Examination of Wnt signaling as a therapeutic target for pancreatic ductal adenocarcinoma using a pancreatic tumor organoid library.

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INTRODUCTION

- Pancreatic ductal adenocarcinoma (PDAC) 4th leading cause of cancer deaths.
- PDAC presents at late stage and is refractory to most treatment modalities.
- Low tumor cellularity and high desmoplastic response makes in vitro study difficult, but several mutations have been identified.
- Wnt signaling, activated by pancreatic ductal ligation injury, plays a critical role in proliferation and chemotherapeutic resistance. Wnt signaling, therefore, may serve as a potential therapeutic target.
- Pancreatic tumor organoid libraries (PTOL) allow for accurate investigation of other therapies.

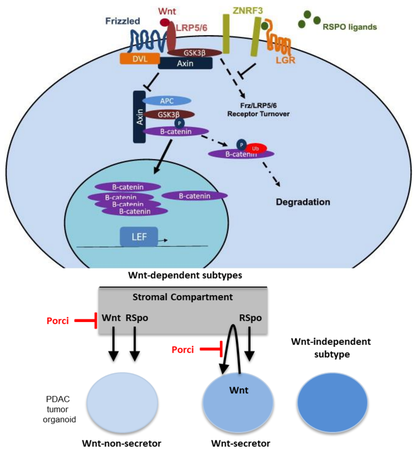
MATERIALS AND METHODS

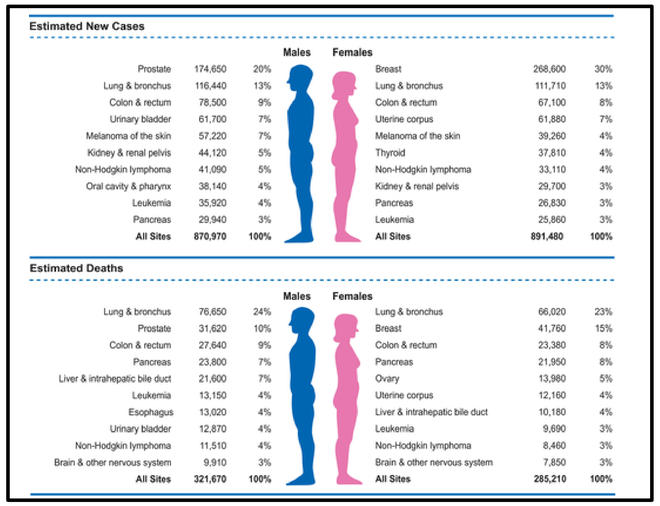
- Seven PDAC organoids grown in Human Pancreatic Stem Cell medium.
- Minimal media conditions required to maintain growth assessed with depletion of the various niche factors Wnt3a, EGF, Noggin, R-spondin, ALK inhibitor, or p38 inhibitor.
- Confirmation of Wnt inhibition by growing organoids in minimal media and treating with Wnt inhibitors ICG001, ETC159, C59.
- Growth assessed with CellTiter Glo 3D.
- Tumors injected into athymuic nude mice and treated for 30 days with assessment of growth rate and tumor regrowth following removal of drug
- Gene signatures for respective organoid and PDX models were determined through RNA-seq
- RT-PCR performed for human Wnt genes

OBJECTIVE

- Subclassify PDAC organoids based on Wnt dependency to determine if combinatory treatment with Wnt inhibitors and chemotherapy would serve as a feasible treatment.

PATHWAYS





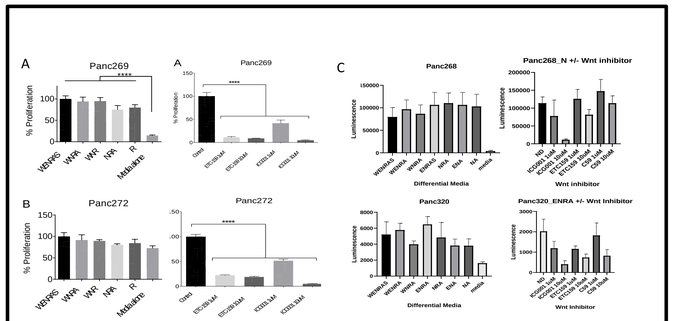


Figure 1: Pancreatic organoids growth factor dependency and confirmation of Wnt dependency through the utilization of Wnt pathway inhibitors: ICG001, ETC159, C59.

A. Wnt/R-spondin dependent B. Wnt dependent C. Wnt and R-spondin independency

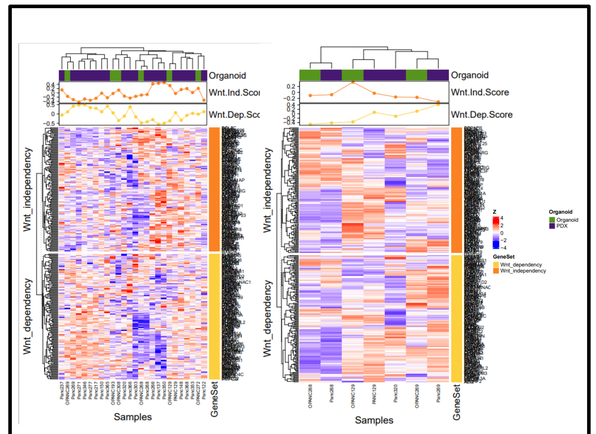


Figure 2: Wnt (in)dependency gene signatures according to those identified by Seino et al.

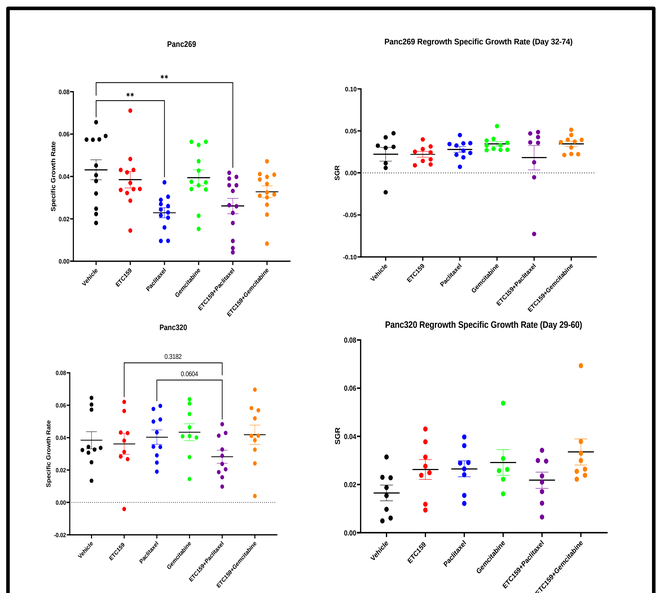


Figure 3: *In Vivo* Combinatory Drug Treatment

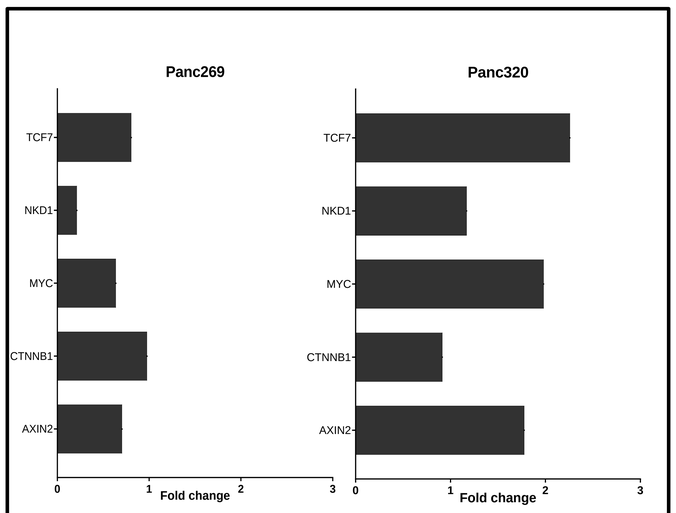


Figure 4: RT-PCR gene expression analysis of organoids post-treatment for key genes contributing to Wnt dependency as described by Madan et. al

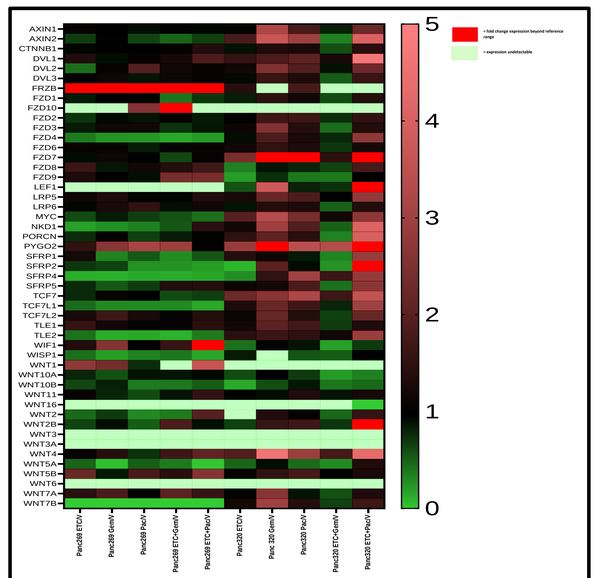


Figure 5: Heat map of Wnt gene fold change expression for post-treated pancreatic tumors

CONCLUSIONS

- Each organoid demonstrated different niche factor dependencies, providing an avenue for targeted therapy, particularly Wnt inhibition.
- Combinatory treatment with Wnt inhibition and chemotherapy *in vitro* and in patient-derived xenograft models suggests beneficial application of combinatory treatment
- Gene signature and expression analysis of each organoid suggests correlation between genotype and Wnt (in)dependency observed *in vitro*.

ACKNOWLEDGEMENTS

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WINGS OF HOPE for PANCREATIC CANCER RESEARCH

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