Abstract Title: RABL6A, a new driver of pNET pathogenesis *in vivo*

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Background: Pancreatic neuroendocrine tumors (pNETs) are rising in incidence and current therapies fail to improve overall patient survival. Greater understanding of mechanisms governing pNET pathogenesis will help identify meaningful prognostic biomarkers and new therapeutic targets. RABL6A (a RAB-like GTPase) is an oncogenic driver of pNET cell survival and proliferation that is highly expressed in patient NETs. We hypothesize that RABL6A signaling promotes pNET development and angiogenesis *in vivo*. This study investigates that idea using a genetically engineered mouse model of spontaneous pNETs.

Methods: RIP/Tag2 (RT2) mice express SV40 large T-antigen (Tag) under the rat insulin promoter (RIP). This causes islet β cell transformation and development of hyperplastic islets, angiogenic islets, and insulinomas in a time-dependent fashion. We crossed RT2 mice with RABL6A knockout (KO) mice to generate four cohorts: a) WT, b) RT2, c) RABL6A KO, and d) RT2-RABL6A KO. At specific time points, pancreata of euthanized mice were used to isolate islets for molecular analyses or fixed for histopathological examination.

Results: Loss of RABL6A significantly reduced the tumor burden in 8-10-week female mice and 10-12-week-old male RT2 mice. Those results correlated with decreased pancreatic endocrine area, angiogenic islets and islet mitoses in RT2-RABL6A KO females compared to RT2 controls, with similar trends in RT2-RABL6A KO males. While statistical significance was not reached, a trend towards improved survival was seen in RABL6A deficient RT2 mice vs RT2 controls. Our gene expression analyses revealed that loss of RABL6A elicits downregulation of *c-Myc* and *Vegfa* transcripts in normal mouse pancreatic islets.

Conclusions: RABL6A promotes the angiogenic switch and pNET development in the RT2 model with greater effects observed in female mice. Findings are consistent with increased mRNA expression of pro-angiogenic pNET oncogenes, *c-Myc* and *Vegfa*, in RABL6A-positive islets.