Written Testimony of
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Good morning, Chairman Blunt, Ranking Member Murray (my Senator), and distinguished Members of the Subcommittee. Thank you for the opportunity to testify today about the value of medical research, which is something I do every day. It is an honor to appear before your today to provide my view of the pivotal role NIH funding plays in our efforts to counter Alzheimer's disease, one of the central challenges in biomedicine.

My name is Thomas J. Grabowski, Jr. I am a neurologist at the University of Washington, where I direct our clinical and research Centers for Alzheimer Disease and other memory disorders, including the NIA-funded University of Washington Alzheimer Disease Research Center, and the UW Medicine Memory and Brain Wellness Center. My own research focuses on new brain imaging approaches in Alzheimer's disease and other degenerative diseases, using MRI imaging approaches.

Background

Some 5 million Americans have Alzheimer's dementia, including one in nine people over age 65. It is the rare person whose circle has not been touched by this disease. Alzheimer's dementia in a person has an outsized impact, emotional and material, on an entire family. Alzheimer's is the only leading cause of death that can't be cured, prevented, or even slowed in 2017. Consequently, increasing numbers of persons are living with Alzheimer's dementia, and dying from it, and the numbers are set to more than double and even triple by 2050.

If these facts aren't enough to call us to action, even larger numbers have latent pre-symptomatic disease. Alzheimer's dementia is a relatively late consequence of a disease process that has gone on in the brain for 15 years or more. The rate of outright dementia at age 65 is less than 1%, but by age 65 fully 20% of persons, despite normal memory, already have moderate to severe levels of amyloid plaques in the brain, as has been demonstrated by spinal fluid tests or amyloid PET brain scans.

Framing Alzheimer disease around its full course like this is critical to progress. The National Plan to Address Alzheimer's Disease has an overriding first goal to prevent and effectively treat Alzheimer's disease by 2025. The long pre-symptomatic phase is a window of opportunity for intervention. During this time period, different disease processes conspire to damage brain cells.

Meanwhile positive lifestyle choices can postpone, literally by years, the tipping point at which the disease finally affects cognition. There is thus a clear opportunity for prevention of dementia by a combination of "precision medicine," brain health programs, and early intervention. If we can slow the disease process down by 5 years (out of those 15 pre-symptomatic years), we would cut Alzheimer's dementia in half. The search for a scalable imaging biomarker and early diagnosis and intervention are important priorities for our NIH-funded Alzheimer's Disease Research Center, and are goals shared by many of our peer Centers.

Toward Precision Medicine for Alzheimer's Disease

AD often is co-morbid with related chronic illnesses such as microvascular brain injury and Lewy body disease (LBD). Moreover, genetic risk for AD now clearly highlights the potential for multiple molecular drivers and perhaps multiple pathogenic pathways. The vision of the University of Washington (UW) AD Research Center (ADRC) is to bring individual clarity to this enormous complexity—to achieve precision medicine for AD so that the right person is treated at the right time with the right prevention or therapeutic.

Three key elements of precision medicine (Cholerton et al, 2016) are stratification by risk, detection of pathophysiological processes as early as possible (ideally before the disease manifests clinically), and alignment of mechanism of action of intervention(s) with an individual's molecular driver(s) of disease. Now gaining broad currency in cancer care, a precision medicine approach is beginning to be adapted to cognitive impairment and dementia.

Under NIH funding, and the leadership of Drs. George Martin, Murray Raskind, Thomas Montine, and most recently myself, the UW ADRC has been helping to develop this approach to AD for 33 years. During its initial 20 years, our Center focused on AD genetic risk. Although we continue these efforts, the nature of AD genetics research has evolved and now is accomplished within large consortia rather than a single Center Project. Ten years ago, UW ADRC made 'Biomarkers and Experimental Therapeutics' our theme, recognizing that even the most sophisticated risk stratification will have limited impact without meaningful measures of preclinical disease and new therapeutics. The UW ADRC has been an incubator for development of recent national multicenter clinical trials, including the EXERT trial of aerobic exercise in Alzheimer disease (led by Dr. Laura Baker, now at Wake Forest University), a trial of Prazosin Treatment for Disruptive Agitation in Alzheimer's Disease (led by Drs. Elaine Peskind and Murray Raskind, UW), and the Study of Nasal Insulin to Fight Forgetfulness (SNIFF) led by Dr. Suzanna Craft, now at Wake Forest University.

Our current research projects advance our theme by pursuing fundamental research on mechanisms of aging and their intersection with Alzheimer disease pathogenesis, innovative development of novel therapeutics through protein design, and dynamic functional connectivity fMRI as a new window into pathophysiologic processes of preclinical AD. Our Center has been designed to create the knowledge and tools needed to advance pre-clinical biomarkers, to lay the groundwork for novel experimental therapeutics, to collaborate substantively in multicenter clinical trials, and to reach out to underrepresented populations.

UW ADRC vision and mission resonate strongly with the principles of the National Plan to Address Alzheimer's Disease. Ultimately, our efforts, combined with others, will drive optimally targeted and timed preventions and interventions for AD and related causes of dementia.

Overview of the University of Washington ADRC

The structure of our NIA-funded Alzheimer's Disease Research Center includes five Core resources, including a Clinical Core that characterizes and follows hundreds of research subjects; three formal research projects; and a Satellite Core that reaches out to American Indian and Alaskan native populations.

In research Project 1, ADRC Investigator Dr. Matthew Kaeberlein, also the Co-Director of the Nathan Shock Center on Basic Biology of Aging (funded by NIA), investigates the mechanisms by which two important and highly conserved signaling pathways involved in cellular aging determine cellular resistance to amyloid beta toxicity, using a roundworm animal model. The Project aims for fundamental insights into the conserved cellular responses to amyloid beta and the identification of new therapeutic targets in Alzheimer's disease.

In Project 2, ADRC Investigator Dr. David Baker, also the Director of the UW Institute for Protein Design, is designing small molecules that bind specifically to different forms of amyloid beta (such as soluble monomers) using the Rosetta software suite for rational protein design, coupled with a distinctive crowdsourcing approach that his laboratory has used to great success in HIV and influenza. The idea is that rational protein design will enable evaluation of therapeutic approaches that target different hypotheses as to the precise mechanism of amyloid toxicity.

In Project 3, ADRC Investigator Dr. Thomas Grabowski, also the Director of the UW Integrated Brain Imaging Center (which has received major funding from NINDS), is investigating new functional MRI imaging approaches for preclinical detection of Alzheimer disease. Functional connectivity fMRI (fcMRI) can map brain networks based on detecting synchronized activity across separate brain regions. In particular, the brains "default network" is systematically affected in early Alzheimer disease. In this project, fcMRI measures of default network integrity are being validated against CSF protein markers of Alzheimer's disease, extending our Alzheimer's Disease Research Center's work on preclinical biomarkers.

Therapeutic Pipeline Project (TPP). In 2015 the Ellison Foundation made a $6M gift to UW Medicine to foster the development of a "therapeutic pipeline" for AD, based on precision medicine principles. This project leverages our Center's NIH-funded resources, and includes next-generation whole-exome sequencing to stratify trial-ready subject groups, and the use of induced pluripotent stem cells to develop subject-specific neuron cultures that can be used as disease models to understand the different molecular pathways that drive Alzheimer disease in different individuals. We are turning to these tools to investigate Alzheimer disease mechanisms that include mTOR aging pathway, immune inflammatory responses by microglia, and endosomal trafficking of amyloid beta.

Our Satellite Core is led by Dr. Dedra Buchwald of Washington State University, also the Director of Parterships for Native Health. Drawing on the vast experience of Dr. Buchwald's group in carrying out research in this unique, underserved, and complex population, the Satellite Core will follow 450 aging reservation-dwelling American Indians at three sites in Oklahoma, Arizona, and South Dakota for progression of cognitive impairment and imaging markers of neurodegenerative disease.

Besides the Washington-based Centers mentioned above, the UW ADRC is closely partnered with the Adult Changes in Thought study, a longitudinal population-based prospective cohort study of brain aging and incident dementia in the Seattle metropolitan area, based at the Group Health

Cooperative in Seattle, directed by Drs. Eric Larsen and Paul Crane, and continuously funded by the National Institute on Aging for 28 years.

On a Foundation of Care and Community Trust

Our ADRC is partnered with the UW Medicine Memory and Brain Wellness Center clinic, a comprehensive multidisciplinary evaluation and treatment service for disorders affecting memory and cognition. Our combined mission is to promote the well-being of persons living with memory loss and their families, by providing exceptional care, advancing scientific understanding, and building dementia-friendly communities. The themes of the Memory and Brain Wellness Center clinic are early and accurate diagnosis, strengths-based reframing and treatment, and community transformation. Patients have access to state of the art genetic and imaging studies, integrated mental health care, cognitive rehabilitation, educational programming, and the option to participate in research via our patient Registry, through which they may connect to the ADRC, clinical trials, brain health studies, and others.

For most people, even medical providers, ideas about Alzheimer disease are framed around dementia. To really transform medicine for Alzheimer's disease, we must also transform the way we (patients and families, physicians, and our society) think about the disease. For example, unless we counter the stigma attached to Alzheimer disease, neither patients nor primary care physicians are likely to cooperate with the important agenda of early detection. At the University of Washington, we and our community partners have realized the importance of educating the public to understand the entire course of Alzheimer disease, including its pre-symptomatic and mild cognitive impairment stages, and the strengths a person retains in the midst of it, as well as the importance of strengths-based programs for persons with memory loss.

Our Washington state community partners include Momentia, a grassroots social movement in Seattle of persons living with early stage memory loss, transforming what it means to live with memory loss through empowerment and engagement in the community; the Western and Central Washington State Chapter of the Alzheimer's Association; the Dementia Action Collaborative implementing the Washington State Plan to Address Alzheimer's Disease; and other groups providing advocacy or engagement programming.

We envision a world in which people live well with memory loss and can rely upon the best care, within a community of support. Leading-edge research really advances on a foundation of best care and community trust.

Critical Importance of NIH Funding

Progress in understanding of AD ultimately requires more detailed data from each research participant, and aggregating these data nationally. Our field has a record of successful large-scale cooperation, beginning with the Alzheimer's Disease Centers program of the National Institute on Aging that has operated for more than 30 years. Ours is one such Center in this network, which forms the backbone, and maintains subject registries and tissue repositories for American AD research. Cross-institutional initiatives regularly leverage these resources. For example, the NIH-funded Alzheimer's Disease Sequencing Project (funded by NIA and the National Human Genome Research Institute) and Dominantly inherited Alzheimer Disease Network (DIAN, funded by NIA) make use of our resources. The Alzheimer Disease Neuroimaging Initiative has been pivotal to understanding early disease biomarkers and disease heterogeneity, and has set a standard for data

sharing and productivity, continued and extended by other open neuroscientific initiatives from NIH (e.g. the Human Connectome Project) and charitable sources (e.g. the Allen Institute for Brain Science and Sage Bionetworks, both in Seattle). NIH- and industry-sponsored treatment trials also make use of the resources of the Alzheimer Disease Centers. At our Center, these have included the DIAN Trials Unit, the Biogen EMERGE study of Aducanamab, and the Anti-Amyloid in Asymptomatic Alzheimer's Disease (A4) study (funded by NIA and a public-private consortium).

NIH funding is simply critical to all these efforts. It underlies most of the effort I have outlined in my testimony. NIH funding is what gives longevity to the research infrastructure, brings about standardization and thematic direction, enables cooperation at scale, trains new scientists, and ultimately will achieve the 2025 goal. We need to bring about even more cooperation across NIH, industry, and charitable groups; and new standards of data sharing to promote progress.

The Alzheimer's Accountability Act authorized the NIH Director to analyze research funding requirements, beyond the NIH base budget, to remain on track to achieve the goals of the National Plan, with specific, targeted milestones Dr. Collins has submitted a Professional Judgment Budget for FY 2018. I urge it on you with enthusiasm, and with optimism that we can defeat this disease.

Resources

UW Medicine Memory and Brain Wellness Center: http://www.depts.washington.edu/MBWC
UW Alzheimer's Disease Research Center: http://www.pathology.washington.edu/research/adrc
Momentia: http://www.momentiaseattle.org
Precision Medicine for Alzheimer's Disease: Cholerton B, Larson EB, Quinn JF, Zabetian CP, Mata IF, Keene CD, Flanagan M, Crane PK, Grabowski TJ, Montine KS, Montine TJ. Precision Medicine: Clarity for the Complexity of Dementia. Am J Pathol 186:500-6, 2016.