

IDENTIFYING COMPOUNDS THAT INHIBIT S100P - RAGE BINDING AS A NOVEL THERAPY FOR PANCREATIC CANCER

D. Ogbeni, R. Camara D.Y.S. Chau, , P. Patel, S. B. Kirton, L. S. Mackenzie, S. Rossiter
Department of Pharmacy, Pharmacology and Postgraduate Medicine,
School of Life and Medical Sciences, University of Hertfordshire, Hatfield, UK, AL10 9AB.

Pancreatic ductal adenocarcinoma (PDAC), with a 5-year survival of less than 5%, remains a major challenge in oncology. High levels of the calcium-binding protein S100P are found in PDAC; S100P enhances cell survival, proliferation and invasion through interactions with intracellular targets and *via* extracellular interaction with the receptor for advanced glycation end products (RAGE). Previous *in vivo* studies have shown that inhibition or silencing of S100P reduces tumour growth and metastasis, and enhances response to gemcitabine therapy. As such, S100P has emerged as a promising biological target for novel anticancer drug design.

Computational modelling of a small-molecule binding site in S100P was used in a virtual screen to identify hit compounds, predicted to bind S100P and inhibit its tumour-promoting effects. This study aims to develop a screening technique to rapidly identify S100P-inhibiting compounds, to aid development of a novel therapy for PDAC. An enzyme linked immunosorbent assay (ELISA), to detect S100P-RAGE binding, was developed based on a published protocol; hit compounds (purchased or synthesised in-house) were then screened for inhibition of S100P-RAGE interaction. Ninety-three compounds, at concentrations ranging from 1nM-1 μ M, were screened in triplicate (n=9). 18 compounds with statistically significant S100P/RAGE inhibition were selected from this assay and tested for their effects on cells using MTS (metabolic activity) and LDH release (cell toxicity) assays. Transwell migration and invasion assays were performed on two human pancreatic cancer cell lines; S100P-overexpressing cells (BxPC-3) and cells not expressing S100P (Panc-1), to assess the effects of treatment with hit compounds.

MTS and LDH release assays revealed that the compounds did not exhibit general cytotoxicity. For 13 of 18 compounds, BxPC-3 cells treated for 48 hours at (10 μ M); demonstrated a significant reduction in cell invasion but there was no effect on Panc-1 cells; evidence of an S100P-specific mechanism.

In conclusion, results from this study confirm that the measurement of S100P-RAGE binding by ELISA can be used as a screen to identify compounds that have functional effects in S100P-expressing pancreatic cancer cells and enable further development of a potential therapy for pancreatic cancer.