Generating a lentiviral system for high-throughput screening

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Ischemic heart disease (IHD) is the leading cause of mortality on a global scale. Two primary causes of IHD are left ventricular hypertrophy (LVH) and coronary artery disease (CAD). Phospholipase C (PLC) enzymes, and more specifically, PLCβ, are essential to normal cardiovascular function. These enzymes hydrolyze phosphatidylinositol 4,5-bisphosphate (PIP_2) at the membrane, leading to the production of diacylglycerol (DAG) and inositol phosphates (IPs). IPs increase intracellular calcium, a key secondary messenger in cardiovascular activity. Changes in PLCβ expression or activation has also been found to play a critical role in cardiac hypertrophy and contractility. Despite the importance of these enzymes, a reliable inhibitor for studying their function in cells and animal models has not yet been discovered. In the first step to address this unmet need, I am designing a lentiviral expression platform to express human PLCβ3 and its two major activators, the heterotrimeric G protein subunits $G\alpha_q$ and $G\beta\gamma$. These constructs will be utilized to establish a high-throughput screening methodology with the aim of identifying a specific inhibitor of PLCβ and potentially PLCs more broadly.