Title: Small Molecule Tau Oligomerization Inhibitors

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Background: Numerous studies have clearly demonstrated the role of tau oligomers in the initiation and progression of tau pathology in Alzheimer's disease (AD) and associated tauopathies. We have taken a highly differentiated approach to identify novel small molecule inhibitors of tau oligomer formation using proprietary AD relevant in vitro and cell assays, along with the htau mouse model. Here, we present recent progress in the identification of leads for in vivo efficacy and IND enabling studies.

Methods: In vitro assays were developed to screen a compound library. Selected candidates identified in the primary screen were subjected to medicinal chemistry studies to identify potential lead compounds after characterization in secondary and cell based assays. A number of lead compounds were also tested in vivo to assess preliminary metabolic stability, pharmacokinetics, off-target activity and acute toxicity. An in vivo study in htau mice will be initiated using vehicle and three doses of a lead.

Results: A number of small molecule inhibitors of tau oligomerization with high potency, drug-like properties and with IC50's in the nanomolar to micromolar range, have been identified. Preliminary metabolic stability using mouse liver microsomes showed a half-life in the range of hours for select compounds. In addition, certain compounds had a brain-plasma distribution of approximately 1:1 and were not toxic when administered daily by i.p. injection to wild type mice for 5 days.

Conclusions: From an initial primary screen, we have performed lead optimization studies which have led to novel tau oligomerization inhibitors with improved properties.

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