A Multiple Ascending Dose Study of HDAC Inhibition for Modulation of Apoj/Clusterin Risk in Alzheimer's Disease

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Background: Clusterin/ApoJ gene (CLU) single nucleotide polymorphisms have been shown to increase AD risk in genome-wide association studies. This effect is dependent on reductions in clusterin/ApoJ expression levels that can be reversed by histone deacetylase inhibition (HDACI) in vitro.

Methods: We conducted a randomized (2:5), double-blind, placebo-controlled, multiple ascending dose study of HDAC inhibition for modulation of ApoJ/clusterin expression in 14 elderly subjects with normal cognition. HDACI was achieved with the use of valproic acid (VPA) 250 mg bid, followed by 500 mg bid, each over a one-month treatment period. CSF and serum measures of clusterin/ApoJ expression were the primary outcome measures.

Results: Treatment was tolerated well in both dose ranges with no SAEs or dose limiting toxicities seen. No significant differences in clusterin/ApoJ expression change scores were seen in an intention-to-treat analysis of combined dosing groups. Subjects receiving placebo and two subjects exposed to HDACI showed no effect of treatment, while the remaining subjects exposed to HDACI showed evidence for the hypothesized increase in clusterin/ApoJ expression as a result of this treatment paradigm (46% increase). Gene sequencing of the two non-responders demonstrated that all were homozygous for the minor CLU allele. Based on these findings, a responder analysis was performed, excluding the subjects homozygous for the CLU minor allele, that demonstrated statistically significant increases in clusterin/ApoJ expression in response to HDAC inhibition in this small sample of subjects ($p<0.05$).

Conclusions: Modulation of AD risk attributed to CLU polymorphisms can be achieved successfully with HDACI in subjects who are not homozygous for the minor allele. Such modulation may be easily achieved with the repurposing of existing and readily available agents with HDACI properties, like VPA. While VPA has failed to influence clinical outcomes in subjects with moderate to severe AD, its use as a safe and effective HDACI suggest it may still have a role in modulation of AD risk. Further clinical studies of HDACI (VPA or others), in subjects not homozygous for the CLU minor allele, for the prevention of AD are warranted. This study represents one of the first attempts at developing genetically-based personalized medicine for the treatment and or prevention of AD.