PhD in Molecular Neuro-Oncology – University of Nottingham

Supervisor: Dr. Ruman Rahman (Assistant Professor in Molecular Neuro-Oncology)
Themes: Cancer Biology
Keywords: Brain cancer, tumour heterogeneity, next-generation sequencing, patient-tailored pharmacology.
Fees: High cost-laboratory based research

Project title: **Integrated genome-wide analyses of glioblastoma intra-tumour heterogeneity: a framework for personalised medicine.**

Background: Glioblastoma (GBM) is among the most aggressive and treatment-resistant primary adult cancers with a median survival of 14 months. Biological differences within each GBM (intra-tumour heterogeneity) resulting from divergent tumourigenic clones, likely accounts for therapy failure. There is an urgent need for more specific therapies based on an understanding of the evolutionary progression of GBM subclones within individual patients.

Aims:
1) Reconstruct GBM dynamics using next-generation sequencing.
2) Target patient-derived GBM cells via tailored pharmacology.

Methodology: (Year 1): Through collaboration with the Queen's Medical Centre Neurosurgery Department, GBM fragments from five spatially distinct regions and based upon clinical scans will be collected. Genome-wide cytogenetic analyses (Affymetrix CytoScan™) will determine the mutation spectra (copy number alterations) across tumour regions, relative to patient-matched blood. Genome-wide gene expression analysis (Affymetrix Transcriptome Array 2.0™) will enable a precise measurement of both coding, non-coding and splice variant transcripts in distinct GBM regions, normalised to cerebral cortex gene expression. Abnormal gene expression will be matched to the underlying mutation previously determined. Ultimately, integrative genomics that combines genetic mutation and gene expression from different tumour regions, will be used to identify common, shared and unique genetic signatures and thereby identify the dynamics within each tumour. (Year 2): Overexpressed genes with associated mutations and which are common to all five GBM regions will be targeted therapeutically *in vitro* using patient-derived cells grown in the 3-Dimensional Rotary Cell Culture System (RCCS) [1]. For each GBM, 2-3 candidate genes will be targeted therapeutically with novel chemotherapy drugs. (Year 3): The single most efficacious treatment regime will be validated and characterised *in vivo* using patient-derived GBM tumours in mice, in collaboration with the Department of Pre-Clinical Oncology, University of Nottingham. This overall strategy represents a framework for personalised medicine using next-generation chemotherapy. The immediate beneficiaries of this research will be healthcare professionals engaged in the diagnosis and treatment of GBM and other malignant brain tumours.

Training: The project will ensure that a high calibre PhD student develops advanced research skills in a translational neuro-oncology setting. The student will gain expertise in computational and statistical methodologies applied to the field of genomics in addition to molecular and cellular biology approaches to evaluate drug targets *in vitro* and *in vivo*. Close interaction with neurosurgeons and neuro-oncologists throughout the project will ensure training in the dynamic interface of basic-translational science.

References: [1] Smith SJ……, Grundy RG, **Rahman R**. A dynamic 3D brain cancer model recapitulates neoplastic phenotypes and molecular signatures with decreased sensitivity to histone deacetylase inhibition. *PLoS One* **7**(12): e52335 (2012).

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