CANCER RESEARCH UK CLINICAL ACADEMIC TRAINING PROGRAMME

TRACC Programme Project Pro Forma

TRACC (to Train and Retain Academic Cancer Clinicians) is a joint Glasgow/Edinburgh programme funded by Cancer Research UK. The **MB-PhD** strand of the programme is an opportunity for medical students from either University to undertake a **3-year** PhD after their BSc year in **any discipline relevant to cancer research**. Students are provided with close mentoring and support to find the project that best fits their interests across Edinburgh and Glasgow. Your MB-PhD project proposal should be suitable for a 2nd or 3rd year medical student undertaking a 3-year intercalated PhD (having previous completed a 1-year intercalated BSc)..

MB-PhD Project title:

Repurposing antipsychotic drugs for brain tumour treatment

Supervisory team:

Primary supervisor: Noor Gammoh – UoE
Secondary supervisor: Stephen Tait – UoG

Lab websites:

NG: https://institute-genetics-cancer.ed.ac.uk/research/research-groups-a-z/gammoh-group
ST: https://www.crukscotlandinstitute.ac.uk/cruk-si-research/cruk-si-research-groups/stephen-tait-mitochondria-and-cell-death.html

Research question:

Glioblastoma multiforme (GBM) is the most common and aggressive brain tumour, with a devastating prognosis of just over a year. Despite extensive research, treatment advancements over the past decade have been limited. Recent findings from our lab highlight a crucial role for autophagy, a lysosomal degradation pathway, in GBM development and survival. Despite compelling genetic evidence suggesting that autophagy promotes the survival and resistance to treatment of multiple cancers, targeting this pathway for therapeutic benefit remains challenging due to the lack of effective inhibitors.

Unpublished studies from the lab identified a panel of psychotropic drugs as potent enhancers of cell death in glioma stem cells (GSCs). We observed that these molecules accumulate in the lysosomes of cells and inhibit autophagy. Interestingly, GSCs seem to be more sensitive to these lysosomotropic agents compared to normal stem cells (NSCs). Given that these drugs can cross the blood-brain barrier (BBB), they present a promising opportunity for drug repurposing in GBM therapy.

The research questions of this project are to understand whether the identified psychotropic agents can be used for GBM therapy and to identify their mechanism of action. The main aims are as follows:

1) Investigate the **mechanism of cell death** elicited by psychotropic drugs in a panel of patient-derived cells (with known genetic mutations) and test the release of immunogenic factors (UoE & UoG).
2) Identify **lysosomal targets** that render cells sensitive to death upon drug binding (UoE).
3) Evaluate the **therapeutic potential** of these agents in suppressing GBM growth in preclinical models as single agents or in combination therapy (UoG).

By integrating molecular mechanism studies with disease modelling, this project aims to advance new therapeutic strategies for GBM treatment.

Relevance to Cancer:

Several factors contribute to the poor prognosis of GBM, including tumour heterogeneity, the BBB, and resistance to treatment. This project addresses a key molecular pathway involved in GBM survival and utilises small molecules with known BBB penetration. Understanding their mechanism of action and the role of lysosomes in cell survival could help identify critical vulnerabilities in GBM. Furthermore, preclinical studies will provide essential proof-of-concept data, potentially paving the way for novel therapeutic interventions for this devastating disease.

Techniques/model systems to be used:

The project will combine basic mechanistic studies with preclinical modelling in order to enhance our understanding of the disease and provide better treatment approaches for GBM. The study will use a number of methodologies, including:

1) Cell death/survival assays in patient-derived GBM cells, including PI staining, FACS sorting, fluorescence imaging, and analyses of cell media.
2) Lysosomal biology studies: isolation of lysosomal fractions, protein identification by mass spectrometry (MS), drug-target interactions, CRISPR/Cas9-gene editing to identify pathways conferring resistance to treatment, and high-resolution microscopy.
3) Preclinical modelling using well-established mouse models. Tumour development will be monitored by imaging and analysed by IHC and MS for markers of cell death and immune infiltration.

Papers of interest:

- Makar AN, Boraman A, Mosen P, Simpson JE, Marques J, Michelberger T, Aitken S, Wheeler AP, Winter D, Kriegsheim A, **Gammoh N** (2024) The V-ATPase complex component RNAseK is required for lysosomal hydrolase delivery and autophagosome degradation *Nature Communications* 15(1):7743

- Simpson JE, Muir MT, Lee M, Naughton C, Gilbert N, Pollard SM, **Gammoh N** (2024) Autophagy regulates PDGFRA-dependent brain tumour development by modulating oncogenic signalling. *Developmental Cell* 59(2):228-243.e7

- Vringer E, Heilig R, Riley JS, Black A, Cloix C, Skalka G, Montes-Gómez AE, Aguado A, Lilla S, Walczak H, Gyrd-Hansen M, Murphy DJ, Huang DT, Zanivan S, **Tait SW** (2024) Mitochondrial outer membrane integrity regulates a ubiquitin-dependent and NF-κB-mediated inflammatory response. *EMBO J*.

- Glover HL, Schreiner A, Dewson G, **Tait SWG** (2024) Mitochondria and cell death. *Nat Cell Biol*

- Debnath J*, **Gammoh N***, Ryan KM* (2023) Autophagy and autophagy-related pathways in cancer. *Nature Reviews Molecular Cell Biology* 2:1-16

- Cao K, Riley JS, Heilig R, Montes-Gómez AE, Vringer E, Berthenet K, Cloix C, Elmasry Y, Spiller DG, Ichim G, Campbell KJ, Gilmore AP, **Tait SWG** (2022) Mitochondrial dynamics regulate genome stability via control of caspase-dependent DNA damage. *Developmental Cell* 57:1211-1225