

# B-6

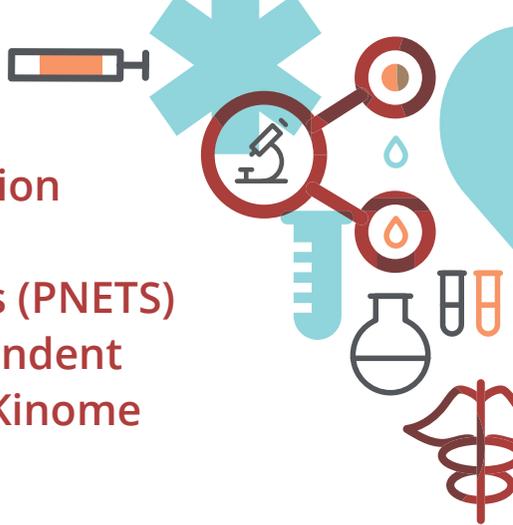
## CDK-Targeted Combination Therapies of Pancreatic Neuroendocrine Tumors (PNETS) Guided by RABL6A-Dependent Regulation of the PNET Kinome and Phosphoproteome

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**BACKGROUND:** More effective therapeutics are needed to improve survival of advanced PNET patients. RABL6A is a novel oncoprotein that drives PNET proliferation and survival through multiple pathways, including suppression of the retinoblastoma (RB1) tumor suppressor via cyclin-dependent kinase (CDK) activation. In recent PNET clinical trials, overall patient survival has not been improved by CDK4/6 monotherapy, warranting the development of combination targeted therapies. Here, we examined the global PNET kinome and phosphoproteome to identify other kinases regulated by RABL6A whose inhibition may synergize with CDK4/6 inhibitor therapy.

**METHODS:** Quantitative proteomics (kinome and phosphoproteome analyses) of PNET cells that express or lack RABL6A was performed. Effects of altered RABL6A expression on cellular protein (immunoblotting), proliferation & survival (trypan blue exclusion, cell counting, colony formation), drug sensitivity (AlamarBlue), and tumor growth / drug response in vivo (mouse xenografts) were measured.



**RESULTS:** RABL6A depletion in PNET cells caused significant downregulation of >1,100 cellular phosphoproteins and reprogramming of the global kinome. Expression of RABL6A was required for activity of many cell cycle, mitotic and tumor-promoting kinases, including CDKs 1/2/6, Aurora kinases A and B, Polo-like kinase 1 and select tyrosine directed and MAP kinases. Cellular analyses verified PNET cell sensitivity to CDK4/6 inhibitors (e.g., palbociclib) was dependent on RABL6A expression. The combination of drugs targeting CDK4/6 and CDK1/2, which more fully activates RB1 tumor suppressive activity, was more effective against PNET growth than either inhibitor alone. Ongoing studies are examining the efficacy of other innovative, rational therapies that combine inhibitors of CDKs with drugs targeting other RABL6A regulated kinases.

**CONCLUSION:** Quantitative kinome and phosphoproteomic analyses, which have not been performed before in NETs, identified a global kinase signature associated with PNET proliferation / survival and RABL6A signaling. This approach allows rational design of novel kinase-targeted combination therapies for NET patients.