B-2
The HNV Pancreatic Neuroendocrine Tumor Model

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BACKGROUND: For most patients with pancreatic neuroendocrine tumors (PNETs), surgery is not possible because of extensive metastatic disease. However, the lack of reliable, widely available models is currently a major impediment to the development of new therapies for patients with pancreatic neuroendocrine tumors. We recently developed a patient-derived xenograft model of PNET called HNV (hepatic neuroendocrine from segment V).

METHODS: A patient with PNET liver metastases producing insulin underwent surgery to ameliorate refractory hypoglycemia. PNET tissue was implanted subcutaneously into nude mice and stained with H&E or with the antibodies indicated for immunofluorescent analysis. Real-time TaqMan RT-PCR assayed for expression of developmental transcription factors specifically expressed in NETs. The radiolabeled somatostatin analog (68)Ga-DOTATOC was used to perform PET-CT of treated PNETs in vivo. Mice bearing PNET xenografts were treated with everolimus. Whole-exome sequencing of PNET was performed with an Illumina HiSEQ2500 (Illumina) and analyzed using the Bina-Roche genomic analysis platform.

RESULTS: We observed that HNV xenografts maintain a well-differentiated NET morphology (Ki67 index 6-8%, G2), chromogranin A and hormone (serotonin, insulin) expression, and a neuroendocrine-specific gene expression signature with serial passage. We detected mTOR pathway activity in HNV by Western blot. Everolimus inhibited mTOR and completely halted HNV growth. Gallium-68 DOTATATE PET-CT clearly detected HNV, suggesting it expresses somatostatin

receptors. To establish the mutational landscape, we performed whole-exome sequencing of the HNV. In preliminary analyses, the HNV contains many mutations in known pancreatic NET-associated genes, such as MEN1, BRCA2, PTEN, and SETD2. Using the PathScan RTK Signaling Antibody Array Kit to evaluate phosphorylated (active) receptor tyrosine kinases and signaling nodes, we observed phosphorylation of S6 ribosomal protein, indicating activation of the mTOR pathway.

CONCLUSION: These data provide strong evidence that the HNV model is a bona fide PNET model, which may be an important resource for the PNET research community.