**Abstract:** Treating Alzheimer’s disease (AD) effectively by targeting single pathways is not likely to be feasible and a successful therapeutic strategy will require pleiotropic interventions. Dual-specificity tyrosine phosphorylation regulated kinase 1A (Dyrk1a) is an emerging target for the treatment of neurodegenerative diseases, attractive for its functional activity on multiple pathways implicated in AD. We and others have shown that Dyrk1a is important for phosphorylation of tau protein on multiple sites. Inhibition of Dyrk1a is thus expected to reduce abnormal tau phosphorylation. Dyrk1a has also been shown to phosphorylate the amyloid precursor protein (APP), resulting in increased amyloidogenic cleavage of APP and elevated Aβ40 and Aβ42 levels. We have generated and validated novel small molecule Dyrk1a inhibitors, confirming that inhibition of Dyrk1a, when pathology is advanced in the 3xTg-AD mouse model, reduces AD-like amyloid and tau pathology and improves cognition. Importantly, we further show that Dyrk1 inhibition prior to the onset of pathology in 3xTg-AD mice significantly delays both amyloid and tau pathologies. We also confirm that a relatively rare mechanism of action, based on inhibitor-induced degradation of Dyrk1a protein, likely contributes to the beneficial effects seen on AD-like neuropathology.