# B-2

## Identification of a recurrent fusion oncogene as a potential therapeutic target in pancreatic neuroendocrine tumors

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### BACKGROUND

Pancreatic neuroendocrine tumors (pNETs) are an understudied cancer type with few effective treatment options. The development of new treatment strategies has been limited by a lack of molecular targets, a challenge that stems at least in part from an incomplete understanding of the genetic drivers of this disease. Applying complementary molecular profiling approaches to a cohort of NET liver metastases, we identified a recurrent somatic gene fusion, *PSIP1::TBL1X*. The chimeric protein combines the N-terminal chromatin binding region of PSIP1 with the full coding sequence of TBL1X, an oncogenic transcriptional regulator and the target of the clinical-stage inhibitor tegavivint. Tegavivint is currently being tested in phase 1 and 1/2 trials across multiple solid tumor types, pointing to a potential therapeutic strategy for this molecular subtype.

### METHODS

*PSIP1::TBL1X* was identified by optical genome mapping and confirmed by PacBio long-read RNA sequencing, amplification of the fusion junction from cDNA, and a novel dual-color dual-fusion FISH assay. Fusion prevalence was assessed across a cohort of primary and metastatic pNET specimens. To evaluate oncogenic function, the fusion was stably expressed in pNET cell lines via lentiviral transduction. Protein interactions were assessed by co-immunoprecipitation and western blotting.

### RESULTS

*PSIP1::TBL1X* was identified in 11% of metastatic pNET specimens and was absent from a cohort of primary resection specimens. Three transcript variants were identified, joining *PSIP1* exon 4, 6, or 9 to *TBL1X* exon 4, which contains the start of the *TBL1X* coding sequence. Because the PSIP1::TBL1X protein retains the TBL1X domain targeted by tegavivint, the fusion represents a potential target for this agent in fusion-positive pNETs. The functional consequences of *PSIP1::TBL1X* expression and tegavivint response are

being evaluated in pNET cell lines to better understand the mechanisms of fusion-driven oncogenesis and the potential for therapeutic targeting in fusion-positive pNETs.

## CONCLUSIONS

Discovered by integrating complementary molecular profiling technologies, *PSIP1::TBL1X* defines a novel molecular subtype of metastatic pNET. Because TBL1X is the target of the clinical-stage inhibitor tegavivint, this subtype may be amenable to a targeted therapeutic approach. These findings demonstrate that sensitive structural variant detection can uncover clinically actionable targets missed by conventional sequencing, expanding treatment options for patients with neuroendocrine neoplasms.

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