Advancing AD

By Lev Osherovich, Senior Writer

The vast majority of dollars from the NIH's recent Alzheimer's disease grants are for clinical research, but the institute also made a trio of awards to academics to develop a systems biology picture of the brain disorder. The teams hope to uncover new mechanisms and targets that may have been overlooked because of the field's traditional focus on β -amyloid.

Two projects are fishing expeditions to find targetable pathways upstream of β -amyloid ($A\beta$) accumulation that act early in disease. The third is focused on the hypothesis that innate immunity and inflammation contribute to late-stage disease.

In 2012, the U.S. government launched the National Alzheimer's Project, a road map to develop therapies and mitigate the social and economic costs of Alzheimer's disease (AD).

As part of the project, the NIH Office of the Director and the **National Institute on Aging** announced in September a \$37.1 million award for three clinical AD trials—a pair of Phase III prevention trials in two different types of genetically at-risk individuals and a Phase I trial of an amyloid-antagonizing steroid.

The trial news deflected attention from the \$4.9 million going to the 3 systems biology teams, which will be eligible for up to an additional \$18.9 million collectively over the next 5 years.

The teams all seek to identify age-related differences that distinguish healthy and AD-stricken brains. The groups will look at genetic markers, gene expression data and proteomic measurements from large collections of postmortem patient samples and controls.

"The goal is to integrate all of these data into one analysis to identify molecular networks that are operating in disease," said one of the team's leaders, Philip De Jager, an associate professor of neurology at **Brigham and Women's Hospital**.

Brain collection

De Jager and coleader David Bennett plan to analyze the world's largest prospectively gathered collection of aged brains to discover new AD biomarkers and targets. Bennett is a professor of neurological sciences at **Rush University Medical Center** and director of the Rush Alzheimer's Disease Center.

"I'm the principal investigator of two cohort studies of common chronic diseases of aging with a focus on AD, as well as a wide range of other neurologic conditions," said Bennett. "The Religious Order cohort

is of nuns and monks without dementia. The other cohort is the Rush Memory and Aging project, which is recruited from the lay population in northeastern Illinois. The condition of entry is that participants must donate their brains after death."

Since the mid-1990s, Bennett's team has conducted annual clinical evaluations and blood draws of each study participant. Bennett said that his team has gathered data from about 3,000 subjects, of whom about 1,100 have died and been autopsied.

Now, Bennett and De Jager plan to analyze genomic and gene expression data, brain pathology, serum markers and clinical observations of memory and cognition to obtain a comprehensive view of AD progression.

The hope is that casting a wide net will identify early biological signs of AD that are independent of $A\beta$ pathology. Until now, researchers have focused on amyloid plaques as the most obvious molecular hallmarks of AD, but efforts to prevent or reverse $A\beta$ accumulation have failed in the clinic.

De Jager and Bennett both said that $A\beta$ pathology strongly correlates with dementia but that not all dementia patients have amyloid plaque deposits and not all individuals with amyloid plaques have dementia.

"Our advantage is that we're using an empirical, data-driven approach with no prior assumptions about amyloid," said De Jager. "Prior studies have been focused on specific hypotheses about amyloid, but amyloid pathology only accounts for a part of dementia. We're looking for something completely novel. Because we have such a deep, integrated dataset,

we have the chance to discover something new."

The team hopes to select a list of 300–400 candidate genes whose activity appears to be different in patients versus controls and will further characterize expression and function of these genes in human brain tissue and preclinical models of AD.

Once the team has identified likely targets involved in early stage disease, the researchers will conduct a small molecule drug screen in induced pluripotent stem (iPS) cells.

The ultimate goal is to identify targets for AD prevention. "Prevention is more tractable than therapy. Once you have clinical impairment, your brain is pretty far gone. I think it will be hard to reverse that," said Bennett.

Big data

The second early stage grant went to a consortium led by Eric Schadt to pursue a computational approach to teasing out early AD players.

Schadt is a professor of genetics and genomic sciences and director of the Institute for Genomics and Multiscale Biology at **Mount Sinai Hospital**. His team will probe 250 AD brains and 50 controls from a brain bank at Mount Sinai's Alzheimer's Disease Research Center. The group will use an array of genomic and proteomic techniques to construct a model of gene interactions that will hopefully point to causal players in AD.

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**—Philip De Jager,
Brigham and Women's Hospital**

The team's technique builds on statistically driven systems biology methods developed by Schadt while at **Merck & Co. Inc.**'s Rosetta Inpharmatics unit and **Sage Bionetworks**, a not-for-profit institute.^{1,2}

Co-principal investigators Jun Zhu and Bin Zhang of Mount Sinai told *SciBX* that the human brain tissue studies will guide subsequent preclinical studies to test hypotheses about which genes contribute to the initiation of disease. Zhu and Zhang are a professor and an associate professor of genetics and genomic sciences, respectively.

"Data generated from human genetic studies, human iPS cells, mouse models and *Drosophila* models will be used to generate, test and refine our network models," said Zhang.

Like De Jaeger and Bennett, the Mount Sinai team is agnostic about what kind of results—markers or therapeutic targets—will arise from its analysis. Ideally, said Zhang, at least a few potential drug targets will emerge.

Innate hypothesis

Finally, a **University of Florida** team led by Todd Golde will pursue a hypothesis-driven approach, focusing on the role of innate immunity and inflammation in AD.

Golde is a professor of neuroscience and director of the University of Florida's Center for Translational Research in Neurodegenerative Disease.

"It's been long thought in the field that proinflammatory stimuli would make A β pathology worse, but we tested this in three models and found this not to be the case," said Golde.³

Likewise, he cited evidence from mouse models of AD that the anti-inflammatory cytokines IL-4 and IL-10 appear to exacerbate A β pathology.

Thus, Golde suspects key aspects of inflammation are regulated differently in the brain than elsewhere in the body and go awry in AD. To identify the critical players, his group will use RNA sequencing to analyze the expression of selected inflammation-associated genes in a panel of 100 typical AD brains, 100 healthy, age-matched controls and 100 more controls with atypical AD-like pathology.

His next step will be to manipulate the expression of 15–20 of the most severely perturbed genes in mouse models of AD.

"We've used an adeno-associated viral transduction method to deliver things to the brain either neonatally or later in life and have been evaluating how altering innate immunity affects AD pathology in mice," said Golde. "This grant lets us increase the throughput by identifying targets using a systems biology approach to directly test whether these changes are good or bad."

Golde is starting from the hypothesis that inflammation plays a role in late stage disease, which is characterized by microglial activation, neuronal death and accumulation of neurofibrillary tangles of microtubule-associated protein- τ (MAPT; TAU; FTDP-17). He suspects that blocking inflammation can prevent TAU aggregation and improve neuronal activity even in patients with advanced disease.

"Our bias is that if we want a therapy that will work at a later stage of disease, we need something that affects TAU deposition," said Golde. "There is evidence that manipulating innate immunity or using innate immune factors could improve TAU pathology and possibly neuronal viability."

Interim results from all three teams are expected a year hence. Meanwhile, the National Alzheimer's Project plans to fund one more discovery-oriented project this year but has not yet announced the recipient.

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COMPANIES AND INSTITUTIONS MENTIONED

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