on precisely the type of research that is most needed. If this chilling effect is not alleviated, we will fail to reap the full benefits of the research expansion that occurred from 1998-2003 . and we will push better treatments farther into the future.

My own field in Neuroscience relates to nerve fiber growth, and provides an example of how high-risk research can succeed in the appropriate environment. In humans, single nerve cells extend fine threads, called axons, for distances as long as a meter. If the cell were magnified to the size of a baseball, the axon would be the width of a pencil and extend for half of a mile. These axons conduct electricity and provide the wiring of the brain. There can be no useful brain function unless these fibers are correctly connected, and failure to connect . or reconnect . contributes to many diseases, from strokes, Alzheimer's and Parkinson's to Multiple Sclerosis and Lou Gehrig's disease.

Twenty years ago when I started in this field, little, if anything, was clear about how the cells of the developing brain become connected over long distances. However, molecular insights into the basis of axonal guidance began in the early 1990s and the pace of discovery accelerated rapidly during the NIH budget doubling. Basic studies led to the identification of dozens of axon guidance molecules and genes with defined roles in the developing brain.

These molecular insights were fascinating from the scientific perspective, but did not immediately improve human health. The next step was to apply this knowledge to settings of brain injury where axonal disconnection occurs. The clearest example is traumatic spinal cord injury. Despite the profound and persistent neurological deficits after spinal cord injury, such as the inability to move or feel, nearly all of the neurons that initiate arm and leg movements and provide skin sensation survive injury. The primary cause of disability is the interruption of nerve fibers, not the loss of cells. This, we learned, has important implications for treatment.

Inside the brain and spinal cord, very little axon regrowth occurs after injury, explaining the poor recovery of adults. Here the translational hurdle emerged: how do we use basic knowledge of embryonic fiber growth to restart axonal growth and restore proper function after injury or disease. As a Neurologist caring for patients while directing a brain development laboratory, I was particularly keen to attack this hurdle. Despite my interest, I would not have pursued this goal in 2000 without the risk-taking climate created by the NIH budget doubling.

We discovered the existence of a molecule, termed Nogo, which prevents nerve fiber growth, and mice lacking the gene for Nogo or its partner NogoReceptor exhibited significant axonal regeneration. Moreover, such animals recover substantial walking after spinal cord injury, or improved paw use after stroke. By analyzing the action of the Nogo molecule, we identified methods to prevent its function. Remarkably, therapy with a NogoReceptor antagonist allowed rats to walk after spinal cord injury and those with strokes recovered greater paw use. Today, a closely related approach using an antibody directed against Nogo is in clinical trials.

While this story illustrates past progress in high-risk research, I am convinced that similar challenges are not being tackled today because of the NIH budget situation. When researchers and peer review panels are faced with many junior investigators failing to achieve NIH research support and established investigators losing support, the first change is a retrenchment to safe science. Scientists pursue those experiments that have the highest probability of achieving an incremental short-term goal, rather than a chance of generating a paradigm-shifting long-term discovery. Researchers have become worriers+focused on how to maintain their laboratories and jobs, rather than explorers+seeking to solve the most crucial translational issues. High-risk, high-payoff studies have the most volatile dependence on NIH funding levels. Nonetheless, we require high-risk endeavors now more than ever to take advantage of basic science and research tools developed during the doubling of the NIH budget.

Dr. Zerhouni and the NIH have recognized the need for high-risk, high-payoff research and have taken steps to foster such work within the confines of restricted NIH budgets. This is important and commendable but it is not a substitute for an investment of federal funds that encourage creativity and reward risk. Specialized programs and set-asides can only affect a small percentage of biomedical research by their very nature. Furthermore, creativity cannot easily be dictated by policy. Only a reversal of the inflation-adjusted decline in the NIH budget can reset the biomedical community's outlook.

Future health care can be dramatically improved if researchers explore the highest risk research areas, allowing researchers to clear the translational hurdle and bring the benefits of expanding basic science to the public. By setting an NIH funding level that, at a minimum, restores recent net losses to inflation and keeps pace with costs in the future, Congress can achieve the research environment required to improve health for all of our citizens. I would be pleased to answer any questions.

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