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BREAKING THE BOTTLENECK IN ALZHEIMER'S DRUG DEVELOPMENT

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Alzheimer's Disease Precision Models Center

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The stats are grim: About 5.4 million Americans are living with Alzheimer's disease, and the Alzheimer's Association projects that number to grow to 13.8 million by 2050.

The costs are huge: This year about $236 billion in this country will be spent on care, for Alzheimer's patients, with another estimated $221 billion representing the economic value of family members' unpaid care.

And, because it robs people of their memories, their ability to recognize loved ones and in some cases even their personalities, Alzheimer's disease wreaks human devastation beyond calculation.

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While several drugs on the market temporarily abate some symptoms of Alzheimer's disease, not one drug can prevent or treat the disease itself. In late November yet another drug, **solanezumab,** failed clinical trials. And a report by the Tufts Center for the Study of Drug Development pegs the cost of bringing a new drug to market at $2.6 billion.

By comparison, one of the largest grants the National Institute on Aging (NIA) has awarded this year — **$25 million over five years to The Jackson Laboratory (JAX) and Indiana University (IU)** — seems modest, yet it could transform the troubled drug development system and deliver new treatments for Alzheimer's disease.

Here's how: "For the first time, we have the tools to build new mouse models that truly represent patients with Alzheimer's disease," says **JAX Associate Professor Gregory Carter, Ph.D.,** one of the principal investigators of the new center for Model Organism Development and Evaluation for Late-Onset AD (MODEL-AD). "Our goal is to break the bottleneck of Alzheimer's drug development."

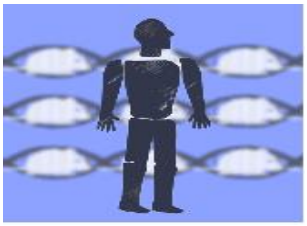
Modeling Alzheimer's disease in the mouse

Alzheimer's disease is a progressive degenerative disorder, and is the most common cause of dementia in people over age 65. The disease attacks neurons, causing them to break connections with other neurons and die, leading to memory loss, language problems and other deficits. The brains of people with Alzheimer's disease typically have beta amyloid plaques and tau tangles, but it's unclear whether these unwanted protein deposits are a cause or effect of the disease.

One of the difficulties in diagnosing and treating Alzheimer's, Carter notes, "is that most of the symptoms of the disease are behavioral, and they don't appear until there's already damage to the brain. If we could identify new early biomarkers that could be used to diagnose Alzheimer's at an earlier age, we might be able to arrest or reverse the damage at an earlier time point."

For more than 100 years, scientists have studied mice to understand the genetic basis for human diseases. Because mice and humans share up to 98 percent of their genes, a mouse with a genetic variation that's analogous to one found in a human with a given disease can serve as an experimental model for that disease. In the 1980s, gene transfer technology allowed scientists to engineer changes in the mouse genome to create transgenic models of human disease, and today gene editing technologies such as **CRISPR** enable even more precise model-building.

The first Alzheimer's disease mouse models carried a genetic mutation associated with a relatively rare, early-onset version of the disease. But most Alzheimer's patients have the late-onset version of the disease, which to date has not been successfully modeled in mice.



Why mouse genetics?
Why is so much medical research done with mice? And what does it mean when scientists talk about a mouse model?

JAX Associate Professor and Alzheimer's disease researcher **Gareth Howell, Ph.D.,** a co-principal investigator of the Alzheimer's disease center grant, comments, "There have been more than 400 unsuccessful clinical trials for Alzheimer's disease since 2004. Some of those were based on research using mouse models. Unfortunately, although those models have been fantastic to teach us about the biology of Alzheimer's disease, they haven't been appropriate as preclinical models, and so a major aim of the MODEL-AD center is to develop models that much more appropriately recapitulate human Alzheimer's disease, particularly nerve cell loss."

The MODEL-AD center is a partnership of JAX and Indiana University (IU), including co-principal investigators Bruce Lamb, Ph.D., whose work includes understanding the role of the immune system in Alzheimer's disease, and biomedical imaging expert Paul Territo, Ph.D.

“Our center also includes individuals that are seeing Alzheimer's disease patients,” Howell says, “all the way through to individuals that are assessing mouse models. We've never had access to this level of data before. For the first time, we have the entire pipeline within one program that will enable us to really determine which aspects of Alzheimer’s disease our new AD mouse strains model. And probably more importantly, which models are most appropriate for performing preclinical testing of new targets”.

Moreover, notes **Michael Sasner, Ph.D.**, a JAX expert in mouse model development and the MODEL-AD center co-manager, a major goal of the center is to put new and better mouse models of the disease in the hands of researchers worldwide.

“Right now the Alzheimer's field is very limited by the available Alzheimer's disease mouse models,” he says. “We know that mouse models will be important for developing and testing new drugs. Once we generate and validate new models of late-onset Alzheimer’s disease, JAX will make them widely available so that anyone in the pharma and biotech industries, as well as academic research, can use them as well as the data and associated protocols that we will provide about them.”

Howell, whose lab has published research **linking the Western diet and Alzheimer’s disease**, notes that genetic factors account for only 40 to 70 percent of an individual’s risk the disease. “We're not only thinking about the genetics of Alzheimer's,” he says, “we're also thinking about aging and environmental risk factors such as diet and levels of physical activity. Aging is the greatest risk factor for Alzheimer's disease, and in previous iterations of mouse models that hasn't been fully appreciated. JAX has a long history in aging research, and we're putting these Alzheimer’s disease genetic variants in the context of aging and really beginning to understand the interplay between genetic susceptibility and the aging process.”

Recent advances in genetic and imaging technologies have enabled a better understanding of the basis of Alzheimer's disease in humans, including genetic and environmental risk factors. Moreover, clinical researchers now have new ways to measure Alzheimer's disease and its progression through advanced, noninvasive imaging techniques, and genomic techniques that characterize the entire brain at the gene-by-gene level.

The JAX-IU center takes advantage of the vast patient datasets that have accumulated across the nation over the last five years or so, notes Carter, a computational biologist. “Our partner, **Sage Bionetworks**, is providing us with data from very large patient cohorts, those without Alzheimer's as well as those with Alzheimer's, so we can to try to identify genetic variants that tend to show up on the Alzheimer's side.”

Using computational approaches, Carter explains, the MODEL-AD team can determine which of those variants, separately or in combination, might be the most relevant and predictive of Alzheimer's, and develop an array of mice with those variants. Neurobehavioral expert **Stacey Rizzo, Ph.D.**, at the new JAX Center for Biometric Analysis will conduct advanced analyses of the new mouse models, providing data to compare with the human clinical data and to inform drug testing.

“We're still learning about the pathologies that lead to full Alzheimer's disease,” Carter says, “and our center and the models we create and share with the community will greatly expand that knowledge, and accelerate the translation of this basic research knowledge into realistic cures for Alzheimer's disease.”