Targeting tumour metabolism to overcome chemo and immunotherapy resistance in ovarian cancer

Project Description

Project duration:	The advertised project is suitable for Honours/master's students as well as for PhD students. The project can be designed according to the HDR degree.
Description:	**Background**

Background

High-grade serous ovarian cancer (HGSOC) accounts for 70% of all ovarian cancers and are highly aggressive and the second most lethal gynaecological malignancy worldwide. Resistance to standard-of-care platinum-based chemotherapy remains a major obstacle in clinical management of HGSOCs. Although initial response to chemotherapy is high (~80%), patients generally relapse within 18 months and eventually succumb to platinum-resistant disease. Hence, there is unmet need to develop an effective treatment for recurrent HGSOC patients, who otherwise have limited treatment options.

Metabolic alterations are linked to resistance to chemotherapies and targeted therapies in different cancers. Multiple and different traits, involving adaptations in both glucose and glutamine metabolism, and mitochondrial activity have been associated with platinum resistance in ovarian cancer cells. We have compelling data that broader inhibition of glutamine metabolism using a glutamine analogue 6-diazo-5-oxo-L-norleucine (DON) can sensitise chemo-resistant HGSOC to carboplatin. Hence, a more comprehensive inhibition of glutamine metabolism may represent an attractive strategy to overcome the rapid metabolic adaptation that leads to chemoresistance in HGSOC patients.

Over the past decade, immune checkpoint blockade (ICB) therapy has significantly improved long-term remission in patients with advanced skin, lung, and colorectal cancers. However, testing of immunotherapies in HGSOC has been disappointing, with modest 5%–15% response rates. Immune microenvironment of HGSOC is immunosuppressive due to presence of exceptionally high aneuploidy driven by copy number changes which can limit immunotherapy efficacy. Spatial transcriptomic profiling of infiltrated T and NK cells in HGSOC has revealed the presence of exhaustion markers, suggesting that tumour infiltrating effector T and NK cells are predominantly exhausted and lack cytotoxic functions. Moreover, HGSOC tumours are heavily infiltrated by immunosuppressive myeloid-derived suppressor cells (MDSCs), which may contribute to their poor response to immunotherapies. In triple-negative breast cancer (TNBC) cells, which are very similar to HGSOCs at the molecular levels, inhibition of the glutamine metabolism has improved cytotoxic function of infiltrating CD8+ T-cells, reduced the tumour infiltration of MDSCs and sensitized the tumours to ICB therapy. Hence, targeting glutamine metabolism may represent an effective therapeutic strategy to sensitize HGSOC tumours to ICB therapy.

Hypothesis

We hypothesize that broader inhibition of glutamine metabolism using a pro-drug version of glutamine analogue DON designated as DRP-104, may re-sensitize chemo-resistant HGSOC tumours to platinum-based chemotherapy by preventing the rapid metabolic rewiring that leads to drug resistance. Additionally, we hypothesize that glutamine inhibition using DRP-104 may alleviate immunosuppressive tumour microenvironment of HGSOCs by reducing MDSC tumour infiltration, activating effector T and NK cells, and may sensitize HGSOCs to ICB therapy.

Aims

1. Examine the effect of glutamine inhibition in re-sensitizing chemo-resistant HGSOC tumours to platinum-based chemotherapy.
2. Deciphering the effect of glutamine inhibition on tumour immune microenvironment in HGSOC in vivo models.
3. Evaluating the effect of DRP-104 in combination with ICB therapy in vivo.

Expected outcomes and deliverables:	PhD or Honours students will acquire hands-on experience of multiple cell and molecular biology techniques and multi-omics techniques. Applicants acquire expertise in developing in vivo mouse models including patient-derived tumour xenografts and syngeneic mouse models to study the anti-cancer activity of drugs, effect of drugs on tumour immune-microenvironment, and underlying molecular mechanism for their efficacy. In addition, student will acquire excellent presentation, communication, and scientific writing skills. Students will get an excellent opportunity to be a part of a multi-disciplinary team and work closely with preclinical and translational scientists and medical oncologists at Mater.
	During the project, students will be expected to acquire a thorough background knowledge on the subject area, acquire training on multiple sophisticated scientific techniques, and develop skills in generating hypothesis, planning and executing experiments, analysing and interpreting the results, presenting their findings in lab meetings and conferences, and write scientific research articles.
Suitable for:	This project is suitable for Honours and PhD students. The successful candidate should have prior experience of working in a research lab and have honours degree completed. Candidate should be motivated and enthusiastic to establish a career in oncology research.
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Further info:	If interested in joining our vibrant and world-class cancer laboratory at the excellent research facility, please submit your detailed CV and a short cover letter with the contact details of two academic referees to Dr Prahlad Raninga.
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