Project title:

Multi-omic analysis of CNS-draining lymph nodes

Supervision:

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Summary:

Background
Analysis of immunologic and inflammatory changes in the CNS is critical for understanding a range of neurologic, including neurodegenerative, disease. However, it is hampered substantially by issues of access to tissue, especially repeated access. There is increasing evidence that the cervical lymph node chain drains CNS lymph. We have recently shown that fine-needle analysis of cervical chain lymph nodes can provide high resolution data on both the cellular content (by scRNAseq) and soluble molecules (by O-Link), measuring features of relevance to CNS homeostasis and disease. Importantly this procedure is safe and very well tolerated, allowing for repeated measures.

Aims
We intend to expand this FNA protocol to explore key parameters of age, sex and stability in a range of healthy donors, using 10x scRNASeq/ATACseq and CITE-seq protocols and further proteomic analysis (including O-Link). Having further validated the system and in particular defined the impact of age, we will address multi-omic changes in a well-defined cohort of patients with neurodegenerative disease presenting as Alzheimers dementia.

Key outputs
This project will provide an atlas of CNS-draining lymph nodes including the environment of key local soluble mediators and biomarkers. It will provide a key resource for studies of neurodegeneration by generation of a substantial dataset across a range of healthy donors. It will also show proof-of-principle at least of the utility of such approaches to disease cohorts and potentially generate key data for larger prospective cohort studies using this minimally invasive approach.

Alignment with therapeutic area and key scientific theme(s):

This is a new enabling platform technology/approach providing a rich data source that aligns well with the 3 key areas outlined:

- Role of the CNS and peripheral immune system in neurodegeneration.
- Using data from human samples, identify potential mechanisms for drug intervention that differ based on disease stage.

- Discovery and validation of biomarkers (from human samples) reflecting various pathophysiologies that can be used to predict patient phenotype and track response to therapy.

Project delivery:

The project is designed around developing and evaluating this new technology/approach. We have already data from the pilot project and a further second study that shows the potential of the sampling approach – we now aim to exploit this important opportunity to see how effectively we can link sampling with genomic/proteomic approaches at scale to define its clinical utility, especially as applied to stratification for trials and interventions. The data science element is inherent in the analysis of the types of data we aim to provide and will be supported strongly by the team of supervisors. We will define clear milestones for progression based on sampling numbers and data types – we can do this effectively based on the experience accrued in the preceding studies. As a broad outline we will train the fellow and establish datasets in year one for the healthy cohort evaluation and then address the disease cohort in more depth in year 2, with year 3 devoted to further data analysis and functional validation of key cellular and molecular hits (eg by further flow studies/ELISA).

Research environment:

The studies are between the departments of medicine, psychiatry and neurology and based on existing strong collaboration around this approach. This was originally developed for the study of autoimmune encephalitis but now we aim to expand this based on the emerging data (see papers below). Some clinical time (around 20% overall) for recruitment and sampling would be suitably embedded in the programme, mimicking previous experience running the scheme for Wellcome Trust funded fellowships at Oxford.

Neurodegenerative fluid biomarkers are enriched in human cervical lymph nodes.
Al-Diwani A, Provine NM, Murchison A, Laban R, Swann OJ, Koychev I, Sheerin F, Da Mesquita S, Heslegrave A, Zetterberg H, Klenerman P, Irani SR.Brain. 2024 Oct 21:awae329. doi: 10.1093/brain/awae329. Online ahead of print.PMID: 39432679

Fine needle aspiration of human lymph nodes reveals cell populations and soluble interactors pivotal to immunological priming.
Provine NM, Al-Diwani A, Agarwal D, Dooley K, Heslington A, Murchison AG, Garner LC, Sheerin F, Klenerman P, Irani SR.Eur J Immunol. 2024 May;54(5):e2350872. doi: 10.1002/eji.202350872. Epub 2024 Feb 22.PMID: 38388988