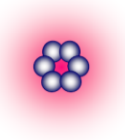

OLIGOMERIX, Inc.


Session 600 - Alzheimer's Disease: In Vitro Therapeutics

600.17 / R5 - Selection of lead tau oligomer inhibitors for in vivo studies

November 15, 2016, 1:00 - 5:00 PM Halls B-H

Authors

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Abstract

There is mounting evidence that tau oligomers have a pathological role in Alzheimer's disease (AD) including leading to the impairment of synaptic function and the spread of pathology. We have undertaken a screening approach to discover small molecule inhibitors that prevent tau oligomer formation at the beginning of the aggregation cascade. Competing programs use methods to select compounds inhibiting the formation of tau fibrils or large aggregates, previously thought to be the most toxic tau species. We hypothesized that by targeting the first step in tau self-association all forms of tau aggregates should be reduced. This work is also highly differentiated from other approaches in that we used full length tau without any mutations that are not relevant to AD. These assays were used to screen a large compound library optimized for drug-like properties. Leads from three chemical series with in vitro IC50 ranging from 300 - 600 nM, molecular weights under 450 Daltons, cLogP 2 - 5, and a polar surface area ranging from 45 to 70 $Å^2$, and which were not toxic to SH-SY5Y neuroblastoma cells, have been selected for further testing of MDCK permeability and stability, as well as pharmacokinetic analysis. The best performing candidate compound will be tested in vivo using htau mice. Mice will be treated at 3 escalating doses for 4 months and their brains will be used for biochemical and histological analysis to assess changes in tau oligomer load and efficacy of our treatment paradigm.