Background

Breast cancer is the leading cause of female cancer deaths worldwide and with an estimated 2.3 million new cases every year. There are significant unmet needs across the subtypes of breast cancer including estrogen receptor positive (ER+) breast cancer and triple-negative breast cancer (TNBC). In ER+ breast cancer that accounts for 70% of breast cancer patients, de-novo and acquired endocrine resistance are observed in approximately 1/3 of cases, with these patients representing up to 1/4 of all breast cancer patients. Whilst triple-negative breast cancer (TNBC, 10-20% of breast cancer patients) is the most lethal form of breast cancer, not responding to both endocrine and anti-HER2 therapies.

Technology Brief

The histone methyltransferase enzyme G9a is over expressed in many malignancies, including breast cancer and regulates expression of genes involved in tumour progression.

QIMR Berghofer researchers, in partnership with drug discovery CRO Domainex, have developed a small molecule inhibitor of G9a (DMX8.1) which shows promising in vitro and in vivo efficacy against ER+ breast cancer and TNBC.

As a monotherapy, DMX8.1 greatly reduced cell viability in a range of breast cancer cell lines while having no effect on normal breast epithelial cells. In human tumour ER+ breast cancer and TNBC xenograft models, DMX8.1 demonstrated a marked reduction in cell viability in vitro and tumour growth in vivo. Additionally, we demonstrate that tumours derived from tamoxifen resistant cell lines are resensitized to tamoxifen when combined with a G9a inhibitor, with the combination inducing tumour regression. Synergistic efficacy is also demonstrated when a G9a inhibitor is used in combination with chemotherapeutics such as doxorubicin. Mechanistically, DMX8.1 has been shown to specifically enhance expression of genes repressed by MYC in cancer setting.

The molecular and physical properties of DMX8.1 are favourable for an orally-administered drug, and the binding affinity is in the single digit nanomolar range. DMX8.1 displays good in vitro metabolic stability, further exemplified by good murine pharmacokinetic data.

Further, we have developed a novel signature that could be used to select breast cancer patients who would benefit most from G9a inhibitor monotherapy treatment, and identified biomarkers for potential use as a target engagement early readout marker.

We have applied the assay to cohorts of a number of cancer types, specifically, NSCLC, Glioblastoma multiforme, Colorectal Cancer, Breast Cancer, Prostate Cancer, Melanoma, Ovarian Cancer, Gastric Cancer and Oesophageal Cancer. Other cancers, eg Pancreatic Cancer, will be examined by the assay when suitable cohorts are compiled.

Using a combination of the signature proteins, we were able to generate an excellent separation of healthy individuals and cancer patients, with an area under the curve (AUC) of 0.96.
Market

The total global breast cancer market was valued at over US$16 billion in 2018, and is poised to reach US$30.6 billion by 2025. Growing at a compound annual growth rate (CAGR) of 9.5%, the market is being driven by the approval of novel targeted therapies including the cyclin-dependent kinase inhibitors. From a competitive landscape perspective, there are currently no other G9a small molecules inhibitors under clinical development.

Partnering Goals

QIMR Berghofer and Domainex are seeking a collaborative development partner for this opportunity. The preferred partnering model would be a research collaboration with an option to license whereby QIMR Berghofer would undertake the biology and Domainex would undertake the chemistry for the development of a clinical candidate. The development partner would develop a IND package and undertake further clinical development.

Intellectual property

QIMR Berghofer holds patent applications on a patient selection signature and predictive biomarker for immuno-oncology response. The composition of matter filing has been delayed to maximise patent life.

Lead Researcher

Associate Professor Jason Lee is Head of the Epigenetics and Disease Laboratory at QIMR Berghofer, and adjunct Associate Professor at University of Queensland and Queensland University of Technology. A/Professor Lee is a recognised expert within the field of cancer epigenetics and transcriptional regulation, is an inventor on 3 patents and has published in top tier international journals including Nature Genetics and Nature Immunology.

Importantly, at a fixed specificity of 95%, the median sensitivity of the diagnostic exosome signature in the 8 cancer types was 77.6% (at 95% CI). We were able to evaluate the sensitivity of the exosome biomarker in stage I compared to stage II-IV in NSCLC, esophageal, and gastric cancer. Importantly, with the sensitivity at 95%, specificity was comparable to later stages in all 3 cancers, demonstrating that the diagnostic exosome signature is capable of identifying early-stage cancer patients, possibly prior to the spread of metastases.

With more than 900 scientists, students and support staff, QIMR Berghofer is one of Australia’s largest and most successful independent medical research institutes. The QIMR Berghofer Business Development Team manages over 160 patent families, offering a wealth of collaborative and commercial opportunities for industry and government. We have a strong track record of partnering with leading pharmaceutical and biotech companies to further develop early-stage technologies, generating over $21 million in annual commercial revenue in the last financial year. In addition to licensing and partnering outcomes, we facilitate contract research and consulting projects for industry clients. Our team includes specialists in commercialisation, IP protection, patent law, clinical trial and project management and industry-backed grant opportunities.