Development of novel dual-target agents to treat neuroblastoma that combine selective protein degradation with synergistic inhibition.

Supervisors:

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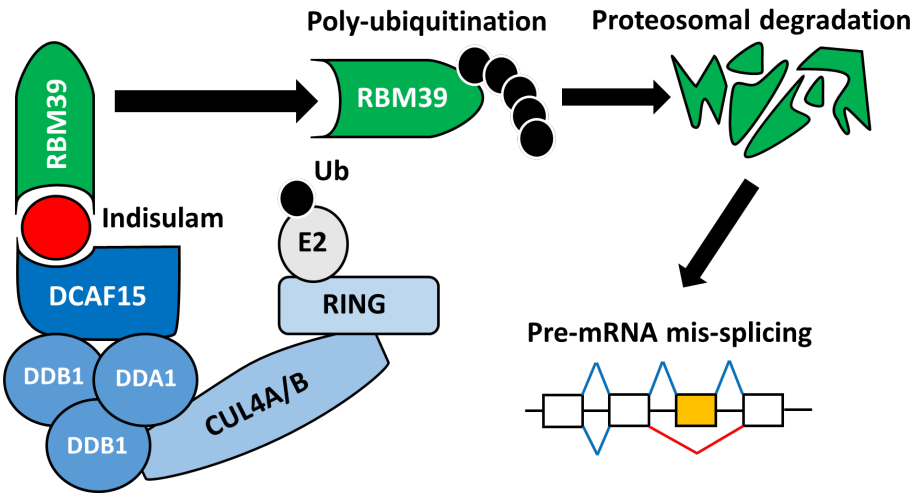
Research Summary

Neuroblastoma is a paediatric extra-cranial cancer and the leading cause of death from cancer in children. High-risk tumours (40% cases) carry oncogenic drivers such as MYCN, ALK and ATRX but current treatment regimens are not personalized or molecularly targeted. Therefore, there is an urgent unmet need for novel targeted therapeutics to improve cure rates.

Aryl-sulphonamides such as indisulam and E7820 are anticancer compounds that act as molecular glues, driving highly selective ubiquitination and degradation of the splicing cofactor RBM39 via interactions with DCAF15-E3 ligase. We (Nijhuis *et al.* Nature Commun. 2022) have recognised that high-risk neuroblastoma models are exquisitely sensitive to indisulam. This is likely because high MYCN expression, associated with high-risk disease, activates a transcriptional program that relies heavily on timely and correct RNA splicing. We hypothesised that indisulam-mediated aberrant RNA splicing leads to vulnerabilities that can be exploited therapeutically and discovered that the combination of RBM39-depletion and other targeted agents demonstrated a strong synergy in neuroblastoma cells.

While these findings suggest that there are therapeutic benefits of combining aryl sulphonamides with other anti-cancer drugs, we propose to generate dual inhibitors that can target two mechanisms simultaneously and reduce the likelihood that clones resistant to treatment arise while avoiding drug-drug interactions. The project will focus initially on synthetic and medicinal chemistry to explore this hypothesis and will also include biological characterisation of the resultant compounds, including: biochemical assessment of dual-target compounds; cellular validation of lead compounds; *in vivo* validation of lead compounds; investigation of the mechanism of synergy through global proteomics, RNA sequencing and bioinformatics.



Literature references

1. *Han, T. et al. Anticancer sulfonamides target splicing by inducing RBM39 degradation via recruitment to DCAF15. Science **356**, doi:10.1126/science.aal3755 (2017).*
2. *Nijhuis, A. et al. Indisulam targets RNA splicing and metabolism to serve as a therapeutic strategy for high-risk neuroblastoma. Nat. Commun. 2022*

Person specification

This project is suitable for a talented graduate or undergraduate student with a chemistry background, ideally with further evidence of experience in biological chemistry/chemical biology. The standard minimum entry requirement is a relevant undergraduate honours degree (First or 2:1). Applications are invited from talented graduates or final year undergraduates. We particularly welcome British applicants from Black and ethnic minority backgrounds, as they are underrepresented at PhD level within Imperial and The Institute of Cancer Research.

The studentship will be registered in the Department of Chemistry at Imperial College London with affiliate status at The Institute of Cancer Research. The student will have access to both institutions and benefit from the world class research infrastructure and expertise across the two institutions. The student will become a member of the CRUK Convergence Science Centre PhD cohort which is a unique group of students working across distinct disciplines to tackle the big problems in cancer. A unique convergence science training programme will provide the skills and language to navigate different disciplines.

Funding and Duration

Studentships will be for four years commencing in October 2022. Successful candidates will undertake a four-year research training programme under the guidance of a supervisory team of world-class researchers. Students will receive an annual stipend, currently £21,000 per annum, and project costs paid for the four-year duration. **Fees for either HOME or OVERSEAS students will be covered.**