PhD in Translational Neuro-Oncology – University of Nottingham

Supervisors: Dr. Ruman Rahman (Assistant Professor in Neuro-Oncology)
Dr. Stuart Smith (Clinical Associate Professor in Neurosurgery)
Themes: Cancer Biology
Keywords: Brain cancer, Glioblastoma, Intra-tumour heterogeneity, precision medicine, invasive margin.
Fees: High-cost laboratory research
Project title: Targeting residual brain cancer cells from the lethal invasive margin of Glioblastoma

Background: Malignant brain cancer (Glioblastoma) kills 4000 people per year in the UK with an average survival of 6 months from diagnosis. Treatment with radical surgery, high dose radiotherapy and chemotherapy carries significant side effects. Attempts have been made to individually tailor therapy to enhance efficacy and reduce side effects, based on the genetic mutations within the cancer cells. It is now evident however, that these mutations vary considerably within each tumour and rarely reflect the residual cancer left behind that ultimately kills the patient. 5-ALA is a clinically used drug that makes cancer cells glow pink, allowing more complete neurosurgical resection of brain tumours. We have developed a technique that allows us to separate out the residual cancer cells from apparently normal brain at the tumour edge using fluorescence. This innovative strategy allows identification of the precise genetic profile of the invasive cancer that is left behind after surgery, responsible for tumour recurrence. By identifying the clinically-relevant mutations within this fraction of the cancer, we can target the disease with selective molecular inhibitors, thereby potentially enhancing patient survival with fewer systemic toxic side effects.

Aims: Characterise and target the invasive margin of glioblastoma using precision therapy.

Methodology: Samples from fluorescence sorted adult glioblastoma patients have been collected with Ethics approval. This project will undertake high quality RNA extraction on isolated fluorescent tumour cells, non-fluorescent brain cells and from a mixed tissue population, aiming to fully analyse up to 10 patients. RNA would also be extracted from non-cancerous brain and from the tumour core region. Samples will be analysed using an RNAseq approach, allowing full genome-wide characterization of the RNA sequence and revealing information regarding gene fusions. In-house biostatistical analysis would be conducted to assess gene expression levels and patterns of mutations exclusive to the invasive glioblastoma cells. The genetic changes would then be validated at the protein level by Western Blotting and immunohistochemistry. Selective molecular inhibitors are available for many altered pathways that would be amenable to a precision medicine approach. Related to this strategy, we are deriving cell lines from the purified invasive tumour regions to act as a representative cytotoxicity model for targeted agents. Such targeted therapy has the potential to improve survival whilst avoiding ineffective drugs that will only cause side effects and decrease quality of life for patients. This is a key collaboration between the University of Nottingham's School of Medicine and the Department of Neurosurgery, Nottingham University Hospitals NHS Trust.

Training: The appointed student will be gain thorough expertise in molecular and cellular biology applied in a dynamic translational neuro-oncology setting and will have the opportunity to attend brain tumour surgery.

Please **email a CV with covering letter** to Dr. Ruman Rahman (ruman.rahman@nottingham.ac.uk), who can supply more information to interested candidates.