

South Yorkshire Foundation School

DESCRIPTION OF A F2 ACADEMIC FOUNDATION PLACEMENT

Year of Placement: August 2009 to July 2010

This form should be completed by Clinical Academics who wish to host a F2 Academic Foundation trainee for a 4 month academic research placement during the 12 month period August 2009 to July 2010. This form will be given to potential F2 Academic Trainees in order to inform their preferred placement choices and will be on the website. This form is 2 A4 sides, and should not be extended.

Educational Supervisor(s) For F2 Academic Placement: Professor Pamela Shaw

Nominated Foundation Programme Director: Mr Jonathan Beard

Academic Unit or Group: Academic Neurology Unit

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Title of Project for the F2 Academic Placement:

Identification of new therapeutic approaches for the protection of motor neurones using experimental models of disease

Where will the Project for the F2 Academic Placement be Based?

Academic Neurology Unit, E Floor Medical School

Description of the Academic Project for the F2 Academic Placement:

Background:

Motor neuron disease (MND) is amongst the most common of adult-onset neurodegenerative diseases, with a prevalence of 5-6 per 100,000. Patients typically develop relentless progressive neuromuscular failure resulting from combined degeneration of both upper and lower motor neurone groups in the motor cortex, brainstem and spinal cord. The rate of disease progression varies between individuals, but the average survival is only 2-3 years from symptom onset. Several mechanisms contribute to motor neurone injury and cell death in MND including genetic alterations such as SOD1 mutations; oxidative stress and mitochondrial dysfunction. Cell culture models established in the host laboratory provide powerful tools to investigate the molecular mechanisms of motor neurone injury and to evaluate potential neuroprotective therapies. Models have been established for mutant SOD1 toxicity; oxidative stress; mitochondrial dysfunction and the anti-oxidant protective response using motor neuronal cells (NSC34) which can be propagated in tissue culture. The relevant neuronal stress can be quantified using measurements of cellular fluorescence. These models can be used to screen drug libraries to identify compounds which have neuroprotective effects.

Project Aims and Methodologies:

Aim of the project: Using a cellular model of motor neuronal oxidative stress, to establish which drugs (from a library of 2000 compounds) are the best candidates as potential neuroprotective agents. These "hit" compounds will then be investigated in more detail to investigate the potency and optimal dose for neuroprotection *in vitro*. The properties of the compounds will also be researched to determine whether they are good candidates for eventual use in human patients. The most promising of these compounds will be evaluated in a murine model of MND and the student will be able to observe the methods used in these pre-clinical studies.

Methods: The F2 trainee will work with a multidisciplinary research team of clinicians and neuroscientists. Skills learned will include cell culture; cellular imaging; toxicity assays using fluorescent read-outs; *in vitro* pharmacological principles; experience in experimental design; statistical analysis and report writing. He/she will also have the opportunity to observe neuroprotective experiments using an *in vivo* model.

Value of the project: The F2 trainee will gain an understanding of the "bench to bedside" approach to neuroprotective therapies for patients suffering from neurodegenerative diseases. This is based on harnessing scientific approaches to understand mechanisms of cellular injury. These mechanisms can

then be modelled in the laboratory and protective therapeutic strategies devised with the most promising agents being tested in *in vivo* models. The project will generate experience which will be valuable for subsequent steps in the academic training pathway and data contributing to a publication.

Description of Training the F2 Academic Trainee Will Receive and Access to Research Facilities:

- The F2 trainee will receive basic training in multiple laboratory techniques as outlined above, as well as the statistical methods for analysing and presenting laboratory data.
- He/ she will receive guidance on performing a review of the relevant clinical and scientific literature and preparation of a research report .
- The trainee will have the opportunity to see in clinic patients whose medical conditions are the focus of the research project.
- Guidance will be given on how to prepare for the next steps in the clinical academic training pathway.

Facilities: Bench space will be provided within the Academic Neurology Unit laboratories on E floor of the Medical School. All equipment required for the project is available within the host laboratories. The F2 doctor will have access to a computer and relevant software programmes.

References (Only Include Top 5):

1. Mitochondrial dysfunction in a cell culture model of familial amyotrophic lateral sclerosis. FM Menzies, MR Cookson, RW Taylor, DM Turnbull, L Dong, DA Figlewicz, PJ Shaw. *Brain* 125:1522-1533;2002.
2. Characterisation of the caspase cascade in a cell culture model of SOD1-related familial amyotrophic lateral sclerosis: expression activation and therapeutic effects of inhibition. S Sathasivam, AJ Grierson, PJ Shaw. *Neuropathol Appl Neurobiol* 31:467-485;2005.
3. Mutant SOD1 alters the motor neurone transcriptome: implications for familial amyotrophic lateral sclerosis. J Kirby, PR Heath, S Allen, E Halligan, C A Loynes, C Wood-Allum, H Holden, J Lunec, PJ Shaw. *Brain* 128:1686-1706;2005.
4. Molecular and cellular pathways of neurodegeneration in motor neurone disease (MND). PJ Shaw. *J Neurol Neurosurg Psychiatry* 76:1046-1057;2005.
5. Impairment of mitochondrial anti-oxidant defence in SOD1 related motor neuron injury and amelioration by ebselen. C Wood Allum, SC Barber, J Kirby, P Heath, H Holden, S Allen, T Beaujeux, SHE Alexson, PG Ince, PJ Shaw. *Brain* 129:1693-1709;2006.

Outline of the F2 Academic Placement Project Plan (including literature review, presentation and writing up and assessment of the placement):

Month 1:

- Literature review and preparation of the background, hypothesis and aims of research report.
- Introduction by nominated laboratory member of staff to the scientific techniques required for the project.
- Compilation of a list of candidate drugs to be tested in the cellular experimental model system.

Months 2 and 3

- Writing of the Methodology section of research report.
- Completion of experimental phase of the project. Identification of drugs which may have a protective effect.

Month 3:

- Optimisation of the dose of neuroprotective drugs using the cellular model system.
- Literature search on previous use of these compounds *in vivo*.
- Observation of *in vivo* testing of neuroprotective agent in an *in vivo* model of motor neuron degeneration.
- Visit the specialist Neuromuscular disorders clinic to gain experience of patients with neurodegenerative disorders.

Month 4:

- Completion of experimental work and data analysis.
- Completion of research report
- Presentation of research to the staff and students in the Academic Neurology Unit.