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Novel compounds for the inhibition of S100P binding with RAGE as a potential therapy for pancreatic cancer

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INTRODUCTION: Recent studies have shown a high prevalence of S100 calcium-binding protein P (S100P) in pancreatic ductal adenocarcinoma (PDAC). S100P activates key cell signalling pathways including mitogen-activated protein (MAP) kinase and nuclear factor-B (NFκB) pathways through its extracellular interaction with the receptor for advanced glycation end products (RAGE) [1-2]. Interaction between the metastasis-promoting protein S100P and RAGE has been shown to mediate pancreatic tumour proliferation, survival, invasion and metastasis progression [2]. This project aims to identify novel hit compounds that attach to and prevent S100P from binding to and activating RAGE to prevent cell proliferation and migration in human pancreatic cells.

METHODS: Hit compounds predicted to bind S100P and inhibit its tumour-promoting effects were designed based on computational modelling of a small-molecule binding site in S100P in a virtual screen. An enzyme linked immunosorbent assay (ELISA), to detect S100P-RAGE binding, was developed based on a published protocol [2]**;** 18 of all 93 hit compounds (purchased or synthesised in-house) which were screened for inhibition of S100P-RAGE interaction using this assay significantly inhibited S100P/RAGE interaction.

The identified hit compounds were further investigated for their effects on a human pancreatic cancer cell model consisting of S100P-overexpressing cells (BxPC-3) and/or cells expressing reduced amounts of S100P (Panc-1) using the MTS assay (CellTiter AQ, Promega, for metabolic activity), LDH release assay (CytoTox, Promega, for cell toxicity), and the Transwell cell invasion assay.

RESULTS: BxPC-3 cells treated with hit compounds [3] for 48 hours, at 10µM, demonstrated a significant reduction (p<0.0001) in cell invasion; whereas no effect was observed for the Panc-1 cells suggesting a S100P-specific mechanism (Figure 1). MTS and LDH release assays revealed that the compounds did not exhibit general cytotoxicity over an extended period of time.

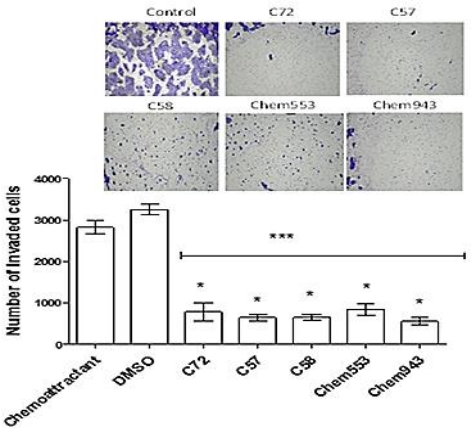

*Fig. 1: Transwell invasion assay of novel hit compounds. A) Invasion of BxPC-3 treated with lead compounds B) Data are mean ± SEM of two independent experiments. Statistical significance was assessed by one-way ANOVA and Dunnet's posthoc test *p<0.0001 vs chemoattractant.*

DISCUSSION & CONCLUSIONS: Results from this project confirm that blocking the interaction between S100P and RAGE can suppress the migration, and invasion of carcinoma of the BxPC-3 cell line which may provide a novel approach for treatment of pancreatic cancer. Further studies aim to investigate the effects of these lead compounds in angiogenesis and their effects on the expression of key cell signalling proteins in the development and progress of pancreatic cancer.

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