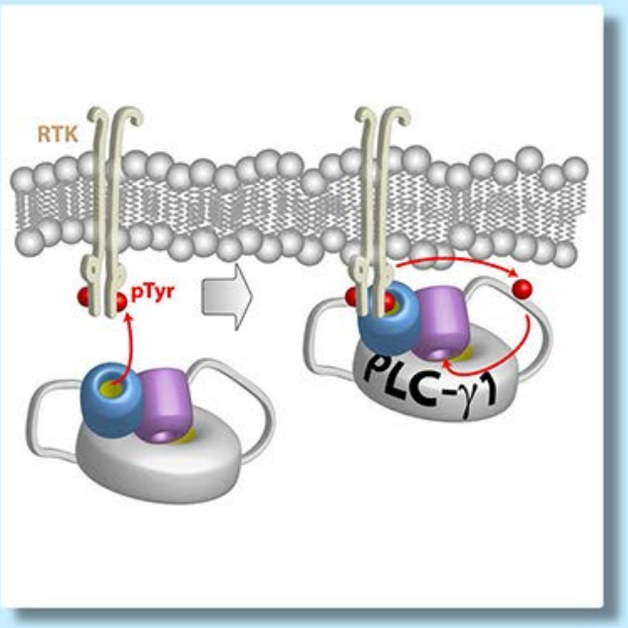
NICHOLAS KEITH

Faculty Research Mentor: Dr. John Sondek
Department of Pharmacology



Phospholipase C gamma 1 activation

Dysregulation of Phospholipase C Gamma 1 Activity in Adult T-cell Leukemia/Lymphoma

Phospholipase C gamma 1 (PLCg1) hydrolyzes membrane-bound phosphatidylinositol 4,5-bisphosphate into the classical second messengers inositol 1,4,5-trisphosphate and diacylglycerol, both of which participate in various downstream signal transduction cascades. These signaling cascades help control various cellular functions, from stimulating intracellular calcium release to helping control actin regulation and cell motility. Interestingly, PLCg1 was recently reported to be mutated with a frequency of ~40% in a cohort of patients with adult T-cell leukemia/lymphoma (ATL), making it the most frequently mutated gene in this cancer. However, it is not known how these mutations affect the catalytic activity of PLCg1, and we hypothesized that mutant forms of PLCg1 found in ATL have elevated phospholipase activity. The accumulation of inositol phosphates, a direct readout of PLCg1 activity, was quantified after transient over-expression of mutant forms of PLCg1 in human embryonic kidney (HEK293) cells. In addition, the activity of these PLCg1 mutants was also quantified separately after receptor-dependent activation. All 20 mutations found in ATL constitutively activated PLCg1, increasing basal activity 8- to 1700-fold relative to wild-type. Furthermore, all mutants also had further enhanced activity in the context of epidermal growth factor receptor activation. These results corroborate other findings suggesting that PLCg1 is an oncogene and may be a viable drug target for treatment of ATL and other cancers.