East of England Neurology Training Fellowships 2016

Neurology training in the East of England deanery is the only neurology training scheme in the UK focused on training in academic neurology. All trainees do 4 years of clinical training, to achieve a CCT, combined with at least one year of research. The expectation is that all trainees will use this year of research to go on to do a PhD or, for those already with PhDs, postdoctoral research. There are 14 clinical neurology posts in total, and there are currently 25 East Anglian Neurology Training Fellows, three Academic Clinical Fellows and one NIHR clinical lecturer; so roughly half of our fellows are in research at any one time.

Clinical Training

Neurological training in East Anglia is flexible and distributed in Addenbrooke's, Norfolk & Norwich, Queen's Romford and the National Hospital for Neurology & Neurosurgery, Queen Square. All trainees spend 8 months at Queen Square, at least 12 months at Addenbrooke's Hospital and the remainder at Romford or Norwich. Clinical and research training are integrated. It is possible, for instance, to do "blocks" of research for 12-18 months separated by clinical attachments. This can be desirable for conducting epidemiological surveys or setting up trials. It is not normally helpful to interrupt a laboratory project in this way. During three years of research, trainees are asked to be on the on-call rota and do up 40 general neurology clinics, often at local district general hospitals.

Research Training

All fellows arriving will be given at least one year of funded research time. For those majority who do not already have a PhD, the expectation is that this year will be used to get pilot data for an application for a research fellowship. This research will be under the supervision of one of the academic neurologists, although joint-supervision from other Cambridge neuroscientists is strongly encouraged. Within neurology, the research themes are multiple sclerosis (Alasdair Coles, Jo Jones, Stephen Sawcer), Huntington's and Parkinson's disease (Roger Barker), neurodegenerative disorders (Giovanna Mallucci, Maria-Grazia Spillantini, Dennis Chan, John O'Brien and James Rowe), stroke (Hugh Markus and Elizabeth Warburton) and head injury (David Menon). Specific research projects are listed overleaf.

Fellows who already have a PhD are welcome on our scheme. But a PhD is not an advantage at interview. We would plan one year of research in order to allow to apply for an intermediate fellowship.

All research students have access to the clinical neuroscience graduate training scheme, which is run by Professor Adrian Carpenter. This includes a regular seminar series, mentorship and training in laboratory and clinical techniques, as well as research management, across all the disciplines working within neurosciences. We also run a specific mentorship scheme for clinicians intending to apply for fellowships (training or intermediate) with mock interviews and proposal-writing workshops. Cambridge Neuroscience (http://www.neuroscience.cam.ac.uk/) is an umbrella organization which brings together all researchers in Cambridge working on the nervous system. Clinical trainees on our fellowship scheme have access to supervision and collaboration from any of these researchers.

Before national recruitment interviews, we would expect you to have approached potential supervisor(s) and, at interview, to be able to discuss your research preferences and future plans.

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Some Specific Research Projects

It may be possible to arrange for you to work on research projects other than these. For instance, you could do research with anyone at Cambridge Neuroscience (http://www.neuroscience.cam.ac.uk/). We will expect you to be able to discuss this at interview, including suggesting an appropriate supervisor.

These projects are funded to start in August 2016:

1. Frontotemporal Dementia And Cortical Microcircuits (James Rowe, Dementia group)

With its integration of cutting-edge research methods and patient-focussed neuroscience, the group is developing new ways to understand how cognitive disorders arise, and how one can assess potential new therapies. This project would examine the impact of frontotemporal dementia on cortical microcircuits, using Cambridge's unique combination of MEG–scanning of brain function with PET-scanning of tau pathology. The clinical fellow would then test the ability to restore brain circuit function with NMDA/Gaba drugs. This project also provides a first-class training in cognitive neurology in a dynamic interdisciplinary team.

2. Understanding novel disease processes underlying cerebral small vessel disease in man and determining whether they can be therapeutically modified (Hugh Markus, Stroke group)

Cerebral small vessel disease (SVD) is the most common cause of vascular dementia. It is also an important pathology contributing to mixed dementia, which accounts for many dementias in older people. Despite its enormous Public Health importance there are few specific treatments for SVD. The current proposal will apply a new dynamic contrast-enhanced MRI protocol (DCE-MRI), which uses an innovative image analysis technique, allowing brain maps of BBB disruption to be obtained in individual patients. It will be combined with ^{11}C-PK11195 PET which allows detection and quantification of neuroinflammation (glial activation) in the cerebral white matter. Using these techniques we will determine the role of BBB permeability and neuroinflammation in the pathogenesis of WMH, and in a proof of concept study we will examine whether therapeutic intervention can modify these pathophysiological processes.

3. New treatments for neurodegenerative disease. (Giovanna Mallucci, Neurodegeneration group)

Giovanna Mallucci's lab has pioneered discoveries about the role of the Unfolded Protein Response (UPR) and its pharmacological manipulation to prevent neurodegeneration. They have used experimental compounds and now repurposed drugs to prevent neurodegeneration in mice. This project will translate these findings into patients with Alzheimer's disease and use PET imaging to measure UPR activation in patients before progressing to clinical trials with drugs targeting the UPR as treatment for dementia.

4. Parkinson's disease (Roger Barker, PD and HD group)

The project would be helping run clinical trials of a first in human stem cell derived dopamine transplant trial in Parkinson's disease (PD) as well as a new gene therapy trial. In addition the candidate also has the potential to undertake basic lab based work looking at inducible neurons (i.e. neurons made by direct transdifferentiation of patient fibroblasts) as a means to study disease pathogenesis in different forms of PD.

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These projects will start in 2017:

Regenerating the optic nerve. (Keith Martin and James Fawcett, Brain Repair Centre)

If damage to the optic nerve or retinal ganglion cells is to be repaired, it is necessary for axons to regenerate from the retina to the brain; at present this is not possible. The project will develop new methods to stimulate axon regeneration from the retina to the brain. The first method will be based on expressing integrins and integrin activators in ganglion cells, which has been dramatically successful in the spinal cord. The second method will be to activate signalling via phosphatidylinositols to stimulate axonal transport and motility. The project will also examine guidance of regenerating axons.

The treatment of multiple sclerosis (Alasdair Coles, Robin Franklin and Joanne Jones, Multiple Sclerosis group)

Having developed one treatment for multiple sclerosis, this group is now looking at potential remyelinating therapies and has started an innovative trial of an agonist of the RXR gamma receptor on people with relapsing-remitting multiple sclerosis, using novel MRI outcome measures. We are examining some of the peripheral immune effects of this drug, especially on regulatory T cells. This project will give training in clinical trials, experimental medicine, advanced imaging techniques and laboratory immunology.

The biology of remyelination (Robin Franklin, Stem Cell Institute)

This project will use a variety of techniques, including single cell sequencing, to explore the heterogeneity of adult CNS stem cells and their contribution to myelin regeneration and plasticity in the adult CNS.

The pathogenesis of Multiple sclerosis (Stephen Sawcer, Multiple Sclerosis group)

In the last decade Genome Wide Association Studies (GWAS) have revolutionised our understanding of susceptibility to multiple sclerosis. In this project you will use this comprehensive genetic map to interrogate the data emerging from the international epigenome project in order to identify the critical immune cell types and biological processes underlying the development of multiple sclerosis. Using the same powerful genetic and epigenetic methods you will also establish factors that influence the course of the disease. These data will enable rational stratification of patients and thereby promote personalised therapy for patients with multiple sclerosis. It is possible the successful applicant will spend one year in Montreal, Canada, with a collaborators.

Novel techniques to promote brain repair (Stefano Pluchino, Multiple Sclerosis group)

We are investigating RNA nanotherapeutics for cell-specific gene silencing as well as directly-induced neural stem cells (iNSCs) for transplantation approaches to animal models of multiple sclerosis, stroke and spinal cord injuries.

Using high field (7T) MRI to understand disease mechanisms in cerebral small vessel disease (Hugh Markus, Stroke group)

The student will take this work further on the new 7T MRI to be installed in Cambridge in June 2016. They will recruit a cohort of patients with small vessel iscahemic disease to determine the underlying disease pathology and how this relates to clinical and other disease features. An important component will be to also image acute lacunar stroke patients to determine what causes acute ischaemic in this patient group and

the role of thrombosis versus haemodynamic compromise. This has important implications for optimising the use of thrombolytic or other therapies in the acute setting in this patient group.

PET imaging of anti-NMDAR encephalopathy (Alasdair Coles and David Menon, Neurointensive Care Groups)

There is increasing recognition of the role of anti-NMDA receptor-mediated encephalitis as a cause of neurological disease, ranging from subtle neuropsychiatric presentation to severe disease presenting with seizures and coma. While the measurement of antibody levels in blood and CSF provide a diagnostic tool, we have no specific imaging biomarkers to support diagnosis, follow disease activity, and monitor therapy response. This project will develop PET imaging tools to address these issues, and correlate these with clinical features, structural and functional MRI, and clinical outcome.

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