**University of Leicester**

|  |  |
| --- | --- |
| **Project Reference** | BRC Studentships |

|  |  |
| --- | --- |
| **First Supervisor** | Dr Gareth Miles |
| **School/Department** | Leicester Cancer Research Centre |
| **Email** | [gjm14@le.ac.uk](mailto:gjm14@le.ac.uk) |

|  |  |
| --- | --- |
| **Second Supervisor** | Prof. Catrin Pritchard |
| **School/Department** | Leicester Cancer Research Centre |
| **Email** | cap8@le.ac.uk |

|  |  |
| --- | --- |
| **Additional Supervisor** | Prof. Jacqui Shaw |

**Section 2 – *Project Information***

|  |  |  |
| --- | --- | --- |
| **Project Title** | ctDNA meets Patient Derived Explants (PDEs): developing ctDNA predictive biomarkers for novel anti-cancer agents derived from PDE meta-data | |
| **Project Highlights:** | 1. | This project sits at the interface of translational and clinical science |
| 2. | Will utilise state-of-the-art preclinical models coupled to high-content data analytics |
| 3. | Significant potential for future patient benefit |
| **Project Summary** | | |
| **Background:** Novel anti-cancer drug attrition is a significant issue, with 95% of drugs reaching Phase-1 trials failing to reach authorisation. A lack of effective pre-clinical models which accurately predict drug responses is a major problem with existing systems, which fail to retain the complex immune microenvironment of human tumours. To overcome this, we have developed Patient Derived Explant (PDEs) models, which retain the autochthonous contexture of human tumours and can generate drug response data which reflects patient outcomes. We have demonstrated the power of using PDEs to identify and evaluate novel predictive biomarkers, supporting the rationale design of novel stratified clinical trials.  We have recruited 60 breast cancer patients to our Breast Cancer Now/Pfizer Catalyst award preclinical study “Preclinical evaluation of drug efficacy using patient-relevant breast explant models: a bench to bedside approach”, and derived PDEs from each. PDE’s have been treated with 3 classes of novel anti-cancer agents, a: 1) small molecule PI3K inhibitor (Gedatolosib), 2) antibody-drug conjugate (PTK7-ADC), and 3) agonistic immunotherapeutic antibody (αOX40). We have drug performance and imaging meta data for predictive and pharmacodynamic biomarkers, and Whole Exome Sequencing (WES) data for each patient.  **Research Plan:** The studentship will finalise this pack of work, by analysing the WES data to: 1) Generate an overview of somatic copy number alterations (SCNAs) and single nucleotide variants (SNVs) for each tumour for genotype-phenotype correlations with PDE drug response data. 2) Use the SCNA and SNV information to build an NGS hotspot ctDNA panel covering the major genetic changes to identify predictive markers in ctDNA to guide stratified clinical trials of the Pfizer drugs. 3) Use SCNA and SNV data to identify novel predictive and pharmacodynamic markers for each Pfizer drug, and develop tissue based multiplexed-immunofluorescent panels. Finally, integrate the PDE drug performance, predictive, pharmacodynamic, WES and ctDNA data, and correlate it with clinicopathological and patient outcome data to allow rationale design of personalised clinical studies, using ctDNA and mIF panels to guide patient stratification.  **Data will be used to:** Generate and validate novel ctDNA and mIF predictive biomarkers derived from PDEs treated with novel Pfizer anticancer agents in clinical development.  **Expected outcomes and impact:** Finalising this package of work will result in:  1) high impact publications  2) opportunities for additional commercial and grant funding  3) rationale design of bespoke stratified clinical trials using the Pfizer drugs under clinical development, which will be delivered through the Leicester Clinical Trials Facility. | | |
| **References** | | |