TDP-43 aggregation inhibitors for the treatment of ALS

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Research Abstract

? DESCRIPTION (provided by applicant): There is currently no therapy for Amyotrophic Lateral Sclerosis (ALS), which is a universally fatal neurodegenerative disease that afflicts over 1 out of every 10,000 individuals. Protein aggregation has been implicated as a primary driving force in ALS and multiple other neurodegenerative illnesses. TDP-43 is the principle component of the protein aggregates in ALS, and mutations in TDP-43 are sufficient to cause disease in patients. There are families that have autosomally dominant inherited mutations in TDP-43 that cause

ALS with 100% penetrance. This places TDP-43, along with other genetically defined mutant genes, in the cell death pathway. TDP-43 also stands out as the only one of these genetically defined ALS mutant genes that is ALSO the hallmark pathology of sporadic ALS. This is why TDP-43 is so important. TDP-43 is a RNA binding protein that is nuclear under basal conditions but translocates to the cytoplasm during stress where it forms cytoplasmic RNA/protein complexes termed “”stress granules”” (SGs). Disease-linked mutations in TDP-43 enhance the ability of TDP-43 to aggregate and form SGs in vitro and in animal models. Cytoplasmic TDP-43 aggregates accumulate and also co-localize with SGs in the spinal cord and brain of patients with ALS, as well as in cellular and animal models of ALS. These integrated observations all point to a strong biological connection between TDP-43, the associated SGs, and pathogenesis of ALS. The strong role of TPD-43 in the pathophysiology of ALS points to TDP-43 as a cogent pharmacological target for disease modification. Aquinnah Pharmaceuticals has licensed 10 lead compounds that inhibit TDP-43 and SG aggregation that were identified in a high throughput screen performed in the laboratory of Dr. Benjamin Wolozin (Boston University School of Medicine). In this Phase I SBIR, we propose to demonstrate the feasibility of targeting TDP-43 with these lead compounds for the treatment of ALS. The goal of this proposal is to identify two lead compounds that exhibit the best brain pharmacokinetics (penetration and half-life), and then to test the ability of the compounds to improve TDP-43 biomarkers in vivo using a transgenic mouse model of TDP-43 of ALS. In Aim 1, we will characterize the general ADME characteristics for each compound, and then investigate the pharmacokinetics in the brain to determine brain penetration and half-life for each of the lead compounds. In Aim 2, we will select the two best compounds, and test them in a pathological TDP-43 mouse model of ALS in collaboration with Dr. Wolozin. We will use acute dosing of these compounds to show biochemical benefit by assessing biomarkers of potential efficacy including TDP-43 aggregation, phosphorylation, and ubiquitination. Success in this Phase I SBIR will result in the identification of 1-2 compounds that enter the CNS and inhibit TDP-43 aggregation in an acute dosing animal model of ALS. This will then allow a more robust drug development program to ensue, including setting the stage for chronic dosing to test the ability of these compounds to delay disease progression in vivo in SBIR Phase II.

Further information available at:

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