

Before the United States Senate Health, Education, Labor, & Pensions Committee

The Honorable Edward M. Kennedy, Chairman

Testimony of Jill A. Rafael-Fortney, Ph.D.

Associate Professor

Department of Molecular and Cellular Biochemistry

College of Medicine

The Ohio State University

I would like to sincerely thank Chairman Kennedy and Ranking Member Enzi for holding this hearing on the very important topic of the serious threat to scientific discovery in our country.

When I was six years old, I started watching the Jerry Lewis telethon for Muscular Dystrophy every Labor Day weekend. I found it horribly sad that children just like me were living their lives in wheelchairs and facing a certain death before I would graduate from college. I did what I could at the time; I saved up my allowance and donated it to the telethon every year and vowed that I would spend my adult life trying to help these children.

In 7th grade science class I first learned about genetics, and I realized that this was the road to fight neuromuscular diseases. I looked for Universities where I could gain hands-on skills in genetic research. For 3 years as an Undergraduate student at Cornell University and during the summers I conducted a research project in a genetics lab and completed an Honor's thesis. I also spent a summer in a clinical genetics

setting where I was able to make an informed decision to not seek a medical degree, so that I could spend more of my young life doing research and more time trying to find cures instead of telling patients that I couldn't help them.

After graduating in the top 10% of my class from Cornell, I went to the most competitive Human Genetics Ph.D. program in the country at University of Michigan. I trained with the leaders in the muscular dystrophy field; Jeff Chamberlain as a Ph.D. student, and Kay Davies as a postdoctoral fellow at the University of Oxford in England. Professor Davies has been honored by the Queen of England for her contribution to biomedical research in the UK and is now a Dame. As a graduate student and postdoc, I published over 20 peer-reviewed papers on muscular dystrophy, including some in the very best journals such as Cell and Nature Genetics.

I accepted a tenure-track faculty position at The Ohio State University because of the clinical strength in neuromuscular and cardiac diseases. I did so with the vision of carrying out breakthrough basic and translational research focused on the skeletal muscle and heart pathologies of muscular dystrophy. Rather than merely continuing some aspect of the work ongoing in the labs of my mentors, I took the difficult path of initiating research projects in my own lab to address two different important scientific questions that weren't being addressed elsewhere. The first project focused on heart disease in Duchenne muscular dystrophy. The second focused on identifying novel mechanisms at the neuromuscular junction.

The neuromuscular junction is the site where the nervous system controls muscles and the root of the problem in neuromuscular diseases. My lab identified receptors that had never before been documented at this site. This discovery highlights

how new knowledge will never be learned if you're only looking for what you already know is there.

Patients with Duchenne and other muscular dystrophies also have heart failure in addition to debilitating skeletal muscle problems. Therefore, we also focused on defining the mechanisms of this heart disease with the long-term goal of identifying novel targets for treatment. We found a gene that is specifically downregulated in muscular dystrophy cardiomyopathy that progresses to heart failure. We confirmed that the protein is lacking only in heart cells of this heart failure model. In collaboration with an OSU cardiologist, we next looked to see if this protein was missing in patients with heart failure. Surprisingly, we found that at least 60% of heart samples collected from patients who had heart transplants showed an absence or major reduction in the levels of this protein. What is so significant about this number is that it represents 60% of people who develop heart failure as a result of a wide variety of primary causes, not just muscular dystrophy. It could be a common pathway to heart failure for at least 60% of the 5 million people who are living with heart failure in the U.S. today and the 500,000 additional cases diagnosed every year. I want to emphasize that these are not people who suffer heart attacks and either quickly recover or die from them. Rather, people with heart failure are hospitalized for long periods of time, are on life support, and are on the waiting list for heart transplants. One can just begin to imagine the economic and quality-of-life benefits that would result from a way to prevent heart failure from this or similar research. To pursue this line of research, we submitted an R01 application to the NIH proposing the next set of definitive experiments. The application proposed to determine the ability of this protein to cause and prevent heart failure in mouse models

and to test specific hypotheses in patient samples of how this protein is lost. It represents a collaboration between me (a molecular geneticist), a cardiac physiologist (Paul Janssen), and a cardiologist (Phil Binkley). That application received a score that would have been funded a few years ago, but missed the funding line in the current environment. This example is just one of hundreds of exciting, potentially groundbreaking biomedical science projects that are not being funded today.

While we can't predict exactly how these research projects will benefit patients or impact the economics of the U.S. healthcare system, biomedical research is on the cusp of a breakthrough. It has been said that the 20th century was the Century of Physics with incomprehensible advances in flight, communication and silicon technology. The 21st century is the Century of Biology. The Director of the Research Institute at Nationwide Children's Hospital, Dr. John Barnard, gave a perfect example in a speech I heard a few days ago. At the beginning of the Century of Physics the Wright Brothers probably couldn't envision that their invention would evolve into the global companies of Boeing or Netjets or that John Glenn would travel into Space, but they knew they were onto something big. At the present, while we can't predict where we'll be at the end of the century, or even in 10 years, we know we are on to something big. We have advanced to the point of having all of the right tools and all of the background knowledge. We, as scientists, know that we are on the verge of major breakthroughs in Biology and Medicine.

So what's the problem with the flat NIH budget? Well, it comes down to the same economic issue as everything else. A flat budget equates to a loss of buying power. It is certainly not going to flamboyant salaries, although I'm happy to report that

we do provide healthcare for our trainees and employees. In addition to this obvious economic issue, funding of individual investigator-initiated innovative science via hypothesis-driven R01 grants has been impacted to an even greater extent. The public push to translate everything in the research pipeline into clinical applications has led to the creation of milestone driven research. While milestone-driven translational research is important and certainly should be funded by the NIH, research designed to meet milestones results in discarding any novel observations made along the way. This type of research design will push anything with clinical potential out of the pipeline. The question is: what will fill the pipeline?

The individual initiated R01 is the grant mechanism that feeds the pipeline. The payline for R01's is currently around the 10th percentile. From my perspective also as a grant reviewer, you have to bet on 1 grant out of a pile of 10. When you can select only 1 grant, it is against human nature to not select the grant from the established lab with the long track record, where many of the proposed experiments are already complete. As one colleague said, "it has the horrible consequence of pushing research agendas to the 'tried and true' variety rather than the risky, innovative, and high pay-off, even for senior investigators." That effect is even more dramatic for junior investigators who have not built powerhouse labs, but have the really innovative ideas that are not getting funded. These junior investigators are spending inordinate amounts of time writing and rewriting their proposals instead of actually conducting innovative research. The low NIH budget is driving young scientists into teaching careers, industry, publishing, or sending them to law school. We're losing a generation of scientists.

They're people like me. People who graduated at the top of their classes from Ivy League Universities; people who were trained by the best scientists in the world; people who have had a passion for what they do their whole lives. I'm not talking about people who were never successful. I'm talking about people who have multiple first author papers in the best scientific journals: Cell, Nature, Science. They're people who may have had their first R01 successfully funded, but can't get a renewal funded; and will lose all of the trained personnel in their labs while they're trying. We're losing them. The U.S., which has been a world leader in scientific discovery is falling behind.

We're losing physician scientists who have had enough passion for finding new ways to treat human disease to obtain both M.D. and Ph.D. degrees or who do a research fellowship. My clinician scientist colleagues are going into private practice when they can't get their R01's funded. They're making this decision not based on personal financial reward, but based on the funding situation that prohibits their progress towards what they passionately believe will aid humankind.

Behind us, we're losing the students and postdocs that we're training, because they don't want to go through the rejection and adversity that they're seeing us go through. So, we're really losing 2 or more generations of scientists.

As we allow inflation to erode NIH funding, it declares to the international community that the U.S. does not believe that science will play a role in the development of its society. It is short-sighted.

To me, the biggest disappointment is that we've come to a point where science and medicine have so much overlapping technology and there is so much common knowledge between the bench and the bedside, that scientists and physicians are really

poised to work together to do momentous things. The effects of losing our generation will be devastating.

So what will I do if my R01 doesn't get funded? I'll still be a co-investigator on a milestone-driven multi-investigator translational project that will support a part-time person in my lab. I'm part of another large translational application that will be reviewed soon. If that gets funded, my salary won't get cut and it will keep my lab slowly moving along, but only to refine what we already know, not on any of our promising new discoveries. While working in large groups of clinicians and scientists on these large translational projects are also exciting and have immediate potential impact on patients, they're not enough for me. They let me use my organizational and technical skills, but not my passion that leads me to innovate and envision the potential to make the completely novel breakthroughs. I feel fairly confident that I could get funded to do research on some minutia of the known, but that's not a good enough reason to spend that much time away from my wonderful 5-year-old son and 2-year-old daughter.

I am confident that the innovative research from my laboratory will lead to dramatic improvements in the quality of life for patients with muscular dystrophy and heart failure while at the same time dramatically decreasing healthcare costs. There are countless other cases like mine. If NIH funding was in the same relative state a decade ago, children with leukemia would still be dying, instead of going on to live normal lives. We would not have the imaging capabilities to detect and prevent many cases of breast and prostate cancer and the treatments that extend survival and improve quality of life. In the next decade we are likely to have treatments for diabetes, Alzheimer's disease and heart disease, but not if the NIH funding crisis continues. As a

country, we should be thinking not of how we are going to solve this crisis for the coming year, but we should be developing a 50 year plan to maintain the expertise of scientists and remain at the forefront of scientific discovery and applications to healthcare. We need to invest in the next generations of scientists and we need to do it now.