Testing a therapeutic strategy for hippocampal sclerosis of aging, a key AD mimic

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Research Abstract

? DESCRIPTION (provided by applicant): Diseases that mimic Alzheimer’s disease (AD) are understudied causes of cognitive impairment in the elderly. Poor understanding of these diseases has hampered AD clinical trials while leaving important illnesses largely unaddressed from a clinical research perspective. A common and high-morbidity “”AD mimic”” is hippocampal

sclerosis of aging (HS-Aging). HS-Aging is characterized by cell loss and astrocytosis in the hippocampus, with phosphorylated TDP-43 (P-TDP-43) pathology, not correlated with AD-type pathology, nor with APOE genotype. HS-Aging affects 10-25% of persons above age 85 years. The PI of the current proposal has studied HS-Aging extensively, including the first HS-Aging genome-wide association study (GWAS). A genetic polymorphism in the ABCC9 gene is linked to HS-Aging pathology. Importantly, we recently (Jan 2015) published a paper that replicated this observation in a separate group of research volunteers. The ABCC9 mutation enables us to address a central as-yet unrealized promise of genomics studies: clinical relevance. Remarkably, the GWAS-identified HS-Aging risk gene ABCC9 is a “”druggable target””-both agonist and antagonist drugs are used widely in humans. In a prior published study, we found that exposure to sulfonylureas (oral anti-diabetic drugs that antagonize ABCC9 protein function) is associated with increased risk for HS-Aging pathology in humans, controlling for other factors. We need to assess the potential to target ABCC9 in a preclinical model for more rigorous control of experimental parameters. That will enable us to test the impact of an ABCC9 agonist drug, with the opposite effects of sulfonylureas, as a potential therapy for clinical HS-Aging. Overall Hypothesis: Pharmacologic ABCC9 regulation provides a therapeutic strategy for HS-Aging. We propose proof-of-concept preclinical studies to test the specific hypothesis that ABCC9 agonist nicorandil attenuates pathologic and behavioral features of HS-Aging in a mouse model. Specific Aims: 1. Characterize the first preclinical model of HS-Aging. In GRN knockout (GRN-KO) mice, our studies indicate the presence of brain changes that model features of human HS-Aging, including hippocampal P-TDP-43 pathology and hippocampus-related neurobehavioral deficits. 2. Based on studies in humans, test in the GRN-KO mouse model the hypothesis that a sulfonylurea drug (glimepiride) which antagonizes ABCC9, exacerbates HS-Aging pathology and abnormal behavior. 3. Test in the GRN-KO mouse model the hypothesis that nicorandil, which opens the potassium channel (the opposite activity as sulfonylureas), reduces HS-Aging-related abnormal pathology and behavior. Since there are similar pathologies and genetic susceptibilities, the therapeutic strategy may also be relevant to a separate lethal neurodegenerative disease, frontotemporal lobar degeneration (FTLD).

Further information available at:

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