Predicting Responsiveness to Immunotherapy

Opportunity

Cancer abrogates and disables normal immune function. Recent breakthroughs and encouraging clinical results with various immune checkpoint inhibitors have demonstrated tremendous potential to control cancer by immune activation, this is achieved by employing antibodies that block specific checkpoint proteins (such as PD1, PDL1 and CTLA4) preventing them from binding to their opposite receptor and blocking immune function.

However, resistance to immunotherapy is a major problem. Recurrence of cancer and failure of immune checkpoint inhibitor drugs to induce an effective and sustained immune response are a major problem, with only ~40-50% of melanoma patients having durable effectiveness from immunotherapy (PD1 or PDL1), however if the patient develops new metastatic lesions patient survival and response drops significantly to 6%.

Technology Summary

- We have discovered a novel molecular switch in PDL1 called nPDL1-PTM1 based on extensive cell line, mouse work and clinical patient samples.
- nPDL1-PTM1 controls a mechanism of resistance for immunotherapy and chemotherapy.
- Identifying nPDL1-PTM1 positive and negative patients is a novel diagnostic approach that enables the stratification of patients into responders and resistant to immunotherapy using liquid biopsies.
- We have developed a panel of antibodies against the nPDL1-PTM1 region and confirmed this region is not targeted by currently available commercial PDL1 antibodies.
- In parallel we are developing companion therapeutics to treat resistant patients positive for nPDL1-PTM1.

Patients received first line treatment of monotherapy Nivolumab, Pembrolizumab or Ipilimumab, followed by a second cycle of monotherapy consisting of Nivolumab or Pembrolizumab. Patients failing to respond to monotherapy were placed on dual immunotherapy consisting Nivolumab and Ipilimumab.

This technology has the potential to revolutionize immunotherapy by offering companion therapeutics and diagnostics for patient stratification and personalized medicine. Importantly our technology would increase the utility of immunotherapy in resistant cancers, cancers where immunotherapy is not available, increasing the survival of patients and the efficacy of treatment.
Market

Indications with the highest unmet need include triple negative breast cancer (TNBC), prostate cancer, lung cancer and metastatic renal cell carcinoma.

The performance of immunotherapy in treating TNBC has been subpar with a response rate for mono-immunotherapy of 10 to 18.5% of all TNBC patients (Nanda et al., 2016; Emens et al., 2019). In the context of prostate cancer the situation is more severe. Standard therapy for prostate cancer (medical castration) is ineffective for metastatic prostate cancer which is virtually incurable and while there has been some response to immunotherapy (5% response rate; Sehrawat et al., 2017; Antonarakis et al., 2019) it has been disappointing.

Intellectual property

This technology is the subject of Australian provisional and PCT patent applications.

Partnering Goals

We are seeking a development partner to take this opportunity through clinical development.

Lead Researcher

Professor Sudha Rao is internationally known for her expertise in transcriptional biology and genomic technologies that spans both pharmaceutical and academic settings. The primary focus of her research has been to unravel complex epigenetic-signatures in the immune system, and to understand the deregulatory mechanisms operating in cancer settings. She also helped to establish the clinical genomics platform for therapeutics in the UK, the first world-wide.

Professor Rao has one start up (EpiAxis Therapeutics) sponsoring a clinical trial in metastatic breast cancer that grew out of her work into the epigenetic regulation of cancer stem cells. She has developed partnerships with global technology companies and established novel liquid biopsy clinical platforms, first of its kind in Asia, for non-invasive tracking of blood samples from cancer patients. She also has attracted highly competitive NHMRC, ARC and commercial funding to advance her cancer work. Her work has yielded national and international patents for both novel diagnostics and therapeutics in the emerging arena of immune-oncology. She is currently applying her cutting-edge epigenetic technologies to understanding the role of epigenetic regulation in viral biology and viral based T cell immunity in the context of COVID-19.

QIMR Berghofer Medical Research Institute

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