

Defining and Evaluating Lithium as a Modulator of the Tumour Immune Microenvironment in difficult to treat tumours.

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Pancreatic cancer is projected to become the 2nd most deadly cancer by 2030 (1). A barrier to improving survival is the complex tumour microenvironment (TME), which promotes therapeutic resistance and limits the efficacy of standard-of-care (SOC) therapy (2,3). Metal ion dysregulation is increasingly recognised in shaping the TME through both extracellular and intracellular mechanisms (4). Lithium has been shown to enhance the efficacy of SOC chemotherapy in a limited number of solid cancers, although its effects on the TME remain poorly characterised (5).

Lithium salts are the standard-of-care for those suffering from bipolar disorder and importantly, lithium is an accessible, cost-effective drug (6). Recent findings indicate that lithium may sensitise cancer cells to SOC through inhibition of glycogen synthase kinase-3 beta (7) and inositol monophosphatase (8). Additionally, there is emerging evidence that lithium plays a role in metallo-immunotherapy (5, 9). However, no study to date has taken a whole-tumour approach to examine how lithium reshapes the TME and, in turn, alters the homeostasis of other metal ions.

This project aims to use 2D and 3D models, metabolism studies, in vivo studies and mass spectrometry imaging to clarify the effect of lithium on the immune TME and define the mechanisms of lithium within solid cancers.

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