**Project title:** Enhancing the precision of lung cancer immunotherapy: development of new AI driven biomarkers of resistance utilising samples from the phase III REFINE-Lung study

**Project Summary:** T lymphocytes are capable of recognising and eliminating cancer cells, but they are limited by the action of inhibitory receptors (checkpoints) such as PD-1. PD-1 immune checkpoint inhibitors (CPIs) have improved outcomes for patients with lung cancer, but only 30% of patients with lung cancer obtain a durable benefit. Better biomarkers are urgently needed because: 1. Only ~30% of patients with lung cancer obtain a durable benefit, 2. These drugs have potentially life-changing toxicities. and 3. CPIs are expensive, and their usage is consequently rationed in the UK and around the world. Better biomarkers of CPI response would enable improved selection of patients for appropriate therapy, improve treatment outcomes, and reduce unnecessary toxicities and costs. Thus, biomarker development in this area closely aligns with the aims of the Convergence Science Centre. We have recently developed a novel convergence science approach to immunotherapy biomarker development, based on the notion that immune cell activation state is reflected by cell morphology changes that can be identified using routinely collected data.

Using samples from patients with NSCLC treated at Imperial Hospitals and enrolled to the currently recruiting multicentre UK phase III REFINE-Lung Translational Substudy (Ghorani et al., Lancet Oncology 2023), we propose to investigate two novel biomarkers of immunotherapy response. We will apply artificial intelligence (AI) approaches to develop computational models that can use immune cell morphology data from blood and tissue to predict CPI response and resistance.

The Fellow will develop and test the performance of two approaches to develop predictive biomarkers for response/resistance to CPI therapy in patients with lung cancer:

*1. An AI- driven circulating immune cell morphology-based predictor of immunotherapy response

Circulating T cells respond to immunotherapy by undergoing activation and proliferation. This can be measured by fluorescence flow cytometry (Kamphorst et al., PNAS 2017), but is too laborious to be clinically applicable. Our pilot of 75 patients using cell morphology data computationally extracted from haematology clinical lab analysers suggests significant morphology changes early on treatment can predict outcomes on CPI.

*2. An novel AI approach to identifying T cell activation state using routinely available H&E data to predict immunotherapy outcome

We similarly hypothesised that the activation state of tumour-infiltrating T cells is reflected by their morphology. We have developed a novel AI method trained to identify and enumerate T cell states using scanned H&E images alone, allowing us to evaluate the quality of the immune response without requiring complex and laborious staining procedures. In preliminary work, we have demonstrated the capability of this approach to identify T cell states and predict outcomes amongst patients with early-stage disease.

The supervisory team includes expertise in cancer immunology and biomarker development (Ghorani), large-scale clinical trials in oncology (Seckl), statistical machine learning/AI approaches (Filippi), tissue staining (Lund) and digital pathology (AbdulJabbar), computational immunobiology (Zapata). An-in post bioinformatician in the host lab will contribute to data analysis; a wet-lab based postdoc with expertise in immunology will provide additional support. The Fellow will receive a world class training in; 1. Skills relevant to the conduct of large-scale clinical trials and will join the REFINE-Lung team as a Junior PI, 2. Cancer immunology with a focus on T cell biology, 3. Machine learning and AI applied to biological data, 4. Wet lab skills in flow cytometry and tissue staining.

**Supervisory Team:** Dr Ehsan Ghorani, Prof Michael Seckl, Dr Sarah Filippi, Dr Tom Lund, Dr Khalid AbdulJabbar, Dr Luis Zapata

**Clinical Specialities:** Medical Oncology