Discovery of New Chemical Entities for Alzheimers Disease Tauopathy

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Research Abstract

Project Summary/Abstract Neurofibrillary lesions composed of tau protein aggregates are a defining pathology of Alzheimer's disease (AD). Because lesion appearance correlates with neurodegeneration and cognitive decline, diverse approaches for inhibiting their formation are under investigation as potential therapies against AD progression. An attractive target is the tau aggregation reaction itself, which is closely associated with lesion formation but not normal tau

function. Many tau aggregation inhibitors have been reported on the basis of in vitro screening, demonstrating the feasibility of the approach, but only recently have their potency-driving features, molecular targets in the tau aggregation pathway, and activity in biological models been clarified. The results are promising but point toward liabilities of existing inhibitors with respect to pharmacokinetics and/or inhibitory mechanism. Unlocking the utility of the aggregation inhibition strategy will require the identification of new chemotypes with greater drug-like character than the existing generation of inhibitors. The first objective of this Phase 1 proposal is to meet this need using the computational platform developed by Gradient Biomodeling LLC (Gradient). The platform applies quantum methods to large?scale in silico discovery, facilitating the identification of novel chemotypes that retain the quantum signature of active compounds. Its second objective is to evaluate the activity of selected compounds in established tau aggregation assays. At the conclusion of this project, a validated computation model capable of supporting for lead optimization, and candidate compounds appropriate for in vivo testing, will be in place for Phase 2 SBIR study.

Further information available at:

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