GPER1 and AXP107-11 have tumor suppressing and chemoenhancing functions in pancreatic cancer

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Introduction
Despite advances in cancer therapeutics, pancreatic cancer remains difficult to treat and often develops resistance to chemotherapies. Combination therapy may improve patient survival, but is commonly accompanied with significant toxicity. Emerging pre-clinical evidence indicates that the phytoestrogenic compound genistein has chemoenhancing properties, and a patented crystalline form of genistein, AXP107-11, has completed Phase 1b clinical trial. Thus, we propose an alternative approach to sensitize tumor cells to chemotherapy by using the naturally derived compound genistein or its more bioavailable analogue AXP107-11.

Results
Genistein treatment enhances gemcitabine efficacy in pancreatic cancer cell lines
Genistein has chemoenhancing effects, especially in the more chemoresistant PANC1. RNA-seq of combinatory treatment compared to Gemcitabine mono treatment revealed 154 commonly regulated genes, involved in intrinsic apoptosis in response to endoplasmic reticulum stress, release of sequestered calcium ion into cytosol, response to estradiol, and p-38 MAPK (MAPK14) pathway.

GPER1 is a potential mediator of genistein activity
GPER1 is expressed in clinical samples of PDAC, and higher expression is related to better survival. We propose that genistein/AXP107-11 activates GPER1 and enhances the anti-proliferative and chemoenhancing functions.

Conclusion
Using cell lines and patient-derived xenografts (PDX) models, we show that both genistein and AXP107-11 enhance the anticancer effect of gemcitabine. Our data suggest that G-protein-coupled estrogen receptor (GPER1) is a contributing mediator of this effect, and that activation of GPER1 exhibits anti-proliferative activity in pancreatic cancer. Our results indicate that AXP107-11 and GPER1-activation constitute novel therapeutic options to improve chemo-efficacy in pancreatic cancer.

AXP107-11 has chemoenhancing properties
None of the PDX tissue slices responded to gemcitabine alone. Adding AXP107-11 resulted in 57% sensitive PDX tumors. The sensitive PDX tumors also demonstrated a significantly reduced tumor growth upon combination treatment in vivo.

Planned future work includes a preclinical study of the combinational treatment. Additionally, silencing of GPER1 is required to validate it as a mediator of genistein activity.