



GLADSTONE INSTITUTE OF NEUROLOGICAL DISEASE NEWS

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RECENT DISCOVERIES PAVE THE WAY TOWARD NEW TREATMENTS FOR ALZHEIMER'S DISEASE

Promising research into the causes of Alzheimer's disease, with an emphasis on the roles of such proteins as amyloid-beta and apolipoprotein E, will be the subject of a plenary session presentation on April 29 at the American Academy of Neurology (AAN) 56th Annual Meeting in San Francisco.

Lennart Mucke, MD, director of the Gladstone Institute of Neurological Disease and Joseph B. Martin Distinguished Professor of Neuroscience at the University of California, San Francisco (UCSF), will discuss the latest therapeutic targets and describe molecular markers of cognitive decline that may facilitate the assessment of new treatments for Alzheimer's disease.

"Ongoing studies are beginning to unravel the pathways that lead from the accumulation of toxic proteins in the brain to the biochemical alterations and cognitive decline in patients with Alzheimer's disease," says Mucke.

His talk, "Markers and Mediators of Neuronal Deficits in Dementia," will highlight recent discoveries that shed light on the processes underlying the memory loss and other cognitive deficits associated with Alzheimer's disease. The presentation is part of "Frontiers in Clinical Neurosciences Plenary Session: Beyond the Decade of the Brain," during which several scientists will present recent research findings and discuss their clinical implications.

"Recently, we identified a number of mechanistically informative changes in the brains of transgenic mouse models of Alzheimer's disease, and we have begun to validate the clinical relevance of these findings in human cases," explains Mucke. "For instance, deficits in spatial learning and memory in our mice correlated tightly with the depletion of calcium-dependent proteins in specific brain regions. Similar abnormalities were then found in brains from patients with Alzheimer's disease, and the greatest depletions were seen in the most severely demented people."

Mucke's talk will focus on these and other key findings from studies of transgenic mice and human brain tissues carried out at the Gladstone Institute of Neurological Disease. One study, for example, showed that high levels of amyloid proteins disrupt complex brain circuits in which memories are formed and stored. Mucke's work in this area is contributing to an important paradigm shift in the field. Previously, the most widely held view was that large clumps of amyloid proteins in the brain (referred to as "plaques") cause the neurological decline in Alzheimer's disease. But studies conducted at Gladstone, UCSF, and other centers suggest that much smaller aggregates of these

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proteins are the real culprits. These findings are helping to resolve the controversy surrounding the role of amyloid proteins in Alzheimer's disease.

Other studies he will discuss have identified molecular pathways through which amyloid proteins may impair brain functions and have demonstrated that amyloid proteins can enhance the accumulation and toxicity of other disease-causing proteins. The latter finding may help explain the frequent clinical and pathological overlap between Alzheimer's and Parkinson's disease.

In addition, Mucke will describe findings that explain how apolipoprotein E4—the best established genetic risk factor for Alzheimer's disease—can promote the development of this illness and how its harmful effects might be prevented or reversed with new therapeutic approaches now under development at Gladstone.

Basic research findings are the foundation for developing novel therapeutic strategies and new treatments for diseases such as Alzheimer's. Genetically engineered mouse models are especially useful tools for studying neurodegenerative disease because they allow individual proteins to be studied in the complex environment of the living brain, enabling scientists to determine which of these proteins are the most toxic. Such models are also useful for the preclinical evaluation of new treatments aimed at the toxic proteins themselves or at the disease-causing processes they trigger.

“While the investigation of neurological diseases has promoted basic neuroscientific discoveries for more than a century, there has never been a more promising and exciting convergence of basic and disease-related neuroscience than now,” says Mucke.

The AAN meeting will be held in the Moscone Convention Center from April 24 through May 1. Some 1,300 scientific studies will be presented as platform or poster sessions highlighting the latest research findings on dementia, Parkinson's disease, stroke, epilepsy, headache, multiple sclerosis, and other neurological disorders. The AAN, an association of more than 18,000 neurologists and neuroscience professionals, is dedicated to improving patient care through education and research.

The Gladstone Institute of Neurological Disease is one of three research institutes of The J. David Gladstone Institutes, a private, nonprofit biomedical research institution affiliated with UCSF. For further information, visit www.gladstone.ucsf.edu/gind/

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