Association of British Neurologists

Clinical Research Training Fellowship Scheme

ABN Clinical Research Training Fellowships 2016

Following the introduction of the Clinical Research Training Fellowship fund in 2015 we appointed 5 fellows, all of whom have now begun their fellowship and have posters in this exhibition

Thomas Cope, Cambridge **ABN/Patrick Berthoud Charitable Trust**
MEG reveals Speech Processing Delay in Progressive Non Fluent Aphasia

Ingrid Hoeritzauer, Edinburgh **ABN/Patrick Berthoud Charitable Trust**
The Clinical Features and Prognosis of Scan Negative Uro-Neurological Disorders

Nazia Karsan, London **Guarantors of Brain/ABN**
Investigating the premonitory stage of NTG-triggered migraine attacks using fMRI

James Varley, Oxford **Guarantors of Brain/ABN**
The role of adaptive immunity in Parkinsonian syndromes

Grace McMacken, Newcastle **Guarantors of Brain/ABN**
Adrenergic Signalling and Congenital Myasthenic Syndromes

We are delighted to introduce the new 2016 Clinical Research Training fellows. 4 fellowships were awarded for 2016, one each funded by the ABN and the Guarantors of Brain and two by the Patrick Berthoud Charitable Trust.

The scheme and applications were advertised, peer reviewed and selected, following interview, by a panel consisting of ABN members, lay, charity and scientific representatives.

We are grateful to the ABN members, individual donors, charitable trusts and industry partners whose generosity made this possible.

What is the ABN clinical training fellowship scheme?

Set up in 2009 the ABN clinical research training fellowship scheme's objective was to promote research and to develop new links between the funders of research and clinical trainees. It has been successful in supporting several clinical fellowships in collaboration with funding partners. However, charitable funds are inevitably limited and there are excellent trainees who find it difficult or impossible to obtain research funding. Our aim is to strengthen and extend the fellowship scheme by adding ABN funding to that provided by the neurological charities.

What does the CRTF fund involve?

Our aim is to fund at least one fellowship per year at the cost of approximately £60,000 per fellow per year, plus university fees and consumables. Applied to three year research projects, the annual cost should plateau at around £200,000 by the third year. This level of investment cannot be sustained with our current income, hence the need for additional fundraising.

How is the scheme funded?

Following the formal launch of the ABN Clinical Research Training Fellowship Fund we have been encouraged by the understanding and commitment to the fellowship fund demonstrated by our members, our industry partners and by other friends of the fellowship in addition to the longstanding support from other neurological charities.

A fundraising committee, chaired by Prof Dafydd Thomas, was set up to manage the various routes to support for the fellowships. In 2015 the Patrick Berthoud Charitable Trust sponsored a strategic review of ABN's fundraising capabilities. The review identified a number of additional fundraising opportunities and recommended the appointment of in house fundraising resource. We are currently recruiting for this position. We are grateful for the generous donations already received and, with others promised and additional resource in place, believe that we have a good base upon which to build a successful fellowship programme.

How can I support the scheme?

At the 2015 AGM, ABN members voted to allocate an increase in subscriptions rates (which had not increased in 3 years) to the fellowship fund. This was treated as a voluntary contribution and supported by almost 90% of members. Members are encouraged to complete a gift aid form (available from the ABN stand) to optimise any monies donated.

Additional support may be given in many ways. Individual members may be interested in the 2 following tools.

JustGiving

The ABN JustGiving account **www.justgiving.com/A-B-N**, also known as **BRAIN-DR** (British Appeal Into Neurology Dedicated Research) allows people to make immediate donations and also to nominate the Clinical Research Training Fellowship fund as their target charity for running, swimming, cycling events.

easyfundraising.org.uk feel good shopping

Online shoppers may be interested to learn of our **www.easyfundraising.org.uk/causes/abn** link whereby major companies (see overleaf) will donate a percentage of everything you spend via the portal to the CRTF fund.

To learn more about how you could become involved please visit the ABN stand in the exhibition hall. Information may also be obtained via the ABN website **www.abn.org.uk**

Mark Ellul	ABN Clinical Research Training Fellow 2016 University of Liverpool

Improving the diagnosis of encephalitis through examining whole proteome and host gene expression

Encephalitis (inflammation of the brain) is a devastating neurological condition. Some patients die and most others suffer long-term physical or neuropsychological disability. It may be caused by an acute infection or by an autoimmune process, which require very different treatment. However in up to two thirds of cases the cause is unknown, presenting a clinical dilemma. Many of these patients are treated empirically with immunotherapy, but this may be harmful if there is an undetected infection. My fellowship will address the question: can the diagnosis of encephalitis be improved by examining host responses? Previous data have shown that the patterns of cytokines (inflammatory mediators) produced in infectious encephalitis and autoimmune encephalitis differ. In my project, I aim to utilise these differences to develop a test to help guide the management of these challenging patients. I will investigate both gene expression and protein abundance in blood and CSF collected through ENCEPH UK, a large prospective study of encephalitis in adults. Using microarray and mass spectrometry techniques, I will determine the most effective markers to distinguish infectious from autoimmune encephalitis, and develop these into a concise testing strategy to apply to patients with encephalitis of unknown cause. To show that this new approach really works in practice, I will then apply it to new patients recruited through ongoing studies in the Brain Infections UK network. In addition to providing new insights into host responses in encephalitis, my project aims to provide a new strategy to approach this difficult clinical problem.

James Hrastelj	Guarantors of Brain/ABN Clinical Research Training Fellow 2016 Cardiff University

Investigation of gene expression regulation in CSF-derived $CD4^+$ T-cell dysfunction in multiple sclerosis.

Multiple sclerosis (MS) attacks the central nervous system (CNS) and is a leading cause of chronic neurological disability. Our incomplete understanding of what causes MS is a substantial barrier to developing effective treatments. Studies have revealed over 110 genetic variants linked to MS, but the majority do not encode protein and so how they contribute to MS susceptibility is largely unknown. Growing evidence suggests such genetic variants may function by controlling which genes are active or inactive (gene expression), and this project aims to test this by applying a new technology, RNA-seq, to perform a highly sensitive type of analysis.

Gene expression profiles are highly specific to cell type. $CD4^+$T-cells (a cell type that orchestrates immune responses) are central to MS causation. Analysis of the most relevant cell type is vital in gene expression studies, so we will focus, for the first time, on $CD4^+$T-cells taken from the CNS; the pathological focus of MS.

This project will provide new insights into MS disease mechanisms and will also be relevant to all complex diseases by better defining the relationship between genetic variants and gene expression. By identifying novel cellular pathways involved in disease we hope to provide new potential therapeutic targets.

Anne–Catherine Huys	Patrick Berthoud Charitable Trust / ABN Clinical Research Training Fellow 2016 University College London

Attention and functional movement disorders: its role in symptom generation and sense of agency

Patients and doctors frequently face debilitating physical symptoms that remain unexplained and without clear treatment. The majority of these are of "functional" origin, also called psychogenic or psychosomatic. Functional movement disorders are involuntary, abnormal movements, such as tremor or paralysis, that are illogical in terms of classic neurology. Intriguingly, they typically manifest when patients pay attention to them and disappear with distraction. We hypothesise that misdirected attention brings about these abnormal, involuntary movements. Instead of focusing on the goal, on the desired outcome, patients direct their attention onto the movement itself, onto "how" to perform it, thereby hampering its automatic execution. Analogies are common in healthy individuals: awkward, "unnatural" conduct and movements when being watched, effects of performance anxiety, or "choking" in sportspeople. The idea is to imitate the abnormalities of functional movement disorders - impaired movement performance, decreased sense of agency and abnormal brain activation - in unaffected individuals by getting their attention focused on movement execution. Conversely we aim to partially normalise these abnormalities in functional tremor patients by manipulating their attention onto the goal of the movement. Subjects will reach to a goal, while an additional task will manipulate their attention onto the goal or the movement itself. The effect will be analysed in terms of movement performance, sense of agency and brain activation.

If the characteristics of functional movement disorders can be partially recreated in unaffected individuals by getting their attention focused onto the movement, and conversely improved in functional movement disorders by directing the attention onto the goal of the movement, then a misdirected attentional focus could be implicated in functional movement disorders. Changing the focus of attention would therefore offer a simple and likely effective treatment strategy. Wider potential applications include individuals experiencing transient effects of performance anxiety, such as musicians, actors, speakers or sportspeople.

Thomas Massey	Patrick Berthoud Charitable Trust / ABN Clinical Research Training Fellow 2016 Cardiff University

The role of DNA repair in Huntington's Disease pathogenesis: towards new therapeutic targets

Huntington's Disease (HD) is a life-shortening autosomal dominant neurodegenerative disease characterised by chorea, psychiatric disturbance, and dementia. It is caused by a CAG repeat expansion in the *HTT* gene that results predominantly in medium spiny striatal neuron degeneration. There are currently no disease-modifying treatments. Previous work has implicated DNA repair processes in triggering CAG repeat expansion in striatal neurons, thereby accelerating onset of HD. The work proposed here asks two questions: 1. Are DNA repair proteins (in particular FAN1) and their variants directly involved in CAG repeat expansion? 2. Can selective inhibition of DNA repair pathways slow or prevent repeat expansion?

Genetic, cellular and biochemical approaches will be used to address these questions. Novel variants in DNA repair genes associated with especially early or late disease onset will be identified through targetted exome sequencing of a stratified HD population. A robust system for inducing and measuring CAG repeat expansion in model HD cell lines will be established, and then the effects of introducing repair gene variants into this system analysed. Certain DNA repair proteins of interest (including FAN1) will be expressed and purified, and their activities on CAG repeat-containing DNA assayed *in vitro*. We will then investigate whether small molecule inhibitors of DNA repair proteins can inhibit CAG repeat expansion in our cellular system. If inhibition of a specific DNA repair enzyme or pathway can prevent CAG repeat expansion then there is the potential for development of novel therapeutics that could delay or even prevent disease onset.