PsychoAAD-2013

OMICS Group Conferences
Accelerating Scientific Discovery

International Conference on
Psychology, Autism and Alzheimer's Disease

September 30 - October 1, 2013 San Antonio, Texas, USA

Molecular tweezers - novel protein aggregation inhibitors show promise for treatment and prevention of amyloidoses

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Abstract

Lysine-specific molecular tweezers are a novel class of compounds that inhibit aberrant protein aggregation and therefore are promising leads for developing therapy for amyloid-related diseases. These compounds utilize a unique process-specific mechanism. They bind to exposed lysines with micromolar affinity and interfere with the combination of hydrophobic and electrostatic interactions that mediate aberrant self-assembly of amyloidogenic proteins. Because the forces that mediate the initial steps in the self-assembly process of these proteins are relatively weak, the labile binding of the molecular tweezers is sufficient to inhibit them. At the same time, this labile binding is not sufficient for interfering with the structure or function of stably folded proteins. Hence, the molecular tweezers become toxic only at concentrations that are orders-of-magnitude higher than those needed for effective inhibition of abnormal protein oligomerization and aggregation.

Our lead compound, CLR01, was found to inhibit the aggregation and toxicity of 12 amyloidogenic proteins *in vitro*, including proteins involved in diverse diseases, such as Alzheimer's disease, Parkinson's disease, amyotrophic lateral sclerosis, dialysis-related amyloidosis, systemic amyloidosis, and type-2 diabetes. The compound has shown beneficial effect in six animal models of four different diseases, including Alzheimer's disease, Parkinson's disease, and systemic amyloidosis without apparent toxicity and thus shows great potential as a broad-spectrum inhibitor of diseases caused by protein misfolding and aggregation.

Biography

Gal Bitan completed his graduate studies in organic chemistry at the Hebrew University of Jerusalem, Israel. Dr. Bitan's graduate work on unnatural amino acids and non-conventional peptide cyclization methodologies led him to postdoctoral studies on the structural biology of bone-related ligand-receptor systems including integrins and G protein-coupled receptors at Clark University, Worcester, MA and Beth Israel-Deaconess Medical Center/Harvard Medical School, Boston, MA. Dr. Bitan has made fundamental contributions to the study of early events in the pathologic cascades that cause Alzheimer's disease. In Alzheimer's disease, the amyloid ß-protein (Aß) self-associates to form a variety of oligomeric and polymeric structures with potent neurotoxic activities. In particular, Aß oligomers have been implicated as the probable cause of Alzheimer's disease. For example, Aß oligomers have been found in brains of Alzheimer's disease patients but not in those of age-matched healthy individuals. Dr. Bitan introduced the use of novel photochemical protein cross-linking techniques for investigation of Aß assembly and discovered one of the earliest oligomers in the assembly cascade, the paranucleus. In 2004, Dr. Bitan joined UCLA where he is currently an Associate Professor of Neurology in the David Geffen School of Medicine. In recognition of his achievements, in 2005, Dr. Bitan received the Turken research award for the study of Alzheimer's disease.

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