TRAM (Train and Retain Academic Musculoskeletal clinicians)
MB-PhD Project Summary

PhD project Title
The insula: a key to behavioural comorbidity in inflammatory arthritis?

PhD supervisors (please provide name, affiliation and email) *[At least two supervisors]*	
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Background

Among the many significant challenges faced by patients living with inflammatory arthritis are features that are often referred to collectively as sickness behaviour, namely: low mood/depression, fatigue and cognitive difficulties ("brain fog"). Along with pain, these are the most commanding symptoms described by patients. They also increase the burden of underlying disease upon the individual, their family and wider socioeconomic community. More specifically, they mediate a significantly negative impact on treatment adherence, response, and disease outcomes. These symptoms are especially prominent in people with rheumatoid arthritis (RA). For example, depression has a prevalence of around 20%, chronic pain 50% and fatigue 70%. This high level of additional symptom burden provokes significant negative effects in the co-existing arthritis in terms of functional progression and treatment responses. Notably, expensive RA biological therapies are 30% less effective in the context of comorbid depression. Combined this leads to an increased likelihood of substantial disability and mortality. Understanding the mechanisms underpinning sickness behaviour has proved to be elusive because of the difficulty in disambiguating the causal from coincidental relationships. However, this is changing.

There is now strong evidence for a bi-directional relationship between brain and periphery in the context of systemic inflammation. While the impact of peripheral inflammation on the brain has been recognized for some time (Harrison et al, 2009) more recent data show the brain regulating peripheral immunity (Koren et al, 2021).

A key brain region involved in both responding to the body's physiological state e.g. peripheral inflammation and in controlling the peripheral response is the insular cortex.

This project affords an opportunity to explore this in a mouse model of inflammatory arthritis and to dissect potential neurobiological mechanisms that underpin these common and difficult-to-treat comorbidities.

Aims

Using the CAIA model of inflammatory arthritis, this project aims to answer the following research questions:

What are the cellular and molecular responses to systemic inflammation in the insula?

How do these insular responses relate to mood and fatigue-relevant behaviours?

How does specific cytokine inhibition, effective in RA, affect molecular and cellular response in the insula and how do these relate to behavioural changes?

Training and experience provided *[Include types of methodologies that will be employed]*

The studentship will provide an integrated training opportunity in preclinical models of disease, state-of-the-art molecular techniques and the interface between the brain and periphery compartments. Specifically, it will provide exposure to and training in:

Pre-clinical models of rheumatoid arthritis

Spatial transcriptomics and associated bio-informatics

Microscopy and cellular morphology and characterisation

Immune-mediated behaviour

Disease-relevant behavioural analysis (e.g. anxiety, motivation, learning & memory)

Supported by a team with active grant income >£5M and supervision experience of >20 PhD students. The successful student will be embedded in a unique interdisciplinary group (n=20) of clinical immunobiology researchers and neuroscientists (https://www.gla.ac.uk/researchinstitutes/iii/staff/jonathancavanagh/neuroinflammatoryphenotypesresearchgroup/)
(https://www.gla.ac.uk/researchinstitutes/neurosciencepsychology/staff/mickcraig/#)

Expected outcomes

The studentship will be integrated in a multi-disciplinary team and, as such, will be included in research outputs such as posters for national/international meetings and peer-reviewed data publications. The data generated in these studies will form the basis for developing new approaches for targeting these areas of unmet clinical need. These will include refining the models and linking to human-relevant behavioural change in order to dissect key mechanistic pathways.

References

Harrison NA, Brydon L, Walker C, Gray MA, Steptoe A, Dolan RJ and Critchley HD (2009). Neural origins of human sickness in interoceptive responses to inflammation. Biol Psychiatry 66 415-422

Koren T, et al Insular cortex neurons encode and retrieve specific immune responses. Cell 184 1-14.