

Pankind 2026 Scientific Meeting

Poster Abstract Form

Title: Targeting the NPY/NPY1R signaling axis in mutant p53–dependent pancreatic cancer impairs metastasis

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Pancreatic ductal adenocarcinoma (PDAC) is a particularly lethal malignancy with most patients presenting with advanced-stage disease. The Neuropeptide Y (NPY) signalling axis, best known for its role in controlling appetite and energy homeostasis^{1,2}, has also been shown to advance tumorigenesis in a range of cancers^{3,4}, but its role in PDAC is under-explored.

Here, we show that expression of NPY and its receptor NPY1R are upregulated in mouse PDAC models and human PDAC patients. Pancreas-specific and whole-body knockout of *Npy1r* in the genetically engineered KPC mouse model (*Pdx1-Cre; LSL-Kras^{G12D/+}; LSL-Trp53^{R172H/+}*) significantly decreases PDAC liver metastasis. We also observed an increase in adipose and muscle tissue mass in *Npy1r* knockout settings, providing an additional benefit on top of reducing metastasis in PDAC, since PDAC progression is often associated with tissue wasting⁵. Transcriptomic and proteomic assessment identifies ~500 differentially expressed genes in KPC *Npy1r* knockout tumours, which we are currently investigating further. Importantly, pharmacological inhibition via the NPY1R antagonist BIBO3304 recapitulated the results of our genetic studies, with BIBO3304 significantly decreasing liver metastasis. Immunohistochemical analysis revealed a reduction in cell proliferation, suggesting that NPY1R inhibition reduces metastasis by decreasing metastatic growth.

Our results suggest a requirement for NPY1R in PDAC metastasis. Targeting NPY/NPY1R signalling (including *via* a novel monoclonal NPY-blocking antibody) may represent a highly effective anti-metastatic strategy for future assessment in conjunction with standard-of-care approaches to improve outcomes for PDAC patients.

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