CLARK UNIVERSITY

Gustaf H. Carlson School of Chemistry and Biochemistry

FALL 2021 SEMINAR SERIES

Gal Bitan, Ph.D.
Professor of Neurology
UCLA David Geffen School of Medicine

"Molecular tweezers - versatile, broad-spectrum inhibitors of protein aggregation in vitro and in vivo"

ABSTRACT: Progressive formation of toxic protein assemblies is a major deleterious mechanism underlying over 50 proteinopathies. Despite intensive effort, disease-modifying therapy does not exist for almost any of these diseases. Lysine-specific molecular tweezers (MTs) are supramolecular host molecules that act as broad-spectrum inhibitors of the self-assembly and toxicity of amyloidogenic proteins by a unique, "process-specific" mechanism. Interestingly, these compounds also have been found to destroy viral membranes and inhibit infection by enveloped viruses by mechanisms unrelated to their action on protein self-assembly, and to destroy the biofilm of Gram-positive bacteria. The efficacy and safety of MTs have been demonstrated in vitro, in cell culture, and in vivo, suggesting that these versatile compounds are attractive therapeutic candidates for various diseases, infections, and injuries. In particular, the lead compound CLR01 has been shown to inhibit the aggregation of various amyloidogenic proteins, prevent infection by multiple viruses, display potent anti-biofilm activity, and have a high safety margin in animal models. The inhibitory effect of CLR01 against amyloidogenic proteins has been shown to be highly specific to abnormal self-assembly of amyloidogenic proteins with no disruption of normal mammalian biological processes at the doses needed for inhibition. Therapeutic effects of CLR01 have been demonstrated in various animal models of proteinopathies including Alzheimer's disease, Parkinson's disease, systemic amyloidosis, lysosomal-storage diseases, and spinal-cord injury. MTs also have been found to act as effective inhibitors of infection by HIV-1, Ebola virus, Zika virus, and SARS-CoV-2, and to disrupt the biofilm of staphylococcus aureus. Recent studies have shed light on the intracellular mechanism of action of MTs and provided insight into their unusual pharmacokinetics. The seminar will focus on the activity, safety, and mechanism of action of these compounds in the context of proteinopathy.

Friday, September 17th 2021
12:15 PM | Via Zoom