Abstract Title: Development and comparison of novel bioluminescent mouse models of pancreatic neuroendocrine tumor metastasis

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Background: Pancreatic neuroendocrine tumors (PNETs) are rare, slow growing cancers that lack effective treatments once they become metastatic. Unfortunately, 60% of PNET patients have distant metastatic disease (mainly in the liver) at diagnosis and current therapies fail to improve overall survival. Pre-clinical models of PNET metastasis are greatly needed to advance our understanding of mechanisms driving NET metastasis and develop/test novel therapeutic interventions.

Methods: PNET cell lines stably expressing luciferase (named BON1.luc and Qgp1.luc) were generated by DNA transfection and antibiotic selection. In vitro cell migration was measured using Boyden chamber (transwell) assays. For in vivo studies, the luciferized cells were introduced into NSG immunodeficient mice by intracardiac (IC) or intravenous (IV, tail vein) injection. In one cohort of animals, half of the mice are being treated with an investigational anti-PNET drug (small molecule activator of PP2A, called SMAP) versus vehicle control. Tumor growth in mice has been monitored longitudinally on a weekly basis by non-invasive bioluminescence imaging (BLI). Animals with high tumor burden (i.e., BLI measurements of photons/sec exceeding 10^9) were euthanized and ex vivo BLI performed to verify the tissue sites of tumor growth. Tumor-bearing organs were placed in fixative for histopathological analyses and RNAlater for genetic analyses.

Results: Qgp1.luc PNET cells displayed increased migration in vitro and accelerated metastatic tumor growth in vivo (by both IC and IV routes) compared to BON1.luc cells. Studies are ongoing, but all Qgp1.luc tumors isolated to date have developed in the liver regardless of the route of administration, mimicking the predominant site of PNET metastases in patients. This was highly unexpected since IV delivery of other cancer cell types almost exclusively yields pulmonary tumors. Interestingly, BLI reveals that BON1.luc cells introduced via IC injection are widely disseminated throughout the body, contrasting with Qgp1.luc-IC tumors that preferentially localize to the liver.

Conclusions: We have successfully developed new bioluminescent mouse tumor models of PNET metastasis. Initial data suggest Qgp1.luc cells preferentially form tumors in the liver while BON1.luc cells may have a broader metastatic distribution. This system is a useful platform for testing novel PNET therapies.