SSC in Research Practice 2017/2018

PROJECTS AVAILABLE IN JANUARY & MAY 2018

Project Number	Title and Description	Supervisor
1	**Exploration of Neuropathic Pain Case Ascertainment: A Validation Study** Neuropathic pain (NeuP) affects 7-10% of the population and arises through direct damage to the somatosensory system, either through diseases such as diabetes mellitus, herpes zoster and multiple sclerosis or trauma as in spinal cord injury. It is considered a distinct clinical entity from nociceptive pain (caused by damage to surrounding body tissue) with its own characteristic set of symptoms including electric shocks, pins and needles and burning sensations. However, not everyone with a relevant underlying disease or lesion develops NeuP and those that do have a range of pain severities and differential response to treatment. The reasons for these are not fully understood. Epidemiological studies have the potential to inform approaches to reducing the burden on healthcare resources and improving quality of life for sufferers. In the past, these studies have suffered through lack of well-validated, agreed and practical methods of defining and identifying cases of NeuP. Methods for identifying NeuP in the clinic (such as detailed clinical examination) are not necessarily amenable to a large-scale research setting. It is only relatively recently that simple screening tools such as the DN4 and S-LANSS questionnaires have been developed and a consensus agreed on phenotype definition. This has formed the cornerstone of the Europe-wide DOLORisk study (http://dolorisk.eu/), investigating environmental and genetic risk factors for NeuP. As part of this study two population cohorts, one diabetes based (GoDARTS) and one family based (GS:SFHS) have been tested for NeuP (and neuropathy) using these validated questionnaires. The aim of this investigation is to compare and validate a range of NeuP and neuropathy case definitions derived through DOLORisk research questionnaires (DN4/S-LANSS/MNSI) and routine clinical data (prescriptions/health records). The project will suit up to 3 students with an interest in public health research. Students will be based in the Chronic Pain Research Group and will gain experience of methodological skills in epidemiology, quantitative analysis and data management.	**Dr Harry Herbert & Professor Blair Smith**

2	**Real world applicability of clinical trial evidence for treatment of mental health conditions: systematic review of studies assessing eligibility for randomized-controlled trials** Randomised controlled trials (RCTs) are the gold standard method for evaluating whether treatments are effective because they minimise the risk of bias and confounding. However, they are very often carried out in narrow populations raising questions about how applicable their findings are to the range of patients treated in clinical practice. Working with a DCAT SSC student, we have recently completed a systematic review of studies examining the applicability of trial evidence for the treatment of *physical health conditions* (which will shortly be submitted for publication with the student as first author). As part of that, we have systematically identified but not analysed similar studies for *mental health conditions.* The aim of this project will therefore be to complete a systematic review of real-world applicability of clinical trial evidence for mental health conditions which will involve: (1) Training in systematic review methods; (2) Updating the search using the established strategy; (3) Data extraction, risk of bias assessment and analysis; (4) Writing a paper for publication. Applicability is of great interest to trialists, guideline developers and clinicians and this will be the first systematic review of this topic in relation to mental health conditions. If you would like to discuss the project please contact b.guthrie@dundee.ac.uk	**Professor Bruce Guthrie & Dr Dan Morales**
3	**Evaluating the penetrance and pathogenicity of rare coding variants in hereditary endocrine disease genes** This project will offer the student an opportunity to undertake a project in the area of molecular genetics. In particular, it will provide experience in the methods that may be employed to evaluate the likely pathogenicity and penetrance of germline genetic variants. Through the investigation of a number of hereditary endocrine diseases, the project will use a variety of research methods (mainly bioinformatic) to evaluate rare coding region variants in a number of genes and aim to quantify any associated health risks.	**Dr Paul Newey**
4	**Questionnaire development and evaluation – knowledge of cancer risk** Questionnaires are the most commonly used tool in epidemiological research but few data users are familiar with the theoretical underpinnings involved in their development. The proposed SSC aims to allow the student to explore the development of questionnaires including content and face validity procedures, discrimination and difficulty indices and measures of reliability (including Cronbach's alpha measurement and test –retest procedures).	**Dr Annie Anderson**

	During the course of the SSC the student will develop a protocol for the development of a questionnaire to assess clinician's knowledge of lifestyle and cancer risk using the health belief model from social psychology. Early drafts of the data collection instrument (which includes face validity measures) will also be undertaken and tested. At the end of the SSC an application will be made to university ethics so the complete testing process can be undertaken and written up during a summer vacation studentship It is anticipated that the development process will be prepared for publication (see https://www.ncbi.nlm.nih.gov/pubmed/19904290,) and the final tool will be used in ongoing Scottish Government research. If this work is undertaken by a 3rd student, live data collection and analysis would be suitable for a 4th year project	
5	The Medicines Monitoring Unit (MEMO) is currently conducting a trial that compares two drug prescribing policies in Primary Care. The Evaluating Diuretics in Normal Care (EVIDENCE) study is a cluster randomised evaluation of hypertension prescribing policy. Cluster randomised trials are a relatively new method and have specific ethical considerations around whether, and how, participants should be given the opportunity to consent to taking part. I invite a medical student to assist in the conduct of a systematic review of reasons. This is a systematic review technique aimed at summarising argument-based literature such as can be found discussing the ethics of consent in cluster randomised studies. The review will aim to answer the following question "*"What reasons have been given for the views that cluster randomization of prescribing without individual opt-in consent would, or would not, be an acceptable method of assessing drug safety and efficacy within a healthcare system?"* The student would be required to undertake, with support, a structured data abstraction from identified papers and to assist in the process of writing up the review for publication.	**Dr Amy Rogers**
6	**Potentially drug related hospital admissions: Prevalence and time trends** **Background -** Prescribing medicines is the most common intervention in primary care and although medicines provide significant benefit to patients, they also commonly cause harm and sometimes severe harm. It has been estimated in 2004, that approximately 6.5% of emergency admissions to hospital are drug related, of which 75% are at least potentially preventable. It is currently unknown whether progress has been made in the UK to reduce the incidence of drug related admissions, at	**Dr Tobias Dreischulte**

	least partly because traditional methods of attributing admissions to drug therapy have required expert judgement which is time consuming. **Aims -** The aim of this project is to examine time trends in potentially drug related hospital admissions using electronic data sources routinely available in NHS Tayside **Methods –** Measures of potentially drug related admissions have been defined as emergency admissions for reasons commonly caused by medicines (eg acute kidney injury, bleeding, falls/fractures, cardiac failure/bradycardia, stroke) preceded by a relevant prescription of a medicine within 3 months prior to admission. Quarterly or annual rates of such admissions will be plotted and significant changes in trends determined using appropriate statistical methods. **Benefits to the student –** The student will obtain experience in searching the scientific literature, the handling of large electronic data sets and quantitative data analysis, providing an excellent foundation for a future research career. The supervisor will assist in all aspects of the project as required to complete the project within the given time frame. It is anticipated that the study will lead to a publication in a peer reviewed journal, which the student will co-author.	
7.	**Pirfenidone phototoxicity** Idiopathic pulmonary fibrosis (IPF) is a chronic and progressive lung disease that is extremely difficult to treat and has high mortality. Pirfenidone (Esbriet) is one of very few drugs that has shown efficacy as an anti-fibrotic agent that can slow disease progression and improve survival rates in IPF patients. However, photosensitivity had been noted as an adverse event in clinical trials and there are increasing clinical case reports of photosensitivity in patients treated with pirfenidone. Phototoxicity is the most common mechanism for drug-induced photosensitivity and occurs when a photoactive drug present in the skin reacts with sunlight, resulting in either a molecular change in the drug itself that changes its reactivity with endogenous molecules (direct effect), or in the generation of reactive oxygen species that cause localised skin damage (indirect effect). Phototoxicity often presents as exaggerated sunburn, manifesting as an intense symptomatic erythema. In the Photobiology Unit, we have investigated pirfenidone-induced phototoxicity in patients and have shown abnormal erythemal responses to ultraviolet radiation (predominantly UVA) on monochromator phototesting. The mechanism of pirfenidone-induced photoxicity has not been well established in cells. This project	**Dr Vicky McGuire & Professor Sally Ibbotson**

	will build on SSC project work completed in 2017 which showed that, surprisingly, pirfenidone does not affect cell viability following UVA, UVB or combined UVA/UVB exposure at drug doses up to 200 μM. To further explore how the symptoms seen in patients are caused, experiments will be designed to investigate phototoxicity induced by pirfenidone. A better understanding of how pirfenidone causes phototoxic reactions has the potential to improve the current approaches for preventing and managing cutaneous photosensitivity and to improve the quality of life of patients taking this drug.	
8.	**Inhibition of mTOR signaling by small molecule inducers of cytoprotective responses** The mechanistic target of rapamycin (mTOR) signaling pathway regulates numerous fundamental biological processes, ranging from protein synthesis to autophagy. The transcription factor NF-E2 p45-related factor 2 (Nrf2) allows adaptation and survival under conditions of stress by orchestrating the inducible expression of a broad network of cytoprotective genes. Dysregulated mTOR and Nrf2 signaling has been implicated in the pathogenesis of many chronic diseases, as well as aging. We and others have reported that sulforaphane and phenethyl isothiocyanate, two naturally occurring small molecule inducers of cytoprotective responses regulated by transcription factor Nrf2, can also inhibit mTOR signaling. However, whether other Nrf2 inducers can also inhibit mTOR signaling or whether Nrf2 is required for this inhibition is unknown. This project aims to test the hypothesis that mTOR inhibition is a common property of Nrf2 inducers, and to establish the potential involvement of Nrf2 in the inhibition of mTOR signaling. We will use Nrf2-proficient and Nrf2-deficient (created by CRISPR/Cas9 targeted gene editing) cells, in which we will test a range of small molecule inducers of Nrf2 for their ability to inhibit mTOR and its classical downstream targets. The findings will have implications for therapeutically targeting mTOR and Nrf2 in the clinic.	**Professor Albena T. Dinkova-Kostova**
9.	**Investigating the Potential Utility of the Novel Biomarker Desmosine in Genetic and Acquired Aortic Disease** Both genetic and acquired dilatation of the aorta (aortopathy) can lead to life-threatening aortic dissection. The commonest acquired aortopathy is an abdominal aortic aneurysm (AAA), while the commonest inherited aortopathy is in patients with Marfan syndrome (MFS). Current management in both groups of patients involves regular monitoring of aortic dimensions using imaging, however this not only has extensive resource implications for patients and the health service, but can also be unreliable as the association between aortic size and dissection is not complete. Furthermore, the rate of disease progression is highly variable, therefore a cheap non-	**Professor CC Lang, Dr Anna Maria Choy and Dr Ify Mordi**

	invasive tool to assess the disease activity would be highly desirable. Indeed, although current recommendations are that in patients in whom the aorta reaches a certain size should undergo elective surgery, many patients dissect before they reach that cut-off. Desmosine is an amino-acid cross-link that is specifically found in mature elastin within vessel walls and is only found in serum and urine when there is damage to elastin-containing structures such as the aorta. Our pilot work demonstrating a strong correlation between serum desmosine levels and aortic size in MFS patients suggest a potential role for desmosine as a cheap, non-invasive biomarker. The aim of this study is to extend the pilot study findings by analysing serum desmosine in 2 important well characterised prospectively recruited cohorts of patients with MFS and AAA. The findings of this study will add important new information in this field of research.	
10.	**Experimental investigation of the novel role of the gene 'Ataxia telangiectasia mutated' (ATM) in glucose homeostasis.** Around a quarter of diabetes patients who are prescribed metformin don't get any significant improvement in their glucose control. This implies that there are genetic and/or environmental and/or disease specific influences which dictate the metformin sensitivity of that individual. We have identified the gene Ataxia telangiectasia Mutated (ATM) in a genome wide association study searching for genetic markers of response to metformin. Patients with Ataxia telangiectasia often have impaired glucose homeostasis or insulin sensitivity. If we could understand how ATM influences glucose homeostasis and metformin response it should help us identify those patients that will get no benefit from metformin without having to undergo months of ineffective treatment. In addition it may provide alternative strategies for those patients to either improve their metformin sensitivity or develop new treatments. In this study we will study the effect of chemical inhibitors of ATM on various experimental readouts of glucose homeostasis in rodent cells and tissues. This will involve learning tissue culture, protein isolation, glucose transport assays and data analysis. The SSC will involve a training period of all the techniques involved, then the summer placement will generate the data.	**Dr Calum Sutherland**