**University of Leicester**

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| **Project Reference** | BRC Studentships |

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**Section 2 – *Project Information***

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| **Project Title** | ​PRC2-DNMT1 axis as a synthetic lethal target in BAP1 mutant mesothelioma​ |
| **Project Highlights:** | 1. | Evaluation of a novel synthetic lethal strategy to target BAP1  |
| 2. | Use of live tumour explants to explore the efficacy and genomic correlates of response to treatment in a co-clinical trial setting  |
| 3. | Findings may provide evidence to spearhead a phase II trial in patients with mesothelioma  |
| **Project Summary**  |
| **Background**: ​ Mesothelioma is a rare cancer caused by asbestos that has been increasing in incidence over the past four decades, with the UK having the highest global rate. Unfortunately, survival rates are low, and treatment options are limited with low efficacy. Personalized therapy has been lacking, but it is feasible, as demonstrated by Leicester's recently recruited 5-arm MIST umbrella trial. BAP1 is the most frequently inactivated tumor suppressor in mesothelioma, and it is essential for regulating the level of ubiquitinated histone H2A in promoter-bound nucleosomes. BAP1 inactivation occurs early during mesothelioma evolution, is mostly clonal, and upregulates PRC2 catalytic activity to trimethylate histone H3K27 conferring a vulnerability via DNMT1. Therefore, DNMT1 should be synthetic lethal in BAP1 mutant mesothelioma. Preliminary evidence suggests that DNMT1 inhibition is indeed synthetic lethal with BAP1, but this has not been explored in mesothelioma, and the mechanisms likely to confer an exceptional response or resistance are unknown.**Aim**:  This study aims to determine whether the PRC2-DNMT1 axis is a therapeutic vulnerability in BAP1 inactivated mesothelioma. **Research Plan**:  The research plan includes exploring DNMT1 inhibition in BAP1 CSPR-CAS9 mediated knockout cell lines, BAP1shRNA silenced mesothelioma cell lines, a panel of 30 exome sequenced primary mesothelioma cell lines, and mesothelioma organoids. In parallel, a DNMTi co-clinical trial in exome sequenced mesothelioma explants will be conducted, and pre and post-treatment methylome and transcriptome analysis will be used to explore the pharmacodynamics in sensitive versus resistant tumors. The mechanisms underlying cell fate, such as apoptosis, will be explored using multiplex immunophenotyping. Machine learning will be employed to decipher response-associated drug-gene interactions, and orthogonal validation will be performed across the experimental platforms.**Expected outcomes and impact**: ​The study is expected to confirm a robust actionable synthetic lethal interaction in mesothelioma and will catalyze an industrial collaboration to underpin the execution of a phase II trial. In addition, evidence of synergy between DNMT1i and PARP inhibition will be explored in BAP1 inactivated mesothelioma cell lines. These results will have a significant impact on the development of personalized therapies for mesothelioma and improve patient outcomes. |
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