**Title:** Comparison of Phenotypic and Mechanism-Based Drug Discovery in Oblique Approaches to Alzheimer’s Disease Therapeutics

Alzheimer’s disease and related dementia (ADRD) describes a multifactorial disease with mixed and varied pathologies, without a definitive genetic cause; however, risk is amplified by APOE4, and Type 2 diabetes (T2D) is a comorbidity. Therapeutic approaches that target common underlying causes of T2D and ADRD and address the APOE4 risk factor represent novel, if oblique strategies for ADRD a terrible disease absent any disease-modifying therapeutic strategies. ABCA1, the key cholesterol efflux transporter is responsible for lipidation and formation of HDL in the periphery and HDL-like particles in the brain. Poor lipidation of the Apoe4 isoform of apolipoprotein-ε is a contributor to APOE4 risk. Screening for small molecules upregulating ABCA1 in astrocytes with neutral effects on the lipogenic gene, SREBF1, in hepatocytes led to hits that were validated in cholesterol efflux assays. Both hits and an early lead compound produced positive PK/PD in a mouse model of obesity-driven T2D. NAMPT is the rate-limiting enzyme in rescue of nicotinamide (NAM) and NAD biosynthesis. Depletion of NAD in aging and T2D is being addressed by dietary supplements containing NAM, NAD, and equivalents. Mechanism-based screening for NAMPT positive allosteric modulators (N-PAMs) identified hits with nanomolar potency, which were further optimized using NAMPT co-crystal structures. Comparison of these strategies illustrates the strengths and weaknesses of phenotypic versus mechanism-based approaches to drug discovery and development.