RPWoCaR Summary Report

Project title: Underpinning Metabolic Pathways Involved in Ovarian Cancer Drug Resistance

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Project summary:
This project aims to understand the mechanisms behind the development of drug resistance in ovarian cancer treatment, focusing on targeted therapies, mainly Poly(ADP-ribose) polymerase inhibitors (PARPi). Resistance to PARPi undermines treatment effectiveness and thus life expectancy for ovarian cancer patients. Metabolomics is an emerging omics technology that identifies and quantifies small molecules in biological systems. The project seeks to identify and understand the metabolic adaptations cancer cells undergo to develop resistance to PARPi. By utilising novel mass spectrometry methods, the research will conduct real-time analysis of cellular metabolism, particularly cellular responses to drug-induced oxidative stress. The study will compare metabolic differences between drug-sensitive and resistant clones of ovarian cancer cell lines, focusing on antioxidant pathways like glutathione metabolism, and will validate the findings on a cohort of approximately 100 ovarian cancer tissues.

Progress:
So far, we have made good progress in our in-vitro investigation. Specifically:

- We successfully developed a PARPi-resistant clone of the ovarian cancer cell line A2780 after a 3-month exposure to increasing concentrations of the drug.
- We performed metabolomic profiling using a novel high-throughput live-cell analytical platform and liquid chromatography-mass spectrometry (LC-MS). The results supported our initial hypothesis that cancer cells trigger antioxidant mechanisms to counteract drug-induced oxidative stress. We found that metabolites belonging to the glutathione metabolism pathway, one of the most important antioxidant mechanisms, significantly decreased in the resistant clones, especially in the presence of the drug, indicating that they have been consumed to neutralise the reactive oxygen species produced by the drug.
- We also performed biological assays to confirm this theory. Specifically, a reactive oxygen species assay from Abcam confirmed that reactive oxygen species are decreased in the resistant clones compared to sensitive/control cells.

Prospective experiments:

As outlined in the research proposal, we will also develop a resistant clone of the OVCAR3 high-grade serous ovarian adenocarcinoma cell line and perform metabolomic analysis to confirm the results observed in the A2780 ovarian cancer cell line.

Additionally, we will perform spatial metabolomics on ovarian cancer tissue sections (already obtained from the Imperial College Human Tissue Bank) to visualise the distribution of the metabolites of interest in the tissues and understand the role of the tumour microenvironment in the development of drug resistance.