TRAP1 and FOXO1 as modifiers of progranulin and FTLD

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USA

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TRAP1 and FOXO1 as modifiers of progranulin and FTLD

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2

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PGRN gene, FOXO1A gene, Frontotemporal Lobar Degenerations, small molecule inhibitor, Neurons

Research Abstract
? DESCRIPTION (provided by applicant): Frontotemporal lobar degeneration (FTLD) is the most common dementia among people younger than 60. Presently, there is no therapy that blocks the neurodegeneration or progression of the disease. While a number of proteins contribute to FTLD neurodegeneration, progranulin (GRN) has emerged as one of the most important. Haploinsufficiency of GRN has been linked to familial forms of FTLD and transgenic

mice with GRN deficiency show neurodegeneration reminiscent of FTLD. Because loss of GRN leads to pathophysiology, our hypothesis is that approaches to increase GRN in the CNS will be beneficial in treating FTLD. From a genome-wide siRNA screen, we identified TRAP1(HSP90L) and FoxO1 as regulators of GRN expression. Inhibition of these proteins either with siRNA to block their synthesis or small molecule drugs to block their actions increases GRN levels in primary cortical neurons from mice. In studies proposed in this grant, we will further validate these two proteins as molecular targets to develop novel therapeutics to reverse GRN haploinsufficiency to treat FTLD. To do this, we will first test whether genetic and pharmacological inhibition of TRAP1 and FoxO1 can increase GRN expression in neurons from mice with GRN (+/-, +/R493X) haploinsufficiency, a rodent model of familial FTLD. We will use small molecule inhibitors of TRAP1 and FoxO1 to test if these proteins also contribute to the regulation of expression of GRN in vivo in brains of wild type (WT) and GRN (+/-, +/R493X) mice. Next, we will test whether inhibitors of these proteins can increase GRN levels in human induced pluripotent stem cell derived neurons (i-neurons) from healthy volunteers and patients with FTD (+/R493X) resulting in GRN haploinsufficiency. These studies will test whether TRAP1 and FoxO1 regulate GRN expression in the neurons most relevant to FTLD and determine whether their inhibition can bring GRN levels in brain to levels seen in normal animals or humans. Next, we will investigate mechanisms by which TRAP1 and FoxO1 control GRN expression. We will test whether inhibitors of TRAP1 and FoxO1 stimulate GRN transcriptional activity, affect the turnover of the protein, or influence the subcellular targeting of GRN in vitr in primary neuron models of GRN haploinsufficiency (+/- and +/R493X). Finally, we will investigate the mechanisms by which TRAP1 and FoxO1 regulate GRN expression in vivo. This will be done by testing the efficacy of small molecule TRAP1 and FOXO1 inhibitors to increase GRN expression in the CNS of a unique animal model in which luciferase expression is regulated by the GRN promoter. In these mice, we will be able to test whether TRAP1 and FOXO1 inhibitors increase GRN transcriptional activity as well as GRN levels. If the small molecule inhibitors are able to reverse GRN deficiency in these disease models, the results would support further testing of TRAP1 and FOXO1 inhibitors as potential therapeutics to treat FTLD in future studies.

Further information available at:

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