Two UC San Diego Researchers to Lead Alzheimer’s Disease Cooperative Study

By Scott LaFee
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Two of the nation’s leading physician-scientists in the search to better understand and treat Alzheimer’s disease – William Mobley, MD, PhD, and Michael Rafii, MD, PhD – have been named interim co-directors of the Alzheimer’s Disease Cooperative Study (ADCS), a major initiative formed in 1991 as a cooperative agreement between the National Institute on Aging (NIA) and the University of California, San Diego. The selection was made in collaboration with the NIA.

William Mobley, MD, PhD, and Michael Rafii, MD, PhD, named interim co-directors of the ADCS

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Mobley is chair and Distinguished Professor in the Department of Neurosciences in the UC San Diego School of Medicine. Rafii is assistant professor of neurosciences and ADCS’ medical director. They will serve as co-directors during a national search for a new permanent ADCS director, replacing Paul Aisen, MD, who resigned his faculty position at UC San Diego School of Medicine and position as ADCS director, effective June 21.

“We appreciate Dr. Aisen’s eight years of service to ADCS and wish him well,” said David Brenner, MD, vice chancellor, UC San Diego Health Sciences and dean of UC San Diego School of Medicine. “The selection of Drs. Mobley and Rafii represents an exciting new direction for ADCS. This is a moment of terrific opportunity, a chance to expand, innovate and write a new and bolder chapter, such as development of more creative clinical trial designs.”

“In recent years,” Brenner said, “there have been dramatic advances in our understanding of Alzheimer’s disease (AD). We are on the cusp of creating effective treatments that may, in time, lead to preventing this terrible neurodegenerative scourge. A good deal of this progress is due to the amazing efforts and talents of UC San Diego scientists, doctors and staff. Their outstanding work continues. It is growing, accelerating – and it remains fully and enthusiastically supported by the university and by the AD community.”

For example, Brenner noted future plans could include relocating ADCS into the new seven-story, $269 million Altman Clinical and Translational Research Institute (CTRI) building rising next to the Jacobs Medical Center at UC San Diego Health System, also opening in 2016. The building will include multidisciplinary clinical facilities and a new state-of-the-art research MRI to image the brain in clinical trials.

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“Integrating the ADCS into the medical center research community from its current off-campus site,” said Gary S. Firestein, MD, CTRI director, dean and associate vice chancellor of translational medicine, “would create enormous opportunities with greater collaboration and improved access to laboratory and imaging resources, patients and clinical services.”

The ADCS was founded by the late Leon Thal, MD, a world leader in Alzheimer’s research, to promote the discovery, development and testing of new drugs for the treatment of AD. It is part of a larger AD research and treatment effort at UC San Diego, which includes the Shiley-Marcos Alzheimer’s Disease Research Center, under the direction of Douglas Galasko, MD, and Edward Koo, MD; the Memory Disorders Clinic, headed by Rafii; and the Memory, Aging and Resilience Clinic, a novel center that offers comprehensive cognitive, emotional and physical health evaluations of older adults.

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Interim co-directors Mobley and Rafii bring particular experience and expertise to their new roles. Mobley is among the nation’s most prominent academic neurologists. He is executive director of the Down Syndrome Center for Research and Treatment. Persons with Down syndrome, a genetic disorder, are predisposed to develop AD, and by age 40, virtually all individuals with Down syndrome have the pathology of AD in their brains.

Rafii is principal investigator on numerous AD studies at UC San Diego, including Scarlet Road, an on-going, multi-year, multi-institution study to assess the effects of gantenerumab, an antibody-based drug shown to attack and remove beta-amyloid plaques in animal models. Rafii also is clinical director of the Down Syndrome Center and oversees numerous interventional clinical trials.

Clinical trials like these are powered by basic research. In 2012, for example, a team of UC San Diego School of Medicine scientists and others, led by Larry Goldstein, PhD, Distinguished Professor in the departments of Neuroscience and Cellular and Molecular Medicine and director of both the UC San Diego Stem Cell Program and Sanford Stem Cell Clinical Center, created the first stem cell-derived, \textit{in vitro} models of sporadic and hereditary AD using induced pluripotent stem cells from patients with the disease.

This year, Goldstein and colleagues identified a gene variant that may be used to predict people most likely to respond to an investigational therapy under development for AD. The work is based on experiments with cultured neurons derived from adult stem cells.

Meanwhile, Mark Tuszynski, MD, PhD, director of the Center for Neural Repair at UC San Diego School of Medicine, and colleagues are investigating the use of growth factors delivered by gene therapy to the brain to preserve neuronal survival and cognitive function and forestall the effects of AD. Some of this work has entered later stage clinical trials.

“The depth and breadth of AD research at UC San Diego is without parallel,” said Brenner. “Our faculty, programs and centers have been grappling with the enigma of Alzheimer’s disease for decades. We have a history of achievement. Change is an opportunity to develop a much stronger and more forward-thinking program. We are committed to a bright future for ADCS at UC San Diego – and to improving the lives of millions of Americans who have or might develop AD.”
Researchers believe that the brain’s cerebral cortex encodes long-term memories by forming and stabilizing synapse-bearing dendritic spines. What, then, happens in the hippocampus, which stores memories only transiently? The question has gone unanswered partly because the high spine density in the hippocampus makes it difficult to follow the fate of individual synapses. On June 22 in Nature, researchers led by Mark Schnitzer at Stanford University, California, describe a new computational approach that allowed them to calculate the number and dynamics of hippocampal spines during weeks of live imaging in transgenic mice. The data revealed that dendritic spines, unlike their cortical cousins, do not last. The authors estimated the entire population turns over in six weeks or less, roughly matching the timespan of hippocampal-dependent memory in mice. The results support current models of memory storage but also highlight striking differences between the cortex and hippocampus. The techniques described in this paper could be used to address additional questions about hippocampal memory mechanisms, Schnitzer suggested.

Commentators agreed. “This is a technical tour de force,” said Scott Small at Columbia University, New York. Howard Eichenbaum at Boston University called the data exciting. “The observations reveal new information about how memories last or decay, and so open avenues to explore the mechanisms of memory loss in neurological disorders such as Alzheimer’s,” he wrote to Alzforum.

Previous studies indicated that dendrites and spines in the neocortex wax and wane over time, influenced by an animal’s experience. In live imaging experiments, the neocortex appears to contain a mix of transient and long-lasting dendritic spines, in keeping with its abilities to learn and change as well as store permanent memories. In contrast to the relatively sparser spines in cortex, however, many more spines crowd hippocampal tissue. The two-photon microscopy used for live imaging cannot reliably distinguish many of these closely spaced spines, making visual counts unreliable.

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To solve the problem, Schnitzer and joint first authors Alessio Attardo and James Fitzgerald first compared two-photon microscopy with the more sensitive stimulated emission depletion (STED) microscopy in hippocampal tissue slices from transgenic Thy1-GFP mice. These animals express GFP in a subset of CA1 pyramidal neurons, allowing these neurons and their spines to be visualized. About 30 percent of spines that appeared single in two-photon images in fact were shown to be two, or sometimes three, spines close together in STED images. Two-photon data thus underestimates spine density and overestimates spine stability, since in many cases two spines would need to retract for an apparent spine to disappear from the image. The authors put this data into computer simulations of various hypothetical spine densities and kinetics, which they used to develop a mathematical model for correcting the two-photon data.

The authors then implanted microendoscopes into the brains of four Thy1-GFP mice just above the CA1 region of hippocampus. These needle-thin devices contain lenses that relay a signal back to a two-photon microscope. The authors acquired images every three days for three weeks to track spine dynamics, then analyzed the data using their mathematical model. The best fit for the observed data was a model in which 100 percent of spines turned over, with an average lifespan of about 10 days. This would lead to complete replacement of hippocampal spines every three to six weeks, the authors calculated.

Environmental enrichment has been found to increase hippocampal spine density in some studies. The authors tracked three new mice, first for three weeks in a regular cage and then for 24 days in a cage filled with playthings. However, neither spine density nor turnover changed in the richer environment, bellying earlier studies.

Since NMDA glutamate receptors are known to affect synaptic plasticity in both the cortex and hippocampus, the authors investigated the effects of injecting mice with an NMDA receptor blocker twice daily for 18 days. More spines disappeared after treatment, leading to about 12 percent less spine density. The finding suggests that CA1 dendritic spines require working NMDA receptors to survive.

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Intriguingly, cortical spines appear to need just the opposite. There, blockade of NMDA receptors has been reported to stabilize spines. Moreover, in adult neocortices more than half of spines seem to be permanent, and those that are transitory have an average lifespan of about five days. To compare cortical and hippocampal spine dynamics on an even footing, Schnitzer and colleagues re-analyzed data from previous cortical imaging studies using their mathematical model. The results confirmed that about 60 percent of cortical spines remained stable over long periods of time. “The data highlight that the two systems have very different manners of memory processing,” Schnitzer told Alzforum. In future studies, he would like to investigate the mechanisms that control spine turnover in the hippocampus, and also relate spine dynamics to memory formation and behavior in mice.

Small noted that the differences in structural plasticity seen in the hippocampus and neocortex track well with the known memory durations in each region. “That’s very elegant. There has always been a question about what cellular mechanism underlies the temporal distinction in memory codes,” he said. Moreover, structural changes occur slowly over days or weeks, and therefore may better reflect the brain changes seen during repeated functional MRI or FDG PET than neuronal activity does, Small suggested. It would be interesting to look for a functional imaging correlate for spine turnover, he added. Such a correlate could allow researchers to study these changes in people.

The technique described here could also be applied to animal models of Alzheimer’s and other memory disorders, researchers agreed. Synapses are lost early in AD. “There might be a number of different mouse models of disease that would have altered spine kinetics,” Schnitzer speculated.—Madolyn Bowman Rogers

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In the June 25 Cell Metabolism, researchers led by Kalipada Pahan, Rush University Medical Center, Chicago, report that statins activate a novel pathway that raises levels of two neurotrophins in the brain. The findings could reinvigorate the long-standing debate about whether statins may make good therapeutics for neurodegenerative diseases.

“This group really nailed down a novel mechanism of action of statins,” said Elizabeth Head, University of Kentucky. “It is exciting to consider that neurotrophins could be upregulated in brain through a drug, which has not been feasible in the past.”

Statins, widely used to treat heart disease, are competitive inhibitors of HMG-CoA reductase, an enzyme that dictates the pace of cholesterol synthesis in the liver. By disrupting the pathway of cholesterol synthesis, which affects a number of intermediate signaling molecules (see image below), statins also have a host of pleiotropic effects. They reduce inflammation, encourage vasodilation, and reduce the production of reactive oxygen species.

Studies in mice suggest that statins could also improve cognitive function, learning, and memory, and reduce Alzheimer’s pathology. Epidemiological evidence in people backs that up—statins appear to lower the risk of Alzheimer’s disease and dementia. However, prospective studies have failed to show that statins either reduce dementia risk or treat AD. If there is a cognitive benefit, what could explain it? Pahan and colleagues wondered if statins influence the production of neurotrophins in the brain.

First author Avik Roy and colleagues treated separate cultures of mouse astrocytes, microglia, and cortical neurons with various statins. In all three types of cells, both the mRNA and protein levels rose for brain-derived neurotrophic factor (BDNF) and neurotrophin-3 (NT-3). The same held true in both primary human astrocytes and neurons. In vivo, the scenario looked similar. Mice fed with simvastatin—the statin that most easily crosses the blood-brain barrier—produced more BDNF than normal in astrocytes, microglia, and cortical neurons, according to postmortem immunohistochemistry.

Surprisingly, this effect did not seem to depend on inhibition of HMG-CoA reductase. When the researchers pretreated cultured cells with mevalonate or farnesyl pyrophosphate, downstream products of the enzyme, neurotrophin levels still climbed upon administering simvastatin. This implied that statins rev production of neurotrophins a different way.

Upon closer inspection, the authors discovered that the drugs stimulated a nuclear transcription factor involved in fat metabolism, PPARα. Simvastatin only upregulated neurotrophins in vitro and in vivo in mice when PPARα was present, not when it was genetically knocked out. Various molecular methods confirmed that statins bound directly to the transcription factor, and that simvastatin had the strongest affinity.

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Statins cont’d

However, there was a catch. PPARα does not directly promote production of neurotrophins. How are they connected, then? Roy and colleagues looked to known BDNF promoters, such as cAMP-response element binding protein (CREB). Knocking down CREB prevented statins from raising neurotrophin levels in astrocytes from mice. CREB also rose in mice fed simvastatin, but not if the animals lacked PPARα. The work suggests that statins modulate PPARα and CREB independently of HMG-CoA inhibition (see image).

To find out if this rise in neurotrophic factors imparted a behavioral benefit, Roy and colleagues examined hippocampus-dependent learning and memory in mice. In wild-type mice with intact PPARα, two weeks of daily simvastatin treatment raised BDNF expression in the cortex, and reduced errors in the Barnes navigation maze. The drug also improved memory in 5-month old 5xFAD mice, which have rampant amyloid plaques and poor memory, so long as PPARα was present.

“This paper provides a novel mechanism of how statins might act independently of the cholesterol pathway,” said Jochen Walter, University of Bonn, Germany. “That there is a direct interaction of statins with a transcriptional regulator is pretty surprising.”

Head and Walter agreed that this study might help explain why people who start taking statins in middle age have a lower incidence of Alzheimer’s. Scientists might also look at autopsy tissue from people who took statins to see if the same mechanism is at play, Head said. However, she cautioned that people who take statins have high cholesterol, and healthy people could react differently. The mice Roy and colleagues used ate normal mouse chow and had normal cholesterol levels.

Head noted that the statin doses given to mice in this study were comparable to those prescribed for people, making the finding all the more promising. Given that people take statins for long periods, both Head and Carl Cotman, University of California, Irvine, wondered how mice would have fared on more than two weeks of treatment.

How does this new data reconcile with inconclusive cognitive outcomes in statin trials? Walter said a number of factors could influence those studies, including when treatment begins relative to disease onset, the length of treatment, the types of assessment used, and the permeability of the statin to the blood-brain barrier.

To complicate matters, some studies have reported a decline in memory associated with statin use in elderly people. In the June 8 JAMA Internal Medicine, authors led by Warren Bilker, University of Pennsylvania Perelman School of Medicine, Philadelphia, suggest possible reasons. In a retrospective cohort study, they compared 483,000 statin users to a matched group taking no lipid-lowering drugs and 26,000 people taking non-statin versions. They found that all lipid-lowering drugs were equally associated with memory loss in the first month of use. While it’s still possible that this entire heterogeneous drug class causes memory decline, they argue that the association more likely resulted from detection bias. In other words, people taking the drugs make more visits to their physicians, who are then more likely to pick up on memory problems.—Gwyneth Dickey Zakaib

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ADCS Clinical Trials Enrolling...

For information on the following studies please visit:

http://www.adcs.org/Studies/clinicalResearchStudy.aspx

A4 – Anti Amyloid in Asymptomatic Alzheimer’s Disease

NOBLE A Study for People with Mild to Moderate Alzheimer’s Disease

The CONNECT Study for people with Mild-Stage Alzheimer’s Disease.
On a temporary enrollment hold until further notice:

SNIFF – the Study of Nasal Insulin to Fight Forgetfulness

More studies coming later in 2015.....