**Results**

**Conclusions**

- DGKα and DGKζ were expressed by human immune cells and tumor infiltrating CD8⁺ T cells.
- Pharmacological or genetic targeting of DGKα and DGKζ resulted in increased T cell and NK cell responses to activating stimuli, including antigen-specific T cell stimulation.
- High throughput characterization of > 500 compounds showed improved cellular potency when DGKα and DGKζ were inhibited together, relative to DGKα alone.
- Dual inhibition of DGKα and DGKζ produced superior increases in T cell activation, TCR downstream signaling, and cytokine production compared to inhibitors selective for only DGKα or DGKζ.