CANCER RESEARCH UK CLINICAL ACADEMIC TRAINING PROGRAMME

ICR The Institute of Cancer Research | Imperial College London

TUTT Andrew EOI 2022 – ICR

Project title: Predicting and targeting neoantigens associated with BRCA1/2 reversion mutations in PARP inhibitor and platinum-resistant breast cancer

Project Summary:

Despite the clinical benefit of platinum-based chemotherapies and PARP inhibitors (PARPi) within the subset of breast, ovarian and prostate cancer patients harboring BRCA1/2 mutations, over time virtually all patients develop resistance to these agents. In many of these cases, resistance is caused by reversion mutations restoring the native protein function. Previous work in our lab revealed almost all reversion mutations (Pettitt et al. Cancer Discovery. 2020) are predicted to encode for immunogenic neopeptides, unveiling a novel route to immunologically target PARPi or platinum resistance.

The Tutt and Lord labs, in collaboration with Yin Wu and Adrian Hayday at Kings College London and Susan Domchek at University of Pittsburg, are developing an in silico computational platform and functional validation experiments to analyze patient-specific MHC presentation of these out-of-frame protein sequences and predict patient-tailored immunogenic neopeptide sequences. The proposed reverse-translational project constitutes a multidisciplinary cancer biology and immunology effort teaming with clinicians to identify BRCAmut breast cancer patients pre- and post-platinum or PARPi, as well as anti-PD1/PD-L1 treatments.

The Clinical Academic Trainee will enable and analyse serial biopsies and blood samples to be collected for tissue exome DNAseq and cfDNA testing to detect and characterise the emergence of reversion mutations and PBMCs for subsequential immune profiling to assess neopeptide presentation and T cell priming, with special focus in assessing potential contribution of anti-PD1/PD-L1 agents and predictable neoantigen vaccination in T cell responses to reverted BRCAmut tumors. By identifying the presence of memory T cells capable of recognising these pre-identified reversion peptides followed by TCR sequencing, we aim to develop novel adaptative strategies such as TCR mimicking antibodies or CAR-T therapies as well as to develop a framework for the design of personalised vaccines targeted against HLA-matched patient-specific reversion mutations. We envision these tumour neoantigens might provide a novel therapeutic approach to overcome resistance and restore drug sensitivity, an unmet need in this clinical setting that could directly translate into industry collaborations.

Supervisory Team:

- Prof Andrew Tutt**,** Breast Cancer Research Division, Institute of Cancer Research
- Dr Steve Pettitt**,** Institute of Cancer Research
- Prof Chris Lord, Institute of Cancer Research