THE UNIVERSITY of York

C2D2 Centre for Chronic Diseases & Disorders

C2D2 Projects funded from Third Round

Professor Celia Kitzinger (Sociology), Professor Simon Halliday (Law), Dr Stephen Holland (Philosophy), Professor Sarah Nettleton (Sociology), Dr Alice Hall (English & Related Literature)
Chronic Disorders of Consciousness: An interdisciplinary Research Project.

The development of new medical technologies and procedures is leading to a rapid rise in the number of people it is now possible to keep alive (for years or even decades) after catastrophic brain injuries resulting in chronic disorders of consciousness – states widely referred to as 'coma' – including the permanent vegetative and minimally conscious states. This innovative interdisciplinary project, which will address a range of sociological, legal, philosophical, ethical and literary issues relating to chronic disorders of consciousness, was launched in the previous funding round. Its membership has since expanded and the intention is to continue to establish York as a Centre of Excellence for research in this area (in partnership with our collaborators the University of Cardiff).

Professor Jonathan Timmis (Computer Science), Dr Mark Coles (CII)
Client Focussed Demonstration of Immune and Inflammatory Simulations.

Improved treatments for autoimmune and chronic inflammatory diseases enable better disease management, often with reduced care costs. A major problem for drug companies, however, is the high rate of attrition of pipeline products, particularly through late discovery of problematic side-effects or lack of efficacy. In a project carried out under the auspices of a pre start-up enterprise, *Immune Modelling Solutions* (IMS), a novel computer simulation technology has been developed that can capture the complexity of human disease and model therapeutic interventions. The IMS platform can rationalise the design of clinical trials, highlight key biomarkers, abstract between animal and human physiology and assist decision making during the drug development process to identify potential drug targets, and optimise treatments and concert mixing of therapeutics. These are all key areas of interest for SMEs, pharmaceutical companies and academics working to translate mechanistic science into clinical products. This project will progress the technology and business infrastructure of *Immune Modelling Solutions* to succesfully deliver the product. If successful, the adoption of this technology could potentially save the pharmaceutical industry billions of pounds each year and significantly advance UK competitiveness in the drug development process.

Dr Gareth Evans (Biology), Professor Thomas Krauss (Physics)
Exploring novel multi-modal photonic techniques for live imaging of synaptic activity.

The importance of learning and memory in determining who we are is made starkly obvious in patients with late-stage dementia. Developing therapies to treat dementia therefore requires a fundamental understanding of learning at the molecular level. When we learn, information is encoded in our brains by the strengthening of connections (synapses) between brain cells (neurons). The expertise of a neuroscientist and a physicist will be paired to to develop a novel method for measuring the activity of synapses in neurons that will facilitate basic research into how synapses change when we learn. A microscope that uses changes in the properties of light to detect the binding of neurotransmitters to specific sensors will be constructed to observe the chemical neurotransmitters that are released by active synapses during the course of learning. This novel technique will reveal how networks of synapses behave and so help to elucidate the molecular processes of learning, and how these processes go wrong in dementia.

Dr Betsy Pownall (Biology), Dr Stephen Smith (Electronics)
Zebrafish: a new vertebrate model for Parkinson's disease.

Parkinson's Disease (PD) is characterised by tremors and a slowing of movement called bradykinesia: these symptoms are caused by the death of a specific set of neurons in the brain. Studying the genes that are disrupted in PD patients is key to understanding the molecular basis of this disease. This project aims to develop a novel zebrafish model for PD. Like humans, zebrafish are vertebrates and have the same dopaminergic neurons that die in patients with PD and they have the same genes known to go wrong in PD. A new technique will be employed to remove a PD gene from the zebrafish genome. Following this, movement in these fish will be measured using a non-invasive system developed for the diagnosis of Parkinson's disease in human patients which takes digital measurements of tremor and bradykinesia. Using this method it will be possible to measure the effects of disrupting a specific PD gene in zebrafish and so determine whether this is a good model of the human disease. A zebrafish model of PD has the potential for high throughput in vivo drug screening that is not economically viable using other vertebrate models.

Dr Sean Sweeney (Biology), Dr Deborah O'Connell (Physics), Professor Miles Whittington (HYMS)
The effect of free radicals on synaptic function and connectivity within individual neuronal connections and neuronal circuits.

Oxygen is the single most important source of energy we need to keep us alive and functional. The 'greediest' user of oxygen in our bodies is our nervous system – our brain, spinal cord and all the nerves that provide the signals needed for us to think and move. The body has many ways to ensure the right amount (and chemical type) of oxygen is available where it is needed. This is vital because too much, too little or the wrong type of oxygen can be very detrimental to nervous system function. For example, a long-term failure to control oxygen level and chemical type has been linked to decline in motor (movement) and cognitive (thinking) function seen in many diseases associated with old age. This project aims to understand how such a failure can alter the way nerve and muscle cells communicate with each other. It will measure the changes seen, uncover the mechanisms by which detrimental changes occur and link these changes to problems with motor and cognitive function all too commonly seen in the ageing population.

Dr Daniel Ungar (Biology), Professor Jane Thomas-Oates (Chemistry)
Developing a method for CDG testing from dried blood spots.

CDGs are a family of rare inherited diseases that are very difficult to diagnose because clinical symptoms are extremely varied. Biochemical diagnosis is simple, but the most commonly used test is rarely prescribed because doctors often do not know about the existence of the disease. This project aims to establish a new method of testing that would make automated screening of large numbers of potential patients possible. This would allow much improved diagnostic efficiency, which, given that some subtypes of the disease class are treatable, will improve patient health. The proposal is to develop the test based on dried blood spots (DBS), as opposed to serum. DBS are routinely generated for each new-born, and are therefore commonly available for disease testing, while blood for serum samples is only taken for specific tests that a doctor prescribes. In addition, the project will seek to expand the number of biomarkers for CDG testing in order to improve diagnostic precision.

Dr Dimitris Lagos (CII), Dr Michael Plevin (Biology)
MicroRNA processing: Testing structural biology hypotheses in primary human cells.

A fundamental challenge in biomedical research is to understand the relationship between the structure of individual biomolecules and their function in health and

disease. The aim of this project is to generate an interdisciplinary platform that will facilitate the functional correlation of structural information determined in a test-tube with biological activity occurring in a human cell. It will focus on TRBP, a protein with a fundamental role in development of chronic diseases, such as cancer and chronic inflammation. TRBP is an essential component of a cellular machine that processes a unique class of regulatory molecules called microRNAs. This microRNA-processing machinery is essential for mammalian development. Previous studies have characterised the structural and functional features of TRBP and its interaction with other proteins and RNA. Here, it is proposed to combine these distinct but highly complementary approaches to enhance our understanding of the biology of the microRNA processing machinery. It is intended that this project will provide a springboard for future studies in microRNA biogenesis.

Dr Camilla Speller, Professor Matthew Collins, Dr Sarah Fiddyment (Archaeology); Professor Peter Young, Professor Michael Brockhurst, Dr Peter Ashton, Dr James Moir, Professor Michael Hofreiter, Dr Gavin Thomas (Biology)
By the Skin of your Teeth: Investigating Chronic Periodontal Disease through History.

Chronic periodontal disease is a very common chronic condition which includes the familiar gum disease but can spread to the other supportive tissues around the tooth, potentially resulting in bone deterioration and toothloss. The disease is caused by overgrowth of harmful bacteria in plaque and tartar deposits around the gumline. Beyond its effects on oral health, individuals with chronic periodontitis are also at higher risk for cardiovascular disease, stroke, diabetes, and respiratory illnesses. In order to effectively treat periodontal disease today, we need to have a clear understanding of both the species of bacterial pathogens that cause the disease in the past and today, and how these bacteria have evolved through time. Archaeological studies have known that humans have been suffering from periodontal disease for millennia, although frequency and severity vary between geographic areas and historicalperiods. This study will investigate the genetic diversity and evolution of periodontal pathogens from five historic time periods in Yorkshire through biomolecular analyses of fossilised plaque on human skull remains. It will also examine different human immune responses over time in order to learn more about the bacteria's virulence and adaptability.

Dr Traci Walker (Language & Linguistic Science), Professor Ian Watt (Health Sciences)

Investigating the 'supported conversation' intervention technique: a study of interactions between health care professionals and people with aphasia.

The aim of this bid is to fund the pilot stages of a study of communication between people with aphasia after stroke, and members of the multidisciplinary team of health care professionals caring for them, in order to develop and draft a grant proposal. The objectives of the full study will be to 1) develop linguistically-informed methods to evaluate the efficacy of the communication interventions currently in use in the NHS, with special focus on Supported Conversation; 2) develop good practice guidelines for all members of the post-stroke health care team (eg., occupational therapists and GPs as well as speech & language therapists) and 3) facilitate the involvement of people with aphasia after stroke in their clinical care decisions. The special strength of the project is the combination of a linguistic understanding of aphasia as a language deficit, combined with conversation analytic methodology (an interdisciplinary methodology used in several different academic disciplines including linguistics, sociology, and psychology). The research aims to unpick the demonstrable communicative capabilities of people with aphasia in spite of this (organically-caused) deficit.

Dr Martin Webber, Dr Meredith Newlin (Social Policy & Social Work); Dr Elizabeth Hughes (Health Sciences)

Connecting People Intervention International Research Group

Robust evidence exists to support links between enhanced social capital and improved health and wellbeing for vulnerable populations. However, there is little evidence for health and social care interventions that promote social engagement, particularly in low- and middle-income countries where health services are limited. The World Health Organization and the UK Government recognise the vital need to expand global health partnerships and mental health services to vulnerable adults in low- and middle-income countries through wide dissemination of scientific evidence-based interventions. The Connecting People Intervention, which supports enhanced social networks for individuals with mental health problems, is currently being piloted in the UK. The proposed research will evaluate the feasibility of piloting the Connecting People Intervention in low-resource settings of Sierra Leone.

Using systematic reviews and ethnographic methodology, we will gain an understanding of mental health service delivery and identify needs of service users in Sierra Leone. Combining expertise of an interdisciplinary research team we will develop sustainable international partnerships with stakeholders across areas of policy, research, and practice.