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## Establishment of Two Patient-derived Neuroendocrine Carcinoma Spheroid and Xenograft Models for Drug Testing

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**BACKGROUND:** Gastroenteropancreatic neuroendocrine carcinomas (GEP NECs) are rare neoplasms with poor prognosis. Few reliable pre-clinical models exist to study GEP NECs, limiting investigation of novel imaging and treatment modalities. Here, we describe the establishment and characterization of two patient-derived GEP NEC spheroid and xenograft (PDS and PDX) models and their application for drug testing.

**METHODS:** The NEC913 and NEC1452 cell lines were derived from surgically resected human GEP NEC tumors, originated from nodes from ampullary and small bowel primaries, respectively. Expression of neuroendocrine markers was confirmed by immunohistochemistry, immunofluorescence, and quantitative PCR in vitro,and drug screening experiments were performed and cell viability was measured. Mice were subcutaneously injected with these GEP NEC cells to create PDXs and used in drug treatment experiments.

**RESULTS:** The NEC913 PDS and PDX models expressed neuroendocrine differentiation markers chromogranin A (CgA), synaptophysin (SYP), and somatostatin receptor-2 (SSTR2), as well as NEC markers ASCL1 and CXCR4. They expressed a truncated form of p53 and showed no expression of pRb. The NEC1452 PDS and PDX models only stained positive for CgA and SYP. Both NEC models have a high Ki-67 expression (>90%) and can be maintained in suspension culture as PDSs and used to screen 147 FDA approved anti-cancer drugs and over 300 structurally diverse compounds to identify new inhibitors for NECs. Both PDS lines injected into immunocompromised mice developed into

tumors with >90% uptake rate. Subcutaneous injection of 1x106 cells grew into tumors about 1500 mm3 in size after 4 weeks.

**CONCLUSION:** The NEC913 and NEC1452 PDS lines are useful pre-clinical models for the study of neuroendocrine carcinoma. NEC913 expresses many NEC markers and maintains the histologic morphology of the original patient tumor. NEC1452 expresses few NEC markers. These two NEC models represent a valuable resource for identification of novel treatment modalities for NECs.

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