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TREATING AGITATION AND AGGRESSION IN ALZHEIMER'S DISEASE

SAN DIEGO, CALIFORNIA, November 15, 2013. A group of scientists from academia and industry, and spanning the drug development spectrum from basic science to clinical care, today called for an increased focus on agitation and aggression as targets of Alzheimer's disease (AD) therapy.

Although agitation and aggression are among the most common and disruptive symptoms of AD, no drugs have been approved to treat these symptoms. Agitation, for example, occurs in nearly half of dementia patients across all levels of dementia severity. The lack of adequate treatment for this condition results in diminished quality of life and increased institutionalization of patients, as well as increased caregiver stress.

"Agitation in Alzheimer's disease is an appropriate target syndrome of great importance. Growing recognition of this by the field, and by the FDA, will continue to motivate the development of drugs for this indication," said Constantine Lyketsos, M.D., M.H.S., of Johns Hopkins University. "Since agitation is so prevalent in AD and can be so disabling to patients and caregivers, better treatments are critical to improve patient and caregiver outcomes."

Gene Kinney, Ph.D., Chief Scientific Officer and Head of Research and Development at Prothena Biosciences in San Francisco, California, provided an overview of research done in animal models, which has demonstrated an association between amyloid deposition and aggressive behavior. For example, mouse models have been created in which the gene for the amyloid precursor protein (APP) has been inserted into the mouse's genome. APP is the protein that is cleaved to form beta amyloid, the protein found deposited as plaques in AD brains. These transgenic APP mice show clear aggressive behaviors associated with deposition of amyloid in the brain. More importantly, they have enabled scientists to better understand the neurobiological basis of agitation and aggression as well as to elucidate possible treatment approaches.

Human studies have also helped clarify the mechanisms underlying aggressive behavior. David Sultzer, M.D., professor of psychiatry and biobehavioral sciences at the UCLA School of Medicine used a variety of different neuroimaging techniques to measure different aspects of brain structure and function. "These studies indicate that loss of brain tissue in key areas, low activity in particular brain areas, poorly connected critical brain structures, and low neurotransmitter binding may contribute to symptoms such as excessive pacing, irritability, oppositional behaviors, and verbal or physical aggression in those with Alzheimer's disease," said Dr. Sultzer.

"These early findings are very exciting. They suggest that specific brain abnormalities, along with what's going on in the environment of course, contribute to agitation and aggression in

Alzheimer's disease," said Dr. Sultzer. "This indicates that behavioral problems such as agitation are a fundamental part of the Alzheimer's disease process and related to particular abnormalities. They're not just what happens when someone has a globally impaired brain and behaves oddly as a result."

Taken together the data from animal models and human imaging studies support the notion that agitation and aggression represent a distinct clinical entity with a biological basis in the AD brain. They have also supported investigations into whether a class of drugs called selective serotonin reuptake inhibitors (SSRIs) may be useful in treating agitation and aggression in patients with AD. A trial of one such drug, citalopram, was initiated in 2009 under the direction of Dr. Lyketsos. Dubbed "CitAD", this trial was recently completed although data are not yet available for release.