# B-9

## Establishment of a long term gastric neuroendocrine tumor organoid and matched patient derived xenograft

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### BACKGROUND

Gastric neuroendocrine neoplasms (gNENs) are a rare subset of neuroendocrine tumors. Treatment development has been limited due to low patient trial accrual and a lack of accurate study models. Herein we describe the creation of stable G3 gNEN patient tumor organoid (PTO) and patient derived xenograft (PDX) lines from a primary tumor.

### METHODS

Patient tissue was procured fresh from a clinically indicated surgery at the NIH. Tissue was freshly dissociated into cell suspension, then seeded for long term growth. Passaging occurred as organoids reached >100 uM. PDX establishment was attempted using freshly dissected tissue fragments implanted subcutaneously into NSG mice. Following PDX establishment, PTOs were established from the PDX (PDX-PTO) in a similar manner as patient tissue. Similarly, PTOs were used to establish a new PDX (PTO-PDX). Therapeutic screening on PTOs was performed at passages 0, 3, 6, 9, and 12 and on PDX-PTOs at passage 0. Immunohistochemistry and whole genome sequencing was performed on both PTO and PDX tissues.

### RESULTS

A patient with a germline MEN1 mutation and a history of previous neuroendocrine tumors underwent a gastrectomy in 2023. The patient had previously progressed while on sunitinib. Sequencing analysis did not detect pathogenic mutations, with several other genes of unknown significance detected. Tumor pathology detected neuroendocrine features, with a ki67 = 30%. PTOs from patient tumor have reached >15 passages, with ki67>50%. PDX growth of passage 1 (p1) implants remained non-palpable until day 300, upon which one tumor mass began exponential growth, reaching 1000 $mm^3$ at day 330 and progressed to 3,000$mm^3$ by day 360, which was then resected to establish p2 tumors. Currently expanding in vivo p2 tumors reached 500mm3-1,000$mm^3$ volumes within ~100 days post-implantation which is estimated to have a doubled growth rate compared to p1. Furthermore, PTO-PDX engraftment has demonstrated an approximate 50% acceleration in tumor growth compared to p1 PDX, reaching 500 mm3 at day 210 compared to day 320 for p1 PDX. All organoids and tissues have displayed histopathologic, molecular, and genomic signatures consistent with well-differentiated neuroendocrine tumors, including Ki67>50% and prominent Chromogranin A and Synaptophysin

immunostaining of gNENs. Therapy screening has demonstrated sensitivity towards everolimus, cabozantinib, and capecitabine/temozolomide therapy, while it is resistant towards sunitinib.

## CONCLUSIONS

Long term culture of a matched gNEN PTO, PDX, PTO-PDX, and PDX-PTO remains ongoing and demonstrates promising growth, establishment, and therapy response. Future work will focus on maintaining genomic and phenotypic stability during culture and cryopreservation.

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