145. AAV vectors for direct delivery of shRNA
(University of Florida)

▶ Asset Overview

Product Type	Gene therapy
Disease Area	Oncology
Indication	Pancreatic Cancer
Current Stage	Lead Optimization
Target	Pancreatic islet cells
MoA	shRNA reduces thymidylate synthase (TS) levels, significantly decreasing the progression of pancreatic neuroendocrine tumors (PanNETs).
Brief Description	• This treatment employs an AAV-TS vector that specifically targets pancreatic islet cells. The vector contains small hairpin RNA (shRNA) molecules and releases them into identified pancreatic islet cells. • This reduces thymidylate synthase (TS) levels, significantly decreasing the progression of pancreatic neuroendocrine tumors (PanNETs). TS acts as a biomarker and therapeutic target. • Although TS plays a central role in DNA synthesis/repair and is essential for cell proliferation, high levels of TS correlate strongly with tumorigenesis, poor therapeutic outcomes, and low overall survival rates in cancer patients. • A mouse with an hTS/Men1 (-/-) allele established a model to replicate the human disease of PanNET to test how the interfering RNA targeted the TS.
Intellectual Property	US20190256858A1
Publication	Thymidylate synthase accelerates Men1-mediated pancreatic tumor progression and reduces survival. JCI insight, (2022)
Inventors	Kyungah Maeng, Maria Zajac-Kaye

▶ Highlights

- Overexpression of hTS in inactivated Men1 islet cells shortened the latency for tumor development and reduced survival of both hTS/Men1+/− and hTS/Men1−/− mice.
- High TS levels shortened survival of hTS/Men1−/− and hTS/Men1+/− mice extends inventor's previous work showing that TS expression in patients with TS-positive gastro-enteropancreatic neuroendocrine tumors had worse outcome in comparison with patients with negligible TS expression as determined by univariate and multivariate survival analysis.
- Changes in the level of the cell cycle regulator p21Cip1 by high TS levels and changes of p18INK4c level by deregulation of menin activity may trigger entry to G1/S phase and thus increase islet cell proliferation and tumor progression.
- Elevated TS participates directly in promoting PanNET tumorigenesis using 3 different Men1-mutant animal models. These data emphasize the importance of development of a new class of TS inhibitors to block TS catalytic activity without feedback induction of TS levels.
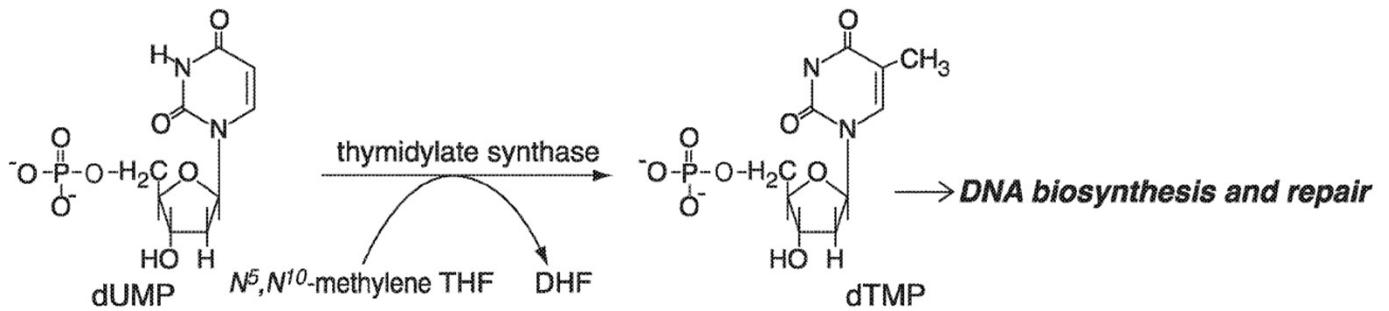
▶ **Key Data**

The conversion of dUMP to dTMP with thymidylate synthetase

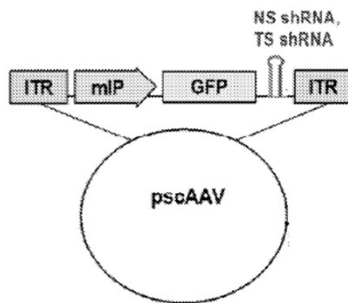## AAV-TS shRNA inhibits PanNET progression

Figure 7A

- FIG. 7A shows a vector map of scAAV-mIP-GFP-NSshRNA and scAAV-mIP-GFP-TSshRNA (containing SEQ ID NO:1 and 2) construct.
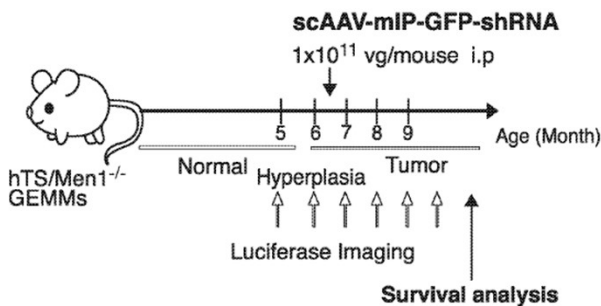

Figure 7B

- FIG. 7B shows schematics of scAAV-mIP-GFP-NSshRNA (AAV-shNS) or scAAV-mIP-GFP-TSshRNA (AAV-shTS) treatment in hTS/Men1$^{-/-}$ mice.

▶ Key Data

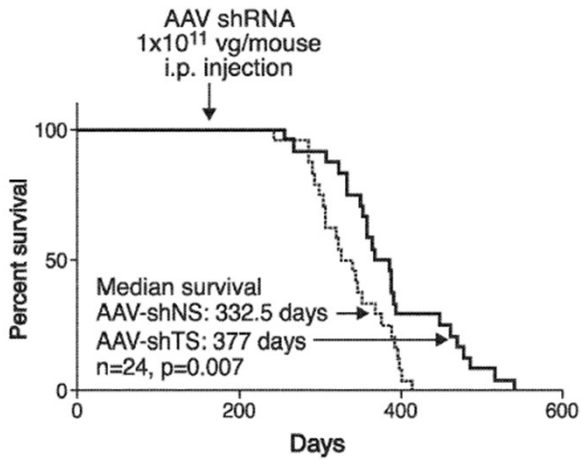### AAV-TS shRNA inhibits PanNET progression

Figure 7C

- FIG. 7C shows survival analysis of pancreas tissues from hTS/Men1 mice after TS shRNA injection (n=24 per group).
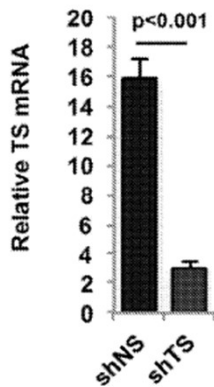

Figure 7D

- FIG. 7D shows TS mRNA expression levels in tumors

▶ **Key Data**

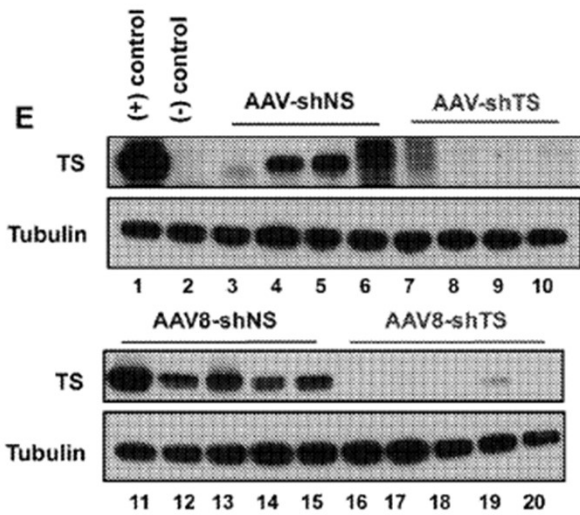## AAV-TS shRNA inhibits PanNET progression

Figure 7E

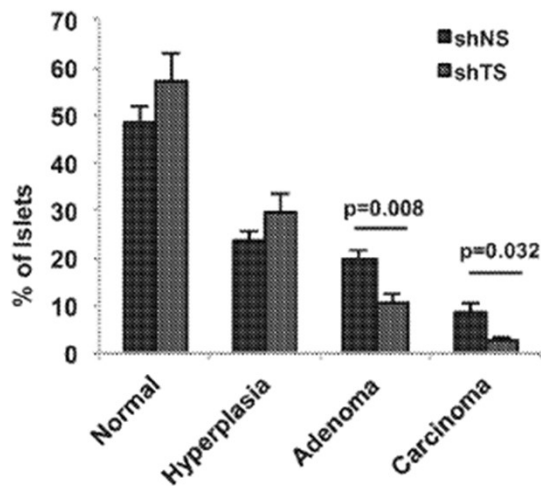- FIG. 7E shows TS protein expression levels in tumors.

Figure 7F

- FIG. 7F shows the percentage of islet tumor lesion (n=9 per group).