



CRUK Cambridge Centre MRes rotation project

Rotation Project Title	Development of treatment strategies for ALK-positive neuroblastoma based on drug repurposing and novel drug combinations
Head of Laboratory (PI) Name	Suzanne Turner
Second supervisor if applicable	
Programme	Paediatric
Supervisor's Email	Sdt36@cam.ac.uk
Laboratory Location	Lab Block Level 3, Addenbrookes Hospital

Project Outline	<p>Research in the Turner lab aims to understand the biological mechanisms that promote tumorigenesis in paediatric cancers harbouring alterations in the gene encoding anaplastic lymphoma kinase (ALK).</p> <p>Neuroblastoma is the most common and most deadly solid extracranial malignancy in children. Around 15% of high-risk neuroblastoma patients are ALK-positive, and clinical trials are underway to assess the efficacy of ALK inhibitors in these patients. However, as with all targeted kinase inhibitors, therapeutic resistance is a fundamental concern. A possible strategy to prevent the emergence of therapeutic resistance is to combine ALK inhibitors with other molecularly-targeted compounds.</p>
Experimental plan	<p>We have recently screened a library of 1,430 FDA-approved drugs across a panel of ALK-mutant neuroblastoma cell lines and identified several drug classes with high anti-proliferative activity. Some of these drugs are not currently used in oncology, but may be repurposed for such use given enough preclinical evidence.</p> <p>This project will evaluate the efficacy of several FDA-approved drugs in neuroblastoma cell lines, alone and in combination with ALK inhibitors. Then, combinations of drugs will be applied to cell lines that are resistant to ALK inhibitors to determine whether resistance can be reversed. The data generated from this project may lead to further work in mouse models of neuroblastoma where the anti-tumour activity of novel drug combinations can be assessed <i>in vivo</i>.</p>
Main Techniques	<ul style="list-style-type: none"> • Tissue culture of neuroblastoma cell lines and patient derived tumours • Biological assays to assess cell death, proliferation and colony formation • Shadowing the treatment of patient-derived xenografts
Key References	<p>Introduction to neuroblastoma, covering epidemiology, causes, diagnosis and treatment: Matthay <i>et al.</i>, 2016. Neuroblastoma. <i>Nature Reviews. Disease Primers</i>, 2:16078.</p> <p>Investigational therapies in neuroblastoma: Esposito <i>et al.</i>, 2017. Neuroblastoma treatment in the post-genomic era. <i>J Biomed Sci.</i>, 24:14.</p> <p>ALK in neuroblastoma: Trigg and Turner. 2018. ALK in Neuroblastoma: Biological and Therapeutic Implications. <i>Cancers</i>, 10(4):113.</p>