REPORT FOR THE CASTANG FOUNDATION

New Frontiers in Understanding and Treating Epilepsy
Informatics Forum, University of Edinburgh, 19 & 20 March 2015

Dear Castang Foundation Trustees and Scientific Committee

We are pleased to offer this report on this very exciting, successful, and productive meeting that we held in Edinburgh on your behalf. We hope that we will be able to demonstrate that it was of benefit in furthering the mission of the Castang Foundation. We enclose a copy of the ambitious programme that lists the invited participants, many of whom are outstanding national and international researchers in their field.

Since the meeting, a number of collaborations and initiatives have been taken forward as a result of the sharing and discussing of each other's work and experiences. Most of these, thus far, revolve around Edinburgh team members (reflecting proximity to the meeting) but we are optimistic that there will be further developments not only amongst Edinburgh participants but non-Edinburgh attendees too. Here are some examples:

Mike Cousin's talk on synaptic vesicle protein 2A (SV2A) concluded a potential mechanistic role of SV2A dysfunction as the basis of seizures in experimental models suggesting it could be the basis of some forms of epilepsy in humans. This is part of a programme of work by the Cousin lab examining the role of neurotransmitter release and synaptic vesicle recycling which may lead to novel therapeutic targets for epilepsy in humans. Taking this forward, Prof Cousin will collaborate with Richard Chin, Ailsa McLellan, and Wayne Lam (clinical geneticist) to identify mutations in the SV2A pathway in children with epilepsy identified through the UK-wide study, Deciphering Developmental Disorders (DDD), with the intention of determining functional consequences of these mutations and developing therapeutic strategies. To examine the functional consequences, they will collaborate with Iris Oren who is developing a wireless rodent telemetry system in Edinburgh.

Iris Oren showed a combination of wireless EEG telemetry, in vitro brain slice electrophysiology, and immunohistochemistry data that suggest inhibitory pathways targeting the dendritic regions of CA1 of the hippocampus may be vulnerable in the early stages of pathogenesis in a transgenic mouse model of Alzheimer's Disease. Matthew Walker (London) and Ben Whalley (Reading) have both offered Iris and her team help to overcome challenges being experienced with obtaining, interpreting and processing data from the wireless rodent telemetry system. Cathy Abbott, who has expertise in creating animal models and molecular characterisation, has now identified 6 patients with novel eEF1A2 mutations through the DDD project. Along with Iris Oren and Richard Chin, they are preparing an application for a Wellcome Trust 4 year PhD Studentship to recreate one or more of the DDD mutations in mice, and doing molecular characterisation and wireless telemetry. Mutations in Leucine-rich Glioma Inactivated gene (LGI) type 1 (LGI1) cause autosomal dominant lateral temporal lobe epilepsy, LGI4 polymorphisms are associated with childhood absence epilepsy in humans and homozygous deletion of LGI2 in dogs causes benign familial juvenile epilepsy. These data lead Dies Mejer to hypothesise that LGI2 mutations can lead to epilepsy in humans. To investigate this, he proposes to also use the DDD project to identify children with epilepsy with LGI2 mutations. He has already obtained some seed corn funding with Iris Oren to generate preliminary data on LGI2 mutations in rodent models with an intention to use the data to leverage grant applications to MRC/Wellcome and or similar grant giving bodies.

Angela Vincent's work showed an increasing understanding of autoantibodies being found in people with epilepsy but less so in people who do not have epilepsy. These included antibodies that bind the voltage-gated potassium channel complex (VGKC-complex) - which is localised in LGI1 and whose role in epilepsy was described above - NMDA, GABA(A or B) or AMPA receptors. The epilepsy in such patients usually emerge as part of a clinical encephalitis and can respond well to immunotherapy. Jay Shetty has now agreed to be the local PI in Edinburgh for a multicentre trial on intravenous immunoglobulin in encephalitis being led by a team from Oxford where Angela Vincent is based. The theoretical basis for such a trial was reinforced by Anna Maria Vezzani's presentation on anti-inflammatory therapy in epilepsy. Angela and Anna-Maria's work also dovetail nicely in recently started or about to start studies in Scotland and the rest of the UK trying to understand the Genetic and Autoimmune basis of Childhood Epilepsy (ERUK funded, Ailsa McLellan as local PI) and Epileptic Encephalopathies Longitudinal Multicentre Omics (FP7 European Funding, Ailsa McLellan as local PI) and a randomised trial of clobazam vs steroids in ESES (Dutch Funding, Richard Chin as local PI).

Presentations by Simon Warfield (Boston) and Kees Braun (Utrecht/Rudolph Magnus Institute) on cutting edge MRI and EEG techniques to understand structural and functional networks in networks provided novel information on how to increase utilisation of currently existing hardware with the help of informatics. They also provided insights on how these network analysis techniques could be used to explain cognitive deficits in people with epilepsy, identify the epileptogenic zone in standard lesion negative scans, and facilitate preoperative assessment and intraoperative surgical planning in pediatric epilepsy. Both Kees Braun and Simon Warfield have now agreed to collaborate with Julie Woodfield, Mark Bastin, Michael Yoong and Richard Chin on a Wellcome Trust funded Edinburgh Clinical Academic Training Fellowship to address whether pre-operative white matter integrity can predict post-operative cognitive outcome. Javier Escudero and Richard Chin are preparing an application for a Wellcome Trust 4-year PhD Studentship to use EEG data from both countries along with UK centres to examine whether EEG networks can be used to stratify epilepsy patients according to cognitive comorbidity. Kees Braun has agreed in principle to consider providing clinical epilepsy/epilepsy surgery fellowship opportunities in their respective institutions for Edinburgh based trainees/consultants.

Mark Cunningham (Newcastle) shared work on use of human neocortical tissue for in vitro brain slice electrophysiological studies that permits unprecedented access to the cellular and synaptic elements that determine the ability of neocortical microcircuits to generate organised electrical activity. This resonated with Robin Grant's work on Brain Tumour Related Epilepsy (BTRE) since the mechanism of MTRE is unclear. Mark shared his proposal to create a network of labs in the UK that can work with fresh human brain tissue (obtained from epilepsy patients, but also patients with tumour associated epilepsy) for the primary goal of employing electrophysiological techniques but also other molecular approaches to understand the mechanism surrounding seizure generation in such patients. He is liaising with Robin Grant on establishing Edinburgh as one of the Centres and since the meeting is in the process of writing a pre-application to the MRC to drive funding that would support the formation of such a network. On another, but related note, following his discussions with Robin, Mark Cunningham was approached by ERUK about the possibility of proposing an Expert Workshop. Robin and Mark proposed an event around tumour associated epilepsy with input from basic scientists and clinicians. That proposal was accepted by the Scientific Advisory Committee of the ERUK and they are now planning for this event to take place in March 2016.

We understand that Ben Whalley and Dmitri Rusakov (UCL, London) have initiated discussions on examining the role of astroglial calcium as a mechanistic target for cannabinoids in epilepsy. Ben Whalley has also kindly offered to share his Dravet model with the Edinburgh team. Prof Whalley provided updated information on the open labelled studies on cannabinoids in all forms of childhood refractory epilepsy which was thought useful for colleagues in managing expectations of families being recruited to randomised controlled trials on cannabidiol. Prof Whalley will also liaise with Mike Cousin (Edinburgh) to optimise the genetic manipulation of SV2A expression in his laboratory.

Presentations by Kari Aaberg and Tomi Ajetunomobi on Norwegian and Scottish epilepsy cohort studies highlighted ways of dealing with the challenges of validation of epilepsy diagnosis and working with large data sets and using routine administrative data. Matthew Hunter showcased work on an inception cohort of children with early onset epilepsy showing clear differences in cognition and behaviour soon after diagnosis compared to controls. Bonnie Auyeung, who has experience with eye tracking assessments in children with neurodevelopmental problems, has arranged to help Matthew with the eye-tracking aspect of his work. Michael Yoong will continue to work alongside Matthew to examine the structural substrates of the neuropsychometric profiles of children with early onset epilepsy and healthy controls, and intends to use these data as a platform for a Clinician Scientist Fellowship towards the end of 2015/start of 2016.

Susan Duncan's presentation revealed the limited knowledge on the frequency of epilepsy related death in adults, the spectrum of causes of such death (including SUDEP), and their risk factors. Since the Castang meeting Dr Duncan and colleagues throughout Scotland, have been able to secure a project grant from ERUK to examine this topic. Chris Derry gave an overview of the sleep in epilepsy with a particular emphasis of the potential role of obstructive sleep apnoea in epilepsy which is the subject of a grant application by Dr Derry *et al* to the Chief Scientist Office in Scotland. Colin Reilly's work on psychosocial and educational aspects of active epilepsy in school-aged children raised interesting discussions on how policy could be influenced in order to provide the care needed for such children, especially in different health systems in different countries. Colin's work was useful too as a potential steer for Matthew Hunter's work exploring similar aspects but in pre-school children.

Lieven Lagae's zebrafish models for epilepsy research provided ideas for future research for Catherina Becker and her group who lead a major programme of work on neuroregeneration using zebrafish. Scott Barbaran (San Francisco) shared his ground breaking work on interneuron transplantation as a possible therapy for refractory epilepsy. The work has stimulated discussion between the Chin and Chandran labs on human pleuripotent stem cell-derived cortical neurons - in particular the oxidative stress/NMDAR-mediated excitotoxic injury models - for high throughput screening of medications including cannabinoids.

After presenting her data showing the potential therapeutic effect of statins in mice displaying auditory seizures in intellectual disability, Emily Osterweil (in collaboration with Andy Stanfield and Richard Chin) is considering submitting a project grant application to the Wellcome Trust/MRC for a trial of statins to reduce the incidence of epilepsy in people with Fragile X syndrome (the most common form of inherited intellectual disability). Funding for a study using routine administrative data by looking at the incidence of epilepsy in people on statins compared to those off statins is also being considered.

Ivan Soletsz's work involving optogenic control of epilepsy is informing Alfredo Gonzalez-Sulser's post-doctoral fellowship application to be submitted in Autumn 2015. Alfredo's aim is to examine whether optogenetic activation of the medial septum projections to the hippocampal formation can ameliorate seizures in both in vitro and in vivo epilepsy models. Preliminary work on this topic will be supported by the Muir Maxwell Epilepsy Centre and the Patrick Wild Centre.

David Henshall's talk on miRNAs in epilepsy and oxidative stress provided opportunities for collaboration with Giles Hardingham, whose own research focusses on the role of the NMDA receptor in both of these pathophysiological events.

We are continuing to build links between researchers within Edinburgh and beyond, and develop grant applications and learn from each other's work and methodologies. We thank the Castang Foundation for so generously supporting the meeting which we are confident will take forward the agenda of improving the outcome and quality of life for children and young people affected with disabilities.

Yours sincerely

Richard Chin and Mike Cousin