Summary Report, June 2024: Dr Sally George
2020 Fergus Scholefield Cancer Research Grant from Penguins Against Cancer

Dr Sally George leads the Developmental Oncology Group and holds a Career Development Faculty position at the Institute of Cancer Research. She is also an Honorary Consultant Paediatric Oncologist at The Royal Marsden Hospital NHS Foundation trust.

Funding from Penguins Against Cancer was used towards lab-based testing of additional PARP inhibitor combination therapies following on from our initial publication (SL George et al, BioMedicine 2020). This has generated preliminary data towards follow on projects in our lab, including a PhD studentship in ATRX mutant neuroblastoma, focusing in more depth on differences in protein binding on DNA following induction of DNA damage - to identify novel treatment strategies for this difficult to treat group of patients.

The following abstract is from the research paper:

Therapeutic vulnerabilities in the DNA damage response for the treatment of ATRX mutant neuroblastoma

Background: In neuroblastoma, genetic alterations in ATRX, define a distinct poor outcome patient subgroup. Despite the need for new therapies, there is a lack of available models and a dearth of pre-clinical research.

Methods: To evaluate the impact of ATRX loss of function (LoF) in neuroblastoma, we utilized CRISPR-Cas9 gene editing to generate neuroblastoma cell lines isogenic for ATRX. We used these and other models to identify therapeutically exploitable synthetic lethal vulnerabilities associated with ATRX LoF.

Findings: In isogenic cell lines, we found that ATRX inactivation results in increased DNA damage, homologous recombination repair (HRR) defects and impaired replication fork processivity. In keeping with this, high throughput compound screening showed selective sensitivity in ATRX mutant cells to multiple PARP inhibitors and the ATM inhibitor KU60019. ATRX mutant cells also showed selective sensitivity to the DNA damaging agents, sapacitabine and irinotecan. HRR deficiency was also seen in the ATRX deleted CHLA-90 cell line, and significant sensitivity demonstrated to olaparib/irinotecan combination therapy in all ATRX LoF models. In-vivo sensitivity to olaparib/irinotecan was seen in ATRX mutant but not wild-type xenografts. Finally, sustained responses to olaparib/irinotecan therapy were seen in an ATRX deleted neuroblastoma patient derived xenograft.

Interpretation: ATRX LoF results in specific DNA damage repair defects that can be therapeutically exploited. In ATRX LoF models, preclinical sensitivity is demonstrated to olaparib and irinotecan, a combination that can be rapidly translated into the clinic.