Advancing Targeted Therapies for Metastatic Breast and Gynaecologic Cancers using RNA-based Therapeutics with Lipid Nanoparticle (LNP) Delivery System

Project Description

Project duration:	Our lab is funded by the national breast cancer foundation (NCBF) and the department of defence of the United States of America (DoD). This funded project is suitable for Honours/Master and PhD as well as clinical students' project that can be scoped as smaller or larger projects depending on the HDR degree/ interest of the student.
Description:	**BACKGROUND** Cancer ranks as the second leading cause of death globally and Breast cancer (BC) stands as the most prevalent malignancy among women. Despite advancements in early diagnosis and personalised treatment approaches for cancer, recurrence and metastasis remain the leading causes of cancer-related mortality (~90%). Conventional chemotherapy yields limited efficacy for metastatic disease and recurrent metastatic breast cancer as well as gynecologic cancers, such as ovarian and endometrial cancer, where the 5-year survival rate remains below 20%. Our research has demonstrated that genetic inhibition of Cep55 reduces cancer progression and metastatic potential in mouse models. However, Cep55 is considered undruggable due to its coiled-coil structure. Therefore, we propose an innovative approach using antisense oligonucleotides (ASOs) to inhibit Cep55 expression at the mRNA level. This strategy aims to provide proof-of-concept for targeting undruggable and hard-to-treat cancers, particularly invasive, aggressive, and advanced cancers, as well as metastasis, through preclinical studies both in vitro and in vivo. **AIMS** 1) Screening ASOs and performing functional assays across a spectrum of human and mouse metastatic breast, ovarian and endometrial cancer cell lines, tumouroids, patient-derived xenograft organoids (PDXOs), and patient-derived organoids (PDOs). 2) Evaluating preclinically whether ASO-Lipid nanoparticles (LNP) impedes cancer growth, progression, and spread and examining the efficacy, stability, specificity, and toxicity in-vivo. 3) Investigating the mechanism of action and functional role of drug in tumour-microenvironment and metastasis by spatial transcriptomics.

Expected outcomes and deliverables:	**OUR MISSION**: We are committed to developing innovative molecular medicines and therapeutics for hard-to-treat cancers and metastasis. Our multidisciplinary team of scientists covers all aspects of drug development, ranging from target identification and validation to payload design, formulation, delivery, and drug testing using state-of-the-art translational research experimental models. **RESEARCH FOCUS**: The Tumour Biology and Therapeutics Lab is dedicated to developing next-generation RNA therapeutics for oncology, focusing on cancer types with extremely poor outcomes, such as triple-negative breast cancer, metastatic ovarian cancer, and endometrial cancer. Currently, our efforts involve designing and developing antisense oligonucleotides (ASOs) coupled with a lipid nanoparticle drug delivery system to target genes of interest with high specificity, aiming to inhibit cancer growth and metastasis. We aim to validate the efficacy of our novel medicines in innovative translational model systems, including patient-derived cells, tumoroids, and organoids, which can serve as personalized patient embodiments. **SIGNIFICANCE** To overcome the challenge of undruggable cancer targets, we will use ASOs which target mRNAs and this strategy can be expanded to other undruggable targets in cancer. We utilised the next-generation ASOs design which enhances the potency, stability, binding properties, reduced toxicity, pro-inflammatory and off-target effects, improved therapeutic index, and extended duration of effect. In our human cells and mouse models, we will test the efficacy of LNP-based drug delivery which shall protect ASOs from degradation and permit cellular uptake and drug release. We expect this project will generate proof-of-concept data on the effectiveness of the ASO-LNP system and provide an on-target mechanistic validation in preclinical models of breast cancer. We anticipate this strategy pave the way for a resolution to treat patients with aggressive cancers and overcome the metastatic burden.
Suitable for:	Suitable for Honours, PhD and clinical students who are interested in wet/dry lab. Competitive applicants for cutting-edge biomedical projects and training for state-of-the-art technologies in a world class laboratory and translational research facilities. This project will apply a wide range of techniques in medical research, cell and molecular biology, tumour immunology, immunotherapy, drug delivery, spatial transcriptomics (wet and dry lab), nanomedicine, drug development to target the cancer cells, and mouse works. The student will become familiar with these techniques and possibly be involved in the publication(s) depending on the achieved results.
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	In order to apply, in addition to meet the university essential requirements, the candidates should send their CV and a short cover letter outlining why they are applying for this PhD. Candidates may apply for more than one of the PhD's opportunities but should make this known in their cover letter. Candidates should also provide the contact details for 2 referees one of whom should be their most recent employer or academic supervisor. Enquiries: Behnam.rashidieh@mater.uq.edu.au