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

PhD project Title
Exploiting leading edge 7 Tesla MRI metabolic imaging of the brain to understand rheumatoid arthritis pain

PhD supervisors (please provide name, affiliation and email) *[At least two supervisors]*	
1. Neil Basu, Professor of Musculoskeletal Medicine & Vasculitis, neil.basu@glasgow.ac.uk	2. Jonathan Cavanagh, Professor of Psychiatry, Jonathan.cavanagh@glasgow.ac.uk
3. Graeme Keith, Research Associate, Centre of Cognitive-Neuroimaging, Graeme.Keith@glasgow.ac.uk	4.

Background
The revolution in rheumatoid arthritis (RA) therapeutics has been transformative for many patient outcomes and yet most patients continue to experience significant pain. Strikingly, even those who achieve full disease remission with state-of-the-art biological treatments report substantially higher levels of pain when compared to the general population. Such disconnect presents one of the greatest contemporary challenges to the care of patients with RA. We believe that RA is a mixed pain state i.e. pain pathways exist in addition to established musculoskeletal based inflammatory mechanisms. In particular, the central nervous system (CNS) may have an important role in determining RA pain. Recently our group were the first to delineate distinct neurobiological pain pathways in the brains of RA patients (e.g. Default Mode Network-Insula) by employing 3T brain MRI. We now want to understand the metabolic abnormalities which underpin these brain pathways. Unlike 3T MRI, ultra-high resolution 7T can distinguish the resonance of key neurotransmitters (e.g. glutamate) from other metabolites. In Glasgow, we benefit from the only clinical environment 7T MRI scanner in the UK and, to our knowledge, are the only group in the world to research scan the brains of RA patients using this technology. By harnessing this capacity to measure brain metabolic measures of our established RA pain pathways and then relating these measures back to the patient's pain experience (employing patient reported outcomes and quantitative sensory testing), we expect to inform the development/repurposing of new analgesics for this (and other) musculoskeletal clinical populations.

Aims
1. To identify abnormal levels of metabolites (e.g. glutamate) within established RA pain processing regions of the brain (e.g. insula) 2. Cross-sectionally relate brain metabolite levels to patient reported and physiological measures of pain

3. Longitudinally relate changes in brain metabolite levels to changes in patient reported and physiological measures of pain following an analgesic intervention

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

The studentship will offer state of the art training in clinical research and imaging methodology.

Specifically, they will acquire proficiency in:

The application and analysis of MRI
Metabolic imaging sequencing
Statistical analyses
Clinical research design, governance and delivery

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 musculoskeletal researchers and neuroscientists (https://www.gla.ac.uk/researchinstitutes/iii/staff/neilbasu/neuroinflammatoryphenotypesresearchgroup/) based at University of Glasgow's Imaging Centre of Excellence (https://www.gla.ac.uk/colleges/mvls/ice/).

Expected outcomes

This studentship will leverage our active portfolio of pre-funded 7T MRI RA studies in order to generate a discovery data set which will include pain questionnaires and conventional MR brain spectroscopy and include longitudinal measures following analgesic interventions (including anti-TNF, vagal nerve stimulation and JAK inhibition). These preliminary data will then inform a newly developed RA cohort, including deeper pain phenotyping (e.g. quantitative sensory testing) and novel metabolic 7T brain imaging paradigms (e.g. CEST) in order to extend brain coverage. This will enable the testing of specific hypotheses to aid our pursuit of new pain alleviating drug targets.

References

Schrepf A, Kaplan CM, Ichesco E, Larkin T, Harte S, Harris RE, Murray A, Waiter G, Clauw D & Basu N. A multi-modal MRI study of the central response to inflammation in rheumatoid arthritis. Nature Communications 2018; 9, Article number: 2243.

Basu N, Kaplan CM, Ichesco E, Larkin T, Harris RE, Murray A, Waiter G & Clauw DJ. Neurobiological features of fibromyalgia are also present among rheumatoid arthritis patients. Arthritis & Rheumatology 2018; 70(7):1000-1007