Phenotypic Discovery and Optimization of Potent T-Cell Modulators: Dual Inhibition of Diacylglycerol Kinases α and ζ

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Blocking the extracellular checkpoints CTLA4 and PD-1 is an effective strategy that overcomes certain cancer's ability to evade immune response. It has been hypothesized that inhibition of intracellular checkpoints DGKα and/or DGKζ could overcome immune system suppression in a similar fashion. Stimulation of T-cells via the T-cell receptor generates diacylglycerols(DAGs) that act as lipid signaling molecules leading to the release of cytokines such as interleukin 2 and interferon γ. Depletion of DAGs via phosphorylation by diacylglycerol kinases (DGK) is known to be an important regulatory step in modulating this pathway to attenuate the immune response. This medicinal chemistry vignette will detail our path to the discovery and optimization of DGK inhibitors driven exclusively by phenotypic assays without prior knowledge that DGK was the biochemical target. The details will include the initial high through-put screen, evidence supporting identification of DGK as the target, efforts to optimize the chemical matter and initial in vivo studies that supported our work toward a clinical candidate.