Down Syndrome: Research & Discoveries Impacting Alzheimer Disease
& Other Major Diseases
Statement of
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Labor, Health & Human Services, Education & Related Agencies
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Chairman Cole, Ranking Member DeLauro, and esteemed Members of the Committee, I thank you for the invitation to testify on the very important topic of Down syndrome research. I am William Mobley, Executive Director of UC San Diego's Down Syndrome Center for Research and Treatment and the Florence Riford Chair of Alzheimer Disease Research. I remember warmly the last time I shared my testimony about Down syndrome research. I commented that research would yield significant benefits for Down syndrome (DS). Just six years later, that promise is being realized. As never before, we are beginning to understand the biology of DS and discovering methods to treat its adverse effects. I argued that funding from private sources as well as NIH would bring new insights and treatments. Today, this is an emerging reality. We are witnessing a transformation in the ability to enhance the wellbeing of those with DS.

I wish to address 3 key elements: 1) the recent change in the NIH focus and approach in DS; 2) progress and accomplishments over the past 6 years supported by NIH and the larger research community; and 3) opportunities to leverage NIH investments in DS research for discoveries impacting Alzheimer research.

To begin, let me speak of a time in which research of DS was met with skepticism. Just 20 years ago the opinion was broadly held that studies of DS would fail because of the complexity that arises from the presence of an entire extra chromosome, the 21st

chromosome. By what reasoning, it was asked, could one possibly argue that an extra copy of one gene would make a difference. And how, it was asked, could one ever hope to decipher the contribution of so many genes to so many different clinical phenotypes. And even if there was progress, surely the changes were fixed at birth and unchangeable. Finally, one would never be able to carry out clinical trials in the DS population. Happily, each of these statements- *too complex to understand, too difficult to study, too hard to translate, too late to make a difference* - are proving to be false. Indeed, in spite of the complex biology of DS, genes and mechanisms responsible for adverse effect are being discovered, targets for treatment are being defined, and one can now confidently forecast successful treatments for those with DS.

In many ways, the existing healthcare landscape for DS has never been better and those with DS have never enjoyed greater longevity. Treating congenital heart disease and leukemia and addressing the many other problems experienced by those with DS have delivered important benefits. But, as is quite apparent, important unmet needs exist across a spectrum of maladies whose presence in DS, though not unique, is markedly increased in frequency. One question is, “how can these very significant burdens be addressed?” Equally important, and highly motivating is the question, “would understanding the genetic and mechanistic basis for increased risk of a disorder in DS serve not just those with DS but the population at large?” In other words, does the biology of DS offer an avenue for enhancing the wellbeing of those with DS as well as others? I argue that this exciting possibility does exist.

Citing a specific example, you may know those with DS are at markedly increased risk for early onset of Alzheimer disease. Alzheimer disease is a progressive dementing

neurodegenerative disorder that leads to death. There are no disease modifying treatments for the estimated 6 million currently affected in the US. The cost of care exceeds $250B annually. With our aging population, the number will increase to 14 million in 2050, with a cost of care that exceeds $1T annually. Remarkably, all of the pathological manifestations of Alzheimer disease are present in the brains of those with DS by age 40 and by age 60 approximately 90% will be demented. The DS population thus represents a very large group whose genetic makeup confers an exceedingly high risk of Alzheimer disease. Imagine how those with DS and their families view the oncoming threat of Alzheimer disease. I can testify that it is a nightmare - one from which they cannot awake at this time.

Some years ago, I committed my research to preventing Alzheimer disease in DS. To understand Alzheimer disease in DS, and to discover effective treatments, my laboratory asked which gene or genes were responsible. Our studies in mouse models of DS pointed to an extra copy of the gene for the Amyloid Precursor Protein as necessary for Alzheimer disease in DS. These findings, now independently validated in people with DS, argue that treatments targeting this gene and its products could prevent Alzheimer disease in DS. Several ‘shots on goal’ are being tested as we speak with promising initial results. We must accelerate this work and ensure that its insights, and those from other laboratories, are quickly translated to clinical trials so that adults with DS can be spared the ravages of Alzheimer disease.

Importantly, we and others believe that the molecular events leading to Alzheimer disease in DS are highly relevant to Alzheimer disease in the general population. Thus, treatments

to prevent Alzheimer disease in DS may well prove effective for those without DS. Accordingly, here is a powerful example of how studies on DS will benefit all of us.

To create a rich future for DS research, it is important to acknowledge that our success was enabled by widespread support and collaborations involving both the private and public sectors. Foundation support was critical – including contributions from the LuMind RDS Foundation, under the leadership of the late Dr. Michael Harpold, the Global Down Syndrome Foundation, the Alzheimer Association, the National Down Syndrome Society, the Lejeune Foundation, and the Cure Alzheimer Fund. Equally significant was support from AC Immune, whose focus on DS resulted in an ongoing Phase 1 trial in adults with DS. NIH's role in DS has been highly significant. Their forward leaning efforts to convene a collaborative discussion among researchers about the biology of DS and to create new opportunities to advance science and care have been pivotal.

Let me speak briefly about the NIH role in DS research. When I first began research on DS, NIH had DS research as a lesser priority in its portfolio and investments were fragmented. This changed substantially with the establishment of the Down Syndrome Working Group recommended by Congress in 2006. We are grateful for Congress' interest and support for DS research. With this came new energy for research, and a valued champion in Yvonne Maddox, at that time Deputy Director of NICHD, who led the creation of the first research plan for Down syndrome. Gratifyingly, the NIH focus on DS has grown. Among its several manifestations are: 1) support for creation of mouse models; 2) creation of DS-Connect, a DS registry; 3) new initiatives to identify biomarkers and track progression of Alzheimer disease; 4) support, under a private/public partnership, of a clinical trial in adults with Down syndrome; 5) meetings to address the

biology and treatment of Alzheimer disease in Down syndrome in 2013; and 6) in 2014, a revised research plan. The recruitment of Dr. Diana Bianchi as Director of NICHD, herself a Down syndrome researcher, is extremely encouraging. There can be no doubt that NIH is now focused on DS and that this has made a significant difference in our research progress. And because NIH has moved DS research to a higher priority, so has the international research community.

Many challenges remain for those with DS. To meet them, the NIH should accelerate the pace and expand the scope of its work. I ask Congress to urge NIH to redouble its efforts by convening new discussions to define research gaps and opportunities, by defining priorities, and establishing new research initiatives. Let us together commit to making the next decade a period of unprecedented success in understanding and caring for those with DS.

In summary, I wish to emphasize these points: 1) in collaboration with the private sector, NIH has significantly contributed to progress in DS research, both nationally and internationally; 2) opportunities for leveraging DS research have never been more promising for understanding and treating Alzheimer disease in DS as well as the population in general; 3) federal investments in research through NIH are critical to addressing the challenges posed by DS; and 4) the NIH should be asked to redouble its efforts to chart a course by which these investments yield significant new benefits for those with DS as well as the entire population.

In closing, I thank the Members of the Committee for their robust support of NIH's mission, including DS and Alzheimer disease. You are making it possible for us to make a difference in people's lives now and into the future.