PROton Spectroscopy Metabolomics In ALS SErum and CSF

The PROMISES Project

Investigator: Dr Martin R. Turner,
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Grant: 143 000€

Project duration: Two years

There is no test for the devastating neurodegenerative disorder amyotrophic lateral sclerosis (ALS). Diagnosis depends on the opinion of an experienced neurologist and the exclusion of other conditions. As well as shortening diagnostic delay, the development of treatments requires the discovery of specific disease markers. Such 'biomarkers' might reveal new pathways containing novel drug targets, or be used to more rapidly assess the response to a candidate drug, or help to individualize planning of care.

The cerebrospinal fluid (CSF) that bathes the brain and spinal cord is a potential source of such biomarkers and substances may also be detected within the blood (serum). As part of the Oxford Study of Biomarkers in Motor Neuron Disease ('BioMOx'), CSF and serum has been collected from group of ALS patients of varying sub-types and speeds of progression, and at multiple time points in many of them. This project will analyse these samples using a sensitive technique called Proton Spectroscopy Metabolomics.

This process can identify large numbers of substances from a tiny amount of fluid, which can be compared with samples donated by healthy volunteers, thus identifying which ones are most linked to ALS. Immune inflammatory responses have been shown to occur in ALS patients' brain and spinal cords, though it is not clear whether these have a primary destructive or 'rescue' role. The project will also perform specific measurements of substances linked to this inflammatory response, and markers of cell loss, within the CSF and serum to identify a specific 'signature' for ALS.

Technical overview of Proton Spectroscopy Metabolomics

This involves the acquisition of a proton nuclear magnetic resonance (^{1}H-NMR) spectrum from the sample, and subsequent principal components analysis (PCA). This enables subtle differences between the spectra from different sub-groups to be identified, with minimal sample preparation required and relatively low cost. Unlike other analytical methods such as mass spectrometry, it is a non-destructive technique so that multiple analyses can be carried out on a single sample if necessary. This metabolomic approach requires no prior assumptions or knowledge. Multivariate pattern recognition can identify distinct patterns of metabolites whose variation as a whole is characteristic of the disease, rather than requiring identification of a unique biomarker.

Martin R. Turner is a Consultant Neurologist and Medical Research Council & Motor Neuron Disease Association Lady Edith Wolfson Clinician Scientist Fellow. He was recipient of the 2012 Young Investigator Award by the European Network for the Cure of ALS (ENCALS). He is Co-Director of the Oxford MND Care and Research Centre (www.oxfordmnd.net).

This research will be conducted at the Oxford University Nuffield Department of Clinical Neurosciences, in collaboration with Dr Nicola Sibson (Gray Institute for Radiation Oncology & Biology) and Dr Daniel Anthony (Department of Pharmacology).

Recent publications relating to biomarker research:

- Menke RAL, Abraham I, Thiel CS, Filippini N, Knight S, Talbot K, **Turner MR**. Fractional anisotropy in the posterior limb of the internal capsule as a prognostic marker in amyotrophic lateral sclerosis. *Archives of Neurology* 2012; in press.
- Otto M, Bowser R, **Turner MR**, Berry J, Brettschneider J, Connor J, Costa J, Cudkowicz M, Glass J, Jahn O, Lehnert S, Malaspina A, Parnetti L, Petzold A, Shaw P, Sherman A, Steinacker P, Süßmuth S, Teunissen T, Tumani H, Wuolikainen A, Ludolph A. Roadmap and standard operating procedures for biobanking and discovery of neurochemical markers in ALS. *Amyotrophic Lateral Sclerosis* 2012; 13: 1-10.
- Evans MC, Modo M, Talbot K, Sibson N, **Turner MR**. Magnetic resonance imaging of pathological processes in rodent models of amyotrophic lateral sclerosis. *Amyotrophic Lateral Sclerosis* 2012; 13: 288-301.
- Bowser R, **Turner MR**, Shefner J. Biomarkers in amyotrophic lateral sclerosis: opportunities and limitations. *Nature Reviews Neurology* 2011; 7: 631-8.
- Kiernan MC, Vucic S, Cheah B, **Turner MR**, Eisen A, Hardiman O, Burrell J, Zoing MC. Amyotrophic Lateral Sclerosis. *Lancet* 2011; 377: 942-55.
- Douaud G, Filippini N, Knight S, **Turner MR**. Integration of structural and functional MRI in amyotrophic lateral sclerosis. *Brain* 2011; 134: 3467-76.