Testimony to Members of the Senate Special Committee on Aging

Changing the Trajectory of Alzheimer's: Reducing Risk, Detecting Early Symptoms, and Improving Data

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The Jackson Laboratory
Leading the search for tomorrow's cures

Good afternoon Chairwoman Collins, Ranking Member Casey, and members of the committee. Thank you for the invitation to be here today and for your work in support of Alzheimer's disease and dementia research. My name is Dr. Gareth Howell and I am an Associate Professor at The Jackson Laboratory in Bar Harbor, Maine and co-Principal Investigator of the MODEL-AD Center.

I am extremely grateful for the opportunity to provide this testimony to the committee. Your leadership on the Aging Committee, and in Congress, is key to the search for treatments for this terrible disease. In particular, we appreciate the committee's support the committee's support of legislation including the National Alzheimer's Project Act, authored by Senator Collins. The research community is also appreciative of the Alzheimer's disease bypass budget and the recently approved increase of an additional $414 million for Alzheimer's and dementia research. I am confident science will overcome Alzheimer's disease; the question is when? Your continued engagement with the research community is vital as we seek to better diagnose, prevent and treat Alzheimer's disease as soon as possible.

The Jackson Laboratory is an independent, nonprofit, 501(c)(3) tax exempt research institute that strives to discover precise genomic solutions for disease and empower the global biomedical community in is shared quest to improve human health. The Laboratory maintains its main campus in Bar Harbor, Maine, and maintains other locations in Farmington, Connecticut, and Sacramento, California. The Bar Harbor campus is dedicated primarily to mammalian genetics research and central operations, while the Farmington campus, also known as the The Jackson Laboratory for Genomic Medicine, is dedicated to human genetics and genomics research. The Sacramento includes state-of-the-art vivarium for breeding and distribution of mouse models as well as laboratory space for in vivo research services.

My scientific research career began as a geneticist at The Sanger Institute in Cambridge, UK where I did my PhD in comparative genomics – identifying errors in genes responsible for human diseases and identifying their counterparts in the mouse genome. Being able to study the genes in mice allowed us to uncover potential therapeutic treatments. After my PhD, I moved to The Jackson Laboratory in Bar Harbor, Maine. Aging research has been a key area of investigation at JAX for many years. However, in the last five years, we have established a vibrant Alzheimer's disease research program that includes more than 40 scientists led by myself and Drs. Gregory Carter, Catherine Kaczorowski and Kristen O'Connell. We aim to identify genetic factors that drive both susceptibility and resilience to AD, as well understanding how modifiable risk factors (e.g. diet/physical activity) and comorbidities (obesity, diabetes, heart disease) contribute to AD.

Ultimately, working with the larger scientific community in the US and worldwide, we hope to leverage these findings to identify and test novel therapeutic targets. My lab's goal is to identify the earliest stages of Alzheimer's disease and dementia, since targeting these provides the greatest opportunity for therapeutic intervention. It is incredibly challenging to identify these stages in human patients since they occur before any recognizable symptoms emerge. However, this is where animal models of human diseases come in. An animal model is a representation of a human disease and we can use

animal models to precisely define key stages of a disease – particularly the earliest stages. Mice share 95% of their genes with humans and so at JAX we focus on building accurate representations of human disease in mice. We then use a variety of genetic and genomic approaches to identify genes and proteins that are key drivers of disease during pre-symptomatic stages. These drivers are the targets for developing treatments that can then be tested in the mouse model. For example, the power of the mouse for treating a human disease was highlighted recently for spinal muscular atrophy (SMA), a disease characterized by muscle weakness and atrophy. A mouse model for SMA was created at JAX, a treatment tested in the mice, and following successful clinical trials, the first treatment to treat children and adults with SMA was approved by the Food and Drug Administration in December 2016. We can also use mice for incorporating non-genetic risk factors – such as diet, physical activity – and other diseases that increase risk for AD – such as cardiovascular disease and diabetes. The expectation is that preventative measures will be more effective than interventions. Therefore, encouraging lifestyle changes in the young and the middle aged should also be a key focus.

Sadly, many clinical trials for Alzheimer's disease have not been successful. There is a multitude of reasons why these trials have not been successful including targeting severe stages of AD, rather than early or presymptomatic stages. Unfortunately, for Alzheimer's disease, and other dementias, there is also a major bottleneck in searching for treatments. There is no single mouse model for the most common form of Alzheimer's disease – known as sporadic or late-onset Alzheimer's disease (**Fig. 1**).

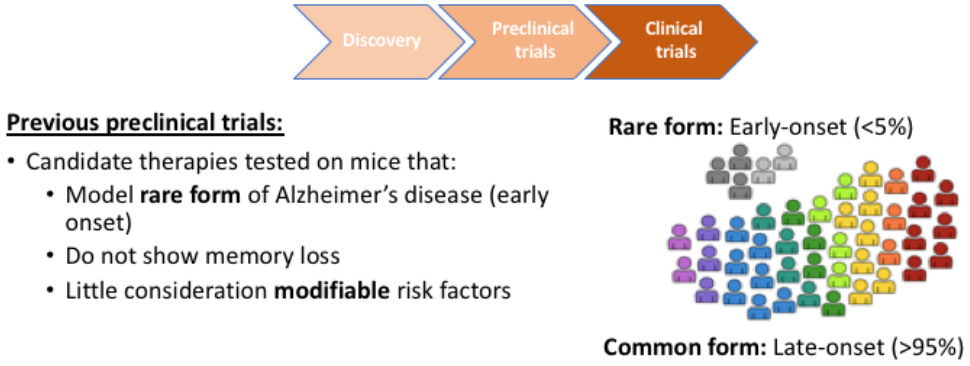

Fig. 1: Clinical trials for therapies for Alzheimer's disease have not worked.

Until mice are developed that reproduce defining features of Alzheimer's disease, the power of the mouse will not be fully realized. Therefore, I am really excited to be a part of MODEL-AD, a collaboration between Indiana University, JAX, Sage Bionetworks and University of California Irvine, that was established through generous funding from the National Institute on Aging (NIA) in the fall of 2016. We are charged with creating new mouse models for Alzheimer's disease (**Fig. 2**), staging and matching the changes we see in the mice to those seen in humans (**Fig. 3**), and testing potential new therapies.

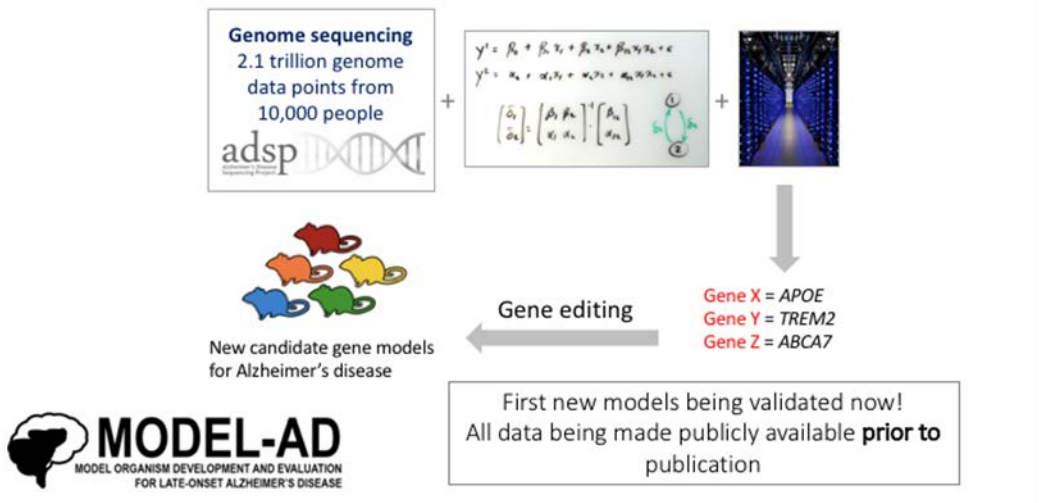

Fig. 2: Finding new gene combinations for Alzheimer's disease. All animal models created by MODEL-AD are based on large genomic datasets from human studies (e.g. Alzheimer's disease sequencing project (ADSP). Combinations of gene changes are 'edited' into the mouse genome to determine how they contribute to AD risk.

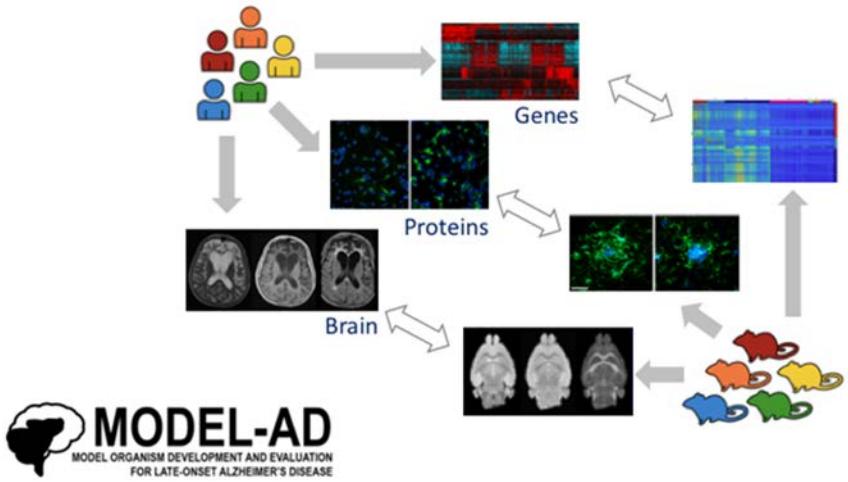

Fig. 3: Matching Alzheimer's disease in humans and mice. All animal models are assessed for AD-relevant outcomes using similar techniques to those used to diagnose AD in humans. This will greatly improve the translatability of our findings, in particular, the relevance of testing potential therapeutic compounds prior to a clinical trial.

It is very rare to have a Center that is capable of both generating the mouse models and testing potential new treatments. Significantly, we also have strong links with pharmaceutical companies, including Eli Lilly and Pfizer, aiming to close what has been a significant gap between academic research findings and translation to clinic.

I believe the structure of the MODEL-AD Center maximizes the chances of our success. The collaborations that occur within the center are successful because the diverse group of researchers with different specialties are banded together, sharing information in real time with each other, allowing us to build on each others research. This type of approach would benefit from an overall public health approach. The amount of data generated by researchers is coming at a fast pace and we would benefit from data clearinghouses to help us crunch it. Based on the recommendations of program officers at the NIA, MODEL-AD is made up of groups of scientists, or 'cores', that are allowing us to generate mice that are most likely to show similar changes to those seen in Alzheimer's disease. We have a **Bioinformatics Core** – which is working with clinician scientists to search through all the data generated from human Alzheimer's disease patients to identify specific genes that may be altered to increase risk for the disease. We have a **Disease Modeling Project** that is introducing those same genetic errors into the mouse equivalent of the human gene to determine how similar the outcomes are to the human condition. We have a **Preclinical Testing Core** that will then use those more precise mouse models of human Alzheimer's disease to assess new therapies before they can be tested in the clinic. All our work is overseen by a group of expert scientists from academia and pharma to ensure our work stays focused on finding new treatments. Most importantly, all mouse models will be made widely available to the scientific community – something JAX has been doing for over 50 years – and all data will be made publicly available through a specially developed web portal designed that was created and is managed by Sage Bionetworks.

We are joining a new era in research where individuals are no longer working behind closed doors to seek the best solution. We are combining our strengths and working together through the concept of open science to accelerate the discovery of cures for Alzheimer's disease. The open science approach focuses on early, broad sharing of research resources with the dual goals of improving transparency and reproducibility in the research process and of ensuring publicly funded resources are made broadly available for reuse across the research community. The NIA has made significant investments into the application of open science for advancing Alzheimer's disease research – first by mandating the use of open science approaches to all scientists working on target discovery within the Accelerating Medicines Partnership in Alzheimer's disease and then by expanding the open research community to work across multiple consortia. We are proud to have MODEL-AD join this effort.

Much of the data that is being generated by large consortia should be considered a resource as much as research findings. Within MODEL-AD, we already benefit hugely from the open science policy instigated by the NIH. Much of the data we are using to predict which mice to make is freely available. We then create and extensively characterize these new mouse models for AD. However, there are always more ways to characterize these mice and also to use them to ask specific questions like "Is my gene or biological process involved in the progression of AD?" or "would my drug slow or prevent AD?". By making these mice and all data available at the earliest opportunity allows for these questions to be asked more quickly and effectively by the wider scientific community.

Our Center aims to create more than 40 new mouse models for Alzheimer's disease and test at least 5 new compounds for their potential to prevent, slow or cure Alzheimer's disease. Although we are only nine months into this five-year project we have made a great start. The first mice, carrying the greatest genetic risk factors for human Alzheimer's disease, have been created and are available to the research community. We have searched through billions of data points and already identified more than 10 new genetic errors that we are testing in mice. We have established procedures by which potential new compounds can be tested in the mice. Obviously, we have a lot of work to do but we are encouraged by the data and confident that we can make a difference.

The MODEL-AD center is already benefiting my research program and Alzheimer's disease research at JAX. My interest centers on the interplay between the immune system and blood vessels in dementia. Changes in immune cells and blood vessels in the brain may occur in as many as 90% of all dementias (including Alzheimer's disease, mixed dementia and vascular dementia). These damaging events can be influenced by genetic changes or by our lifestyle, particularly what we eat and whether we exercise. In my lab, we are studying how genetics and lifestyle factors contribute to blood vessel damage and immune changes. Data from my lab and many others, support modifying our lifestyle, such as eating healthier and exercising more, to reduce risk for dementia (**Fig. 4**). Our work showed that regardless of the diet they consumed, mice that exercised from young to middle or old age remained cognitively normal. Further, using a variety of different assays, we confirmed that the brains of the aged mice were indistinguishable from brain of young mice.

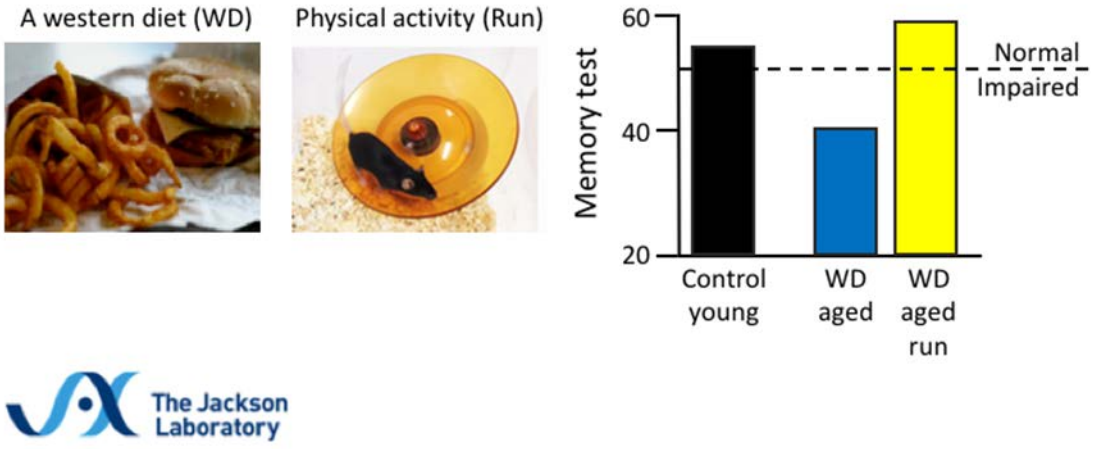

Fig. 4: Targeting modifiable risk factors to decrease incidence of Alzheimer's disease. Mice fed a diet similar to that consumed in the western world became obese and showed memory loss by midlife. However, these damaging effects could be overcome by regular exercise. These data support human studies that suggest changes to lifestyle would significantly reduce Alzheimer's disease cases.

Ultimately, we hope to stop or delay the onset of dementia by preserving the health of blood vessels, even in the face of damaging processes such as amyloid accumulation. We have already incorporated mouse models that were created as part of MODEL-AD into our work and aim to begin to test potential new therapies targeting blood vessel health in the coming months.

A second major interest in my lab that is benefiting from MODEL-AD is whether we can use the eye as a tool to track risk and progression of dementia. The eye is a window to the brain; the retina (where light-sensitive cells process information that is sent to the brain via the optic nerve) is essentially a piece of brain outside the skull that may be susceptible to some of the changes we see in dementias such as Alzheimer's disease. The eye is much easier to monitor than the brain. Although this is somewhat controversial at this time, if we can identify changes in the eye that relate to early, pre-symptomatic changes in the brain, we may be able to diagnose and treat those at earliest stages of dementia through simple eye exams. We are using the mouse models created by MODEL-AD to generate important preliminary data to seek additional funding to fully explore the potential of using the eye as a diagnostic tool.

Finally, a commonly forgotten aspect of mouse studies is that genetically diverse mice exist. These have not been well utilized to study Alzheimer's disease and related dementias. In general, most studies have been performed on one strain of mouse. This would be like studying a single human being over and over again. At JAX, we have access to the latest in genetically diverse mouse strains and are incorporating them into our research programs. Data from multiple labs at JAX show that if you induce amyloid deposition into different mouse strains, some develop dementia-like memory loss, while others do not (**Fig. 5**). This mimics the human population, where some individuals with amyloid deposition develop dementia, while others do not. We are now using these new mouse strains to determine the genetic factors that control amyloid-induced dementia. We anticipate finding new genes and pathways that can be targeted as potential treatments for AD and related dementia.

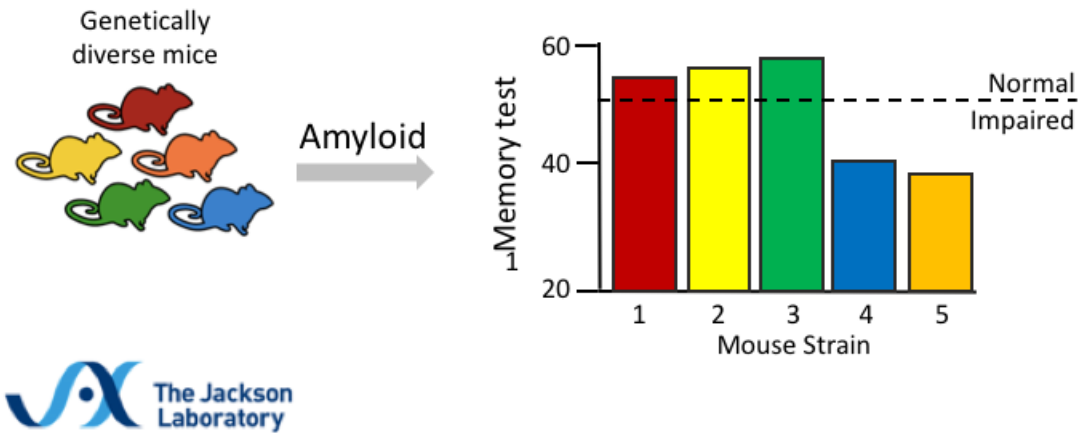

Fig. 5: Genetic context determine susceptibility to Alzheimer's-like memory loss. Genetically diverse mouse strains capture a similar degree of variant as seen in the human population. Different mouse strains show different outcomes after they have been genetically modified to deposit amyloid. Some are resilient to memory loss (red, yellow and green bars), while others are susceptible to memory loss (blue and orange bars). We are now using genetic and genomic approaches to determine the genes driving these different outcomes. This work will lead to the identification of new therapeutic targets.

In summary, research at The Jackson Laboratory, and collaborations such as MODEL-AD aim to deal with a critical bottleneck – namely the creation of mouse models that more faithfully reproduce human Alzheimer's disease. These models will be a vital piece in the puzzle to develop strategies to prevent, slow or treat Alzheimer's disease. I express my thanks to the Committee for this opportunity and for its continued support of Alzheimer's disease research.

Useful resources
For more information about MODEL-AD: https://model-ad.org/

For information about Alzheimer's disease research at JAX see the following resources:
Alzheimer's disease: https://www.jax.org/explore-by-topic/neurodegenerative-disease/alzheimers-disease

Breaking the bottleneck in Alzheimer's drug development: https://www.jax.org/news-and-insights/2017/january/breaking-the-bottleneck

MODEL-AD at JAX: https://www.jax.org/research-and-faculty/tools/alzheimers-disease-center/alzheimers-disease-precision-models-center