**University of Leicester**

**MRC AIM Studentship Project 2025-6 entry.**

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| **First Supervisor** | Dr. Roberto Feuda |
| **School/Department** | Leicester Cancer Research Centre |
| **Email**  | Rf190@leicester.ac.uk  |

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| **Second Supervisor** | Prof. Beth Coyle |
| **School/Department** | University of Nottingham, Children’s Brain Tumour Research Centre, Biodiscovery Institute |
| **Email**  | beth.coyle@nottingham.ac.uk  |

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| **Additional Supervisor** |  |

**Section 2 – *Project Information***

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| **Project Title** | Analysis of Paediatric Medulloblastoma Cellular Heterogeneity Using Single-cell transcriptomic profiling for improved therapeutic strategies. |
| **Project Summary**  |
| Brain tumours are the leading cause of cancer-related deaths in children, with medulloblastoma being the most common malignant paediatric brain tumour. Approximately one-third of medulloblastoma patients present with metastasis at diagnosis. Group 3 (G3) subtype, predominant in infants and young children, has the lowest survival rate. Current treatments are highly aggressive and multi-modal, resulting in severe long-term consequences such as cognitive dysfunction, growth impairments, and secondary malignancies for survivors. Advancing therapies for G3 has been hindered by the limited availability of cell models that replicate the G3 tumour microenvironment and insufficient understanding of the molecular composition underlying G3 cellular architecture, which influences treatment outcomes.The aims of this project are to:1. Use single-cell technology to characterise the clonal landscape and regulatory networks driving G3 metastasis, chemosensitivity, and relapse in next-generation 3D preclinical tumour models.2. Identify predictive biomarkers and gene targets for improving G3 clinical treatment.This high-impact research opportunity bridges advanced biology and clinical medicine. The student will gain exceptional technical skills through training within a cross-disciplinary supervisory team, contributing significantly to novel therapeutic advancements. While led by the University of Leicester, the student will also collaborate at the University of Nottingham to develop 3D in-vitro tumour models. |
| **References** |
| 1. Juraschka, K. & Taylor, M. D. Medulloblastoma in the age of molecular subgroups: a review. (2019) doi:10.3171/2019.5.PEDS18381.2. Linke, F. *et al.* 3D hydrogels reveal medulloblastoma subgroup differences and identify extracellular matrix subtypes that predict patient outcome. *The Journal of Pathology* **253**, 326–338 (2021).3. Danilenko, M. *et al.* Single-cell DNA sequencing identifies risk-associated clonal complexity and evolutionary trajectories in childhood medulloblastoma development. *Acta Neuropathol* **144**, 565–578 (2022).4. Hovestadt, V. *et al.* Resolving medulloblastoma cellular architecture by single-cell genomics. *Nature* **572**, 74–79 (2019).5. Maizels, R. J., Snell, D. M. & Briscoe, J. Reconstructing developmental trajectories using latent dynamical systems and time-resolved transcriptomics. *Cell Systems* **15**, 411–424 (2024).6. Maizels, R. J., Snell, D. M. & Briscoe, J. A protocol for time-resolved transcriptomics through metabolic labeling and combinatorial indexing. *STAR Protocols* **5**, 103356 (2024).7. Rzasa, P. *et al.* BRAFV600E-mutated serrated colorectal neoplasia drives transcriptional activation of cholesterol metabolism. *Commun Biol* **6**, 1–16 (2023).8. Bravo González-Blas, C. *et al.* SCENIC+: single-cell multiomic inference of enhancers and gene regulatory networks. *Nat Methods* **20**, 1355–1367 (2023).9. Aldinger, K. A. *et al.* Spatial and cell type transcriptional landscape of human cerebellar development. *Nat Neurosci* **24**, 1163–1175 (2021).10. Oesper, L., Satas, G. & Raphael, B. J. Quantifying tumor heterogeneity in whole-genome and whole-exome sequencing data. *Bioinformatics* **30**, 3532–3540 (2014).11. A, S. H., Ao, H. & X, Z. CaSpER identifies and visualizes CNV events by integrative analysis of single-cell or bulk RNA-sequencing data. *Nature communications* **11**, (2020).12. Roth, A. *et al.* PyClone: Statistical inference of clonal population structure in cancer. *Nat Methods* **11**, 396–398 (2014).13. Iorio, F. *et al.* A Landscape of Pharmacogenomic Interactions in Cancer. *Cell* **166**, 740–754 (2016).14. Tate, J. G. *et al.* COSMIC: the Catalogue Of Somatic Mutations In Cancer. *Nucleic Acids Res* **47**, D941–D947 (2019).15. Chakravarty, D. *et al.* OncoKB: A Precision Oncology Knowledge Base. *JCO Precis Oncol* **2017**, PO.17.00011 (2017).16. Tamborero, D. *et al.* Cancer Genome Interpreter annotates the biological and clinical relevance of tumor alterations. *Genome Medicine* **10**, 25 (2018). |