UC San Diego to Receive $52 Million to Continue Leadership of the Nation-wide Alzheimer's Disease Cooperative Study

October 17, 2006 |

Leon Thal, Director of the Shiley-Marcos Alzheimer's Disease Research Center at UCSD, heads 70-site consortium funded by National Institutes of Health.

The Alzheimer's Disease Cooperative Study (ADCS), a federally established consortium directed by Leon Thal, MD, Director of the Shiley-Marcos Alzheimer's Disease Research Center at the University of California, San Diego (UCSD) School of Medicine, will receive $52 million over six years to conduct several new clinical trials on Alzheimer's disease, the National Institutes of Health (NIH) announced today. The award is the third renewal of a cooperative agreement between the NIH's National Institute on Aging (NIA) and UC San Diego, which coordinates the consortium of nearly 70 research sites in the United States and Canada.

Thal, Professor and Chair of the Department of Neurosciences at the UCSD School of Medicine, has led the ADCS since its inception in 1991.

"We are very excited to have the ability to test new therapies that may slow the rate of progression of this devastating disease," said Thal."Given the rapid acquisition of knowledge in the field of Alzheimer's disease, we all remain hopeful that an effective treatment will be found within the next decade."

The purpose of the NIA award is to test drugs for their effectiveness in slowing down the progression or treating the symptoms of AD, as well as to investigate new methods for conducting dementia research.

"We have been able to bring together a larger universe of people studying therapies for Alzheimer's, and I think the group of studies we have developed for this phase of the study reflects new thinking in how to approach the disease," said Thal.

In the next six years funded by this award, researchers will focus on possible therapies aimed at affecting the peptide beta amyloid and the tau protein. Douglas R. Galasko, MD, a physician scientist with the UCSD Shiley-Marcos ADRC, was one of the early scientists who determined

that beta amyloid and tau could be measured in spinal fluid and were useful markers for Alzheimer's. It remains to be seen, however, whether plaques and tangles actually cause the disease or are byproducts of Alzheimer's.

"We have learned a great deal from basic and observational research about how Alzheimer's and other neurodegenerative diseases develop," says Richard J. Hodes, MD, Director of the NIA. "The consortium's work will translate this knowledge in clinical trials of interventions that target the mechanisms underlying Alzheimer's disease."

The ADCS consortium was first established in 1991 as an infrastructure of leading researchers to carry out clinical trials for promising new therapies for AD. In his capacity as the principal investigator of the ADCS, Thal has established major, large-scale clinical drug trials, as well as validation tests for methods to evaluate the course of Alzheimer's disease. On the basis of a single study published in the *New England Journal of Medicine* by members of the ADCS, vitamin E has now entered clinical practice for the care of patients with Alzheimer's disease. The ADCS also demonstrated that Vitamin E failed to prevent progression to AD in subjects with mild cognitive impairment. In another ADCS investigation, donepezil was shown to delay the progression from mild cognitive impairment to early Alzheimer's disease. Estrogen replacement therapy was shown to not be useful for the treatment of mild to moderate Alzheimer's disease in women, despite its previous clinical popularity. The ADCS has also spearheaded the development of concepts such as mild cognitive impairment and has fostered the development of new study designs and instruments useful for clinical trials.

To date, approximately 4,600 people have participated in the ADCS studies. Among the new studies to be undertaken are:

- → Docosahexaenoic Acid (DHA) - This study will examine whether treatment with DHA, an omega-3 fatty acid found in fish, will slow decline in AD. Observational studies associate high fish consumption with reduced risk of AD in people, and studies in mouse models of AD show that dietary DHA reduces brain levels of beta amyloid, oxidative damage associated with beta amyloid, and neurotoxicity.
- → Intravenous Immunoglobulin (IVIg) – There is increased interest in passive immunization strategies against AD. IVIg contains naturally occurring antibodies against beta amyloid, and preliminary studies have shown that IVIg may improve cognition. In addition, research has demonstrated that IVIg increased levels of anti-beta amyloid antibodies in plasma and promoted clearance of beta amyloid from cerebrospinal fluid. The new ADCS trial will more definitively demonstrate whether IVIg is useful clinically for treating AD.
- → Lithium – The biological activity of lithium, which has been shown in animal models to block abnormal changes in tau, has created interest in lithium as a novel treatment for AD. ADCS investigators will undertake a pilot biomarker study to see whether the drug can lower tau

and beta amyloid levels in cerebrospinal fluid and be safely tolerated in older AD patients.

- → Home-Based Assessment – Older individuals, particularly the very elderly, may have physical, social and health limitations that make it difficult for them to take part in research trials. This study, conducted in people aged 75 and older, will examine the use of mail-in questionnaires, automated telephone technology and computerized data collection to assess cognitive, functional, and other factors in the home environment to see how home-based assessments might be used in primary prevention trials. Such an approach could significantly reduce the cost and increase the feasibility of participation in these long-term, costly clinical trials.

These projects join ongoing trials on whether statins and high-dose folate/B6/B 12 supplements can slow the clinical signs of AD, as well as a study of valproate to see if it can either slow decline or help delay the agitation and psychosis that often emerge in AD patients.

Thal notes that the selection of compounds for testing was enhanced by seeking ideas from the biotechnology sector as well as from individual investigators and the consortium's long-term members.

As the new round of trials gets underway, on-going public participation will be essential for their success, Thal notes. Patients with Alzheimers disease can be referred to the UCSD Shiley-Marcos Alzheimers Disease Research Center for a variety of studies, including experimental drug studies, by contacting the ADRC at (858)622-5800.

Alzheimer's disease affects an estimated 4.5 million people in the United States. It increases dramatically with age, affecting approximately 40 to 50 percent of people age 85 and older. The numbers of people with AD are expected to rise dramatically with the aging of the population over the next few decades.

The NIA, one of 27 institutes and centers at the NIH, is part of the U.S. Department of Health and Human Services. It leads the federal effort to support and conduct basic, clinical, and social and behavioral studies on aging generally and AD specifically. NIA supports the Alzheimer's Disease Education and Referral (ADEAR) Center, which provides information on clinical studies and other research to the public, health professionals, and the media.

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ABOUT LEON THAL

Leon Thal's entire career has been devoted to the study of aging and dementia. Over the past three decades, he has achieved a remarkable body of research productivity that includes more than 300 peer-reviewed papers. One of the world's leading investigators engaged in development of new therapies for Alzheimer's disease, his efforts have significantly contributed to the world's understanding of the cause, prevention and treatment of AD and related disorders.

In recognition of his accomplishments and leadership in the field of AD research, he was awarded The Potamkin Prize – one of the nation's highest honors in neurosciences – in 2004.

He began aggressively pursuing the cholinergic hypothesis of Alzheimer's disease in the 1970s. After investigations in the laboratory using rat and other models, he translated these studies to humans and subsequently performed clinical trials using choline, lecithin and other precursors of acetylcholine. In 1981, he published his finding that choline chloride failed to improve cognition in Alzheimer's disease. This lack of initial success challenged him to explore alternative and novel ways to treat the cholinergic deficit of Alzheimer's disease using other compounds and routes of administration. The importance of this work is evident by its 1983 publication in the *New England Journal of Medicine*, where Thal provided some of the first evidence that memory could be enhanced in Alzheimer's patients with cholinesterase inhibition.

In the late 1980s, after nearly two decades of intense research activity, his efforts were rewarded with the approval of the first drug (a cholinesterase inhibitor) for the treatment of Alzheimer's disease. In collaboration with Dr. Ken Davis, he organized a landmark clinical trial for evaluating tacrine as a potential treatment. This double-blind, placebo controlled multi-center study was described in a second paper published in the *New England Journal of Medicine* and paved the way for approval of the compound in the United States. This work established his leadership in the testing and development of drugs for Alzheimer's disease.

In addition to his extraordinary efforts in clinical research, Thal has done work involving the enhancement of neuronal function and regeneration. He has shown that grafting nerve growth factor cells improved memory in the rat and that grafting acetylcholine-producing cells has a similar effect.

Thal serves on the editorial board of seven major journals including *Neurobiology of Aging* and *Journal of Molecular Neuroscience.* He is a frequent reviewer and consultant for the National Institutes of Health (NIH), the National Science Foundation and the Veterans Administration. He serves as a permanent advisor on the FDA anti-dementia assessment team and served on the National Advisory Council on Aging of the National Institute on Aging.

In 2003, Thal was invited to meet with the Chinese government in Beijing along with four others experts in Alzheimer's disease to help the Chinese government develop research and treatment programs for this new century. He has trained dozens of scientists who have gone on to be active researchers in Alzheimer's disease and dementia.

"Alzheimers disease remains the most important disease of aging in the 21st century because of its great personal, economic and societal cost," said Thal.

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