

Project title: Exploration of the combination of oncolytic virus and PARP inhibition in triple-negative breast cancer and the effect on the immune microenvironment.

Project Summary: Approximately 50% of women with a germline BRCA1/2 mutation will develop breast cancer in their lifetime, with a median overall survival of less than 2 years for those with metastatic disease. PARP inhibitors (PARPi) are the first effective targeted agent for these patients, exploiting existing weaknesses in DNA repair pathways. Unfortunately, resistance inevitably develops, on average after approximately 7 months.

Synergistic effects between PARPi and immunotherapy have been documented pre-clinically and in early clinical studies. This is thought to occur through accumulation of damaged DNA in the cytosol which drives inflammatory signalling and PD-L1 expression, both positive predictive markers of immunotherapy response. BRCA1/2 and PARPi-driven genomic instability can also be associated with high tumour mutational burden and neoantigen expression, which are also associated with anti-tumour immune responses.

The RP1 virus is a next-generation Herpes Simplex Virus (HSV) platform modified with insertions of GALV-GP-R and GM-CSF designed to cause immunogenic cell death as well as release of neoantigens and promotion of immune cell recruitment. Its effectiveness as an oncolytic agent has been validated in pre-clinical studies and it is currently in phase II clinical trial. The combination of RP1 and PARPi has shown synergy in causing cell death in multiple tumour cell lines, hypothesised to be secondary to the increased neoantigen expression.

This project would build upon this hypothesis, testing the combination of intratumoral RP1 virus in combination with different PARPi in mouse models of triple-negative breast cancer. Immunoprofiling will be undertaken using FACS, RNA bulk, single-cell and T-cell receptor repertoire sequencing to explore the changes in the tumour immune environment and factors which may contribute to tumour suppression.

The project will aim to develop this proof-of-concept into an early phase trial protocol by the end of the fellowship.

Supervisory Team: Prof Kevin Harrington, Prof Alan Melcher

Clinical Specialities: Medical Oncology