SARChI Chair Clinical Neurosciences

Division of Neurosurgery

Faculty of Health Sciences

Call for Masters and Doctoral Students in Clinical Neurosciences

Applications are invited for Neuroscience Masters and Doctoral students for 3 projects in Clinical Neurosciences starting in 2016. These are hosted by the Division of Neurosurgery but involve bench-to-bedside translational science between the laboratory and the clinic, multidisciplinary teams, and international collaborations.

Stipends are funded through the National Research Foundation SARChI Chair of Clinical Neurosciences which can be augmented through additional funds. Project-related costs and travel costs to present at national and international meetings as well as for research visits are made available where appropriate. Each project calls for a Masters and a PhD student.

For more information, contact Prof Figaji: Anthony.Figaji@uct.ac.za

The projects are:

1. Biomarkers of Brain Injury
2. Drug Recovery in the Central Nervous System
3. Molecular Epigenetic profiling of Brain Cancer in a South African Context

Each of the projects is described briefly below:

Biomarkers of Brain Injury

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There are many forms of acute brain injury – traumatic, infective, vascular, metabolic, etc. Many of these involve similar biochemical, metabolic, and inflammatory pathways that aggravate the injury, reducing the chance of a good recovery. Managing brain injury remains challenging because we have few objective means to diagnose and track the severity of the injury or its response to treatment.

Biomarkers for diagnosis and prognosis have had a substantial impact on the management of other conditions, but their use for neurological conditions is yet to have a significant effect on clinical practice, in part because the brain is a complex organ that is difficult to understand in health and disease, and in part because it is relatively isolated from the rest of the body. However, it is a hot topic in science as the impact of various brain injuries over the lifespan has been gradually recognized, in particular with growing concern about the later development of neurodegenerative disease such as Alzheimer's, even after minor head injuries in sports.

At the University of Cape Town we have an aggressive approach to the management of acute brain injury for which we have developed an international reputation. This enables access to several means of sampling biological material which can then be tested for biomarkers, using targeted and unbiased approaches. These samples include serum, cerebrospinal fluid, brain interstitial fluid (from microdialysis) and brain tissue, allowing examination of markers as close as possible to the site of origin. We have the additional advantage of being able to study paediatric and adult populations.

This project will build on pilot data that we have on inflammatory mediators and proteomics in brain injury and hypotheses that these have generated. Students will collaborate with local groups such as the Centre for Proteomics and Genomics research as well as international research groups.

Drug Recovery in the Central Nervous System

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Little is known about how various drugs get into the brain, in part because of the blood brain barrier, in part because the brain is difficult to sample directly. Results are often extrapolated from the serum, which does not necessarily reflect brain concentrations. Cerebrospinal fluid (CSF) sampling is better, but again may not fully reflect actual interstitial concentrations. CSF is also limited because only a single sample is usually available, and is most commonly accessed from a lumbar puncture. This introduces a further limitation because lumbar and ventricular samples are substantially different in some conditions. For example, emerging data in tuberculous meningitis shows that lumbar samples may not reflect ventricular conditions, and are affected by local spinal disease and CSF dynamics.

Microdialysis is an advanced method of monitoring interstitial concentrations of substances in the clinical environment. Substances diffuse along a concentration gradient across a semi-permeable catheter. The collected fluid can be analysed in real time, as we do for monitoring metabolism in traumatic brain injury, or for offline analysis of various substances in research projects, including for drug concentrations.

In this project we aim to analyse drug concentrations in brain interstitial fluid, cerebrospinal fluid, and serum in patients with traumatic brain injury and meningitis. We expect this to yield novel data that can be used as a basis for testing different drugs, dosages and methods of administration. The students will work closely with clinicians and laboratory staff and will collaborate locally with Pharmacology and with international partners. Pilot data at this stage includes Rifamipicin in tuberculous meningitis and morphine and midazolam in traumatic brain injury, for which we have compared microdialysis-derived concentrations in patients with pharmacodynamic modeling in rats in collaboration with Erasmus University in the Netherlands.

Molecular Epigenetic Profiling of Adult and Childhood Brain Cancers in a South African Context

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Brain tumours are one of the most challenging diseases to treat. However, exciting recent molecular insights in brain cancer biology have improved our ability to better classify cancers, understand their genetic basis, and develop tumour-specific targeted therapy. This is an area in which South Africa has not kept pace with fast-moving international trends. Recently, we have been building local capacity for molecular brain tumour research as the first African initiative in brain cancer molecular biology.

Epigenetics refers to heritable changes that are not determined by changes in the DNA sequence but rather by biochemical modifications such as chromatin modification, transcription factor binding and DNA methylation of cystein residues at regions known as CpG islands. DNA methylation alters gene expression in cells and may determine cancer formation and progression. For example, DNA hypermethylation in medulloblastoma may inactivate the tumour suppressor gene RASSF1A and lead to tumour progression. In glioblastoma multiforme the methylator negative phenotype or hypomethylation phenotype portends poor survival. Furthermore, while the link between childhood and adult brain cancers remains elusive, there is evidence that epigenetic drivers may link the two forms of brain tumours in its aetiology.

This study aims to 1) grow local capacity in brain tumour biology using a multidisciplinary local group and international collaborations with key leaders in the field, and 2) create molecular profiles based on tumour epigenomic markers in two common cancers in adults and children, namely glioblastoma multiforme and medulloblastoma. Epigenetic analysis will be performed to identify DNA methylation using bisulphite treatment and Illumina Human DNA Methylation Bead Chip from FFPE specimens of banked tumour samples. This will provide valuable novel information on epigenetic drivers in a South African context and explore links between adult and childhood forms of the disease.