CAF/24/13 - Identifying early theragnostic targets for motor neuron disease

"Theragnostic" (from ***thera***peutic and di***agnostic***) is a term used frequently in the cancer research field that refers to a treatment strategy that combines therapeutics with diagnostics – this is a very powerful approach in diseases where the very molecules we are looking for as a sign of the disease are the same ones that affect symptoms and disease progression. An example of this in cancer is a molecule called PD-1, which we look for in tumours, and if there is a sufficiently high amount of it in the tumour, a therapy targeting PD-1 is given as the primary therapeutic strategy. Using this principle, the goal of this proposal is to identify such targets in MND clinical research. Currently there are none. This will be achieved through the implementation of three interlinked aims exploiting my host lab's clinical pathology knowledge, along with my expertise in human tissue handling, and digital and molecular pathology techniques to develop theragnostic targets for MND.

The mainstay of theragnostic targeting in the cancer research field is based around activation of a particular inflammatory cell called the "T-cell" – so called because they mature in the thymus, a vital organ for the immune system. In many diseases these cells have become inactivated by our immune system and are not working properly. If these cells can be re-activated, they can then clear the protein clumps that accumulate in the brain and spinal cord. Indeed, this has been shown in animal models of Alzheimer's disease.

The advantage of profiling peripheral tissues over blood samples or brain tissue, is that regulation of these inflammatory cells occurs specifically in these organs (e.g. the gut and skin), and so the association between T-cell de-activation and MND-specific pathology can be directly assessed. Furthermore, people with sporadic MND are unlikely to have had pre-symptomatic blood or brain tissue sampling, whereas we already have a cohort of pre-symptomatic peripheral tissues from people with MND. These tissues have been taken during life are made available through the NHS Biorepositories for research use and include tissues such as gut and skin biopsies. Linked tissue- and MND pathology-specific inflammatory cell profiles generated from this study could then be translated to blood tests or even peripheral tissue biopsy, without the need for invasive brain or cerebral spinal fluid sampling.

To our knowledge, this is a completely novel approach to identify new therapeutic targets and biomarkers for MND and, if successful, provides a treatment strategy that could be beneficial for disease prevention as well as treatment of people with advanced symptoms.