Major NIH Grant Funds Novel Alzheimer's Drug Development at UC San Diego

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Scott LaFee

As part of its $50 million Blueprint for Neuroscience Research, the National Institutes of Health (NIH) has awarded researchers at the University of California, San Diego School of Medicine an inaugural grant designed to fast-track development of a novel Alzheimer's disease therapy.

The 5-year, $1 million grant to principal investigator Steven Wagner, PhD, a project scientist in the UC San Diego Department of Neurosciences, will fund development of a promising strategy for treatment of Alzheimer's disease. Wagner and colleagues have identified a series of compounds called gamma-secretase modulators (GSMs) that reduce only those protein fragments believed to play a critical role in the brain cell death and dementia that occurs in Alzheimer's disease.

The NIH Blueprint brings together 15 of the agency's institutes and centers to leverage their resources and expertise in a major national effort to more rapidly move promising candidate drugs into clinical trials and, hopefully, eventual clinical use.

In addition to the grant to the UCSD School of Medicine, six other awards were announced for research into nervous system disorders ranging from neurodegenerative diseases to vision loss and depression. Depending on continued progress over the next five years, the Blueprint Neurotherapeutics Network will provide Wagner and the other investigators with millions of dollars in additional funding and services.

Public funding from the NIH has long helped academic labs and small businesses exploit their ingenuity to pursue new strategies for treating nervous system disorders. Most academic labs, however, lack the resources - time, money, scientific staff, and regulatory expertise - to convert these strategies into effective treatments. The new NIH Blueprint provides academic investigators with direct access to an expert drug development team that includes NIH staff members, pharmaceutical industry consultants and medicinal chemistry and pharmacology service contractors.

"The idea is to take the drug all the way through a Phase 1 clinical trial," said Wagner. "NIH funding will directly fund private contractors to work with researchers in the critical pre-clinical development steps, such as secondary drug compound testings for safety and toxicity and various bio-analytical studies that often spell the end of drug development in academia because there isn't anywhere near adequate funding at the university level."

In research published in 2010, Wagner and colleagues synthesized hundreds of new GSMs that specifically reduced the production of a protein fragment called amyloid-beta (A-beta) 42 peptide, but left other cellular components and activities in the brain alone. High levels of A-beta 42 have been linked to the destruction of neurons and subsequent development of Alzheimer's disease, a neurodegenerative condition that afflicts 5.3 million Americans and more than 26 million people worldwide.

Many existing drugs in development for Alzheimer's disease broadly knock out amyloid peptide activity, but also cause adverse side effects like nausea, cognitive impairment and skin cancer. The GSMs previously

identified by Wagner and collaborators dramatically reduced A-beta 42 levels and plaques in mice without any apparent side effects.

More recently, Wagner - along with UCSD colleagues Soan Cheng, Phuong Nguyen and William Mobley, in collaboration with Rudy Tanzi, PhD, from Massachusetts General Hospital - have synthesized and developed yet another novel GSM series that appears to significantly improve physicochemical properties compared to earlier GSMs. These are focus of the new NIH Blueprint award.

"The new NIH grants are an important key to helping Wagner and others take the next step. More often than not, new strategies for treating nervous system disorders die on the vine from a lack of resources needed to translate a promising idea into an effective therapy," said William Mobley, MD, PhD, and chair of the UCSD Department of Neurosciences, noting that only 10 to 20 percent of candidate drugs for all disease indications survive the early phases of development and reach clinical trials. "These NIH Blueprint awards are an exciting advance in bringing discoveries from the lab to patients."

Media Contacts: Scott LaFee, 619-543-6163, slafee@ucsd.edu