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

PhD project Title
Epigenetic stratification of rheumatoid arthritis patients for response to biological Disease Modifying anti-Rheumatic Drugs

PhD supervisors (please provide name, affiliation and email) *[At least two supervisors]*	
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Background
Rheumatoid Arthritis (RA) is the commonest inflammatory polyarthritis in the UK, affecting >600,000 people. It causes pain, stiffness and disability, and is associated with significant co-morbidity and premature mortality. It is also a major cause of work-related unemployment and incurs enormous costs for patients, society and the NHS. For instance, biological disease-modifying anti-rheumatic drugs (bDMARDs) alone costs NHS Scotland approximately £25-30M pa. Unfortunately, up to 40% of patients fail to respond to their first bDMARD, and only a minority of patients attain low disease activity or clinical remission. Many of these patients do subsequently respond to an alternative bDMARD in a different class. The ability to predict therapy response would enhance 'quality-of-life' for the patients and ease the burden of this disease on society and the NHS, while being able to identify those who won't respond will avoid unnecessary exposure to unhelpful expensive and potentially toxic therapy and facilitate earlier use of potentially more effective treatments. The ability to stratify patients *a priori* into responders and non-responders would therefore be an invaluable clinical tool to select patients in whom one biological agent may confer advantage over another. Traditional biomarker approaches have to date failed to deliver validated biomarkers of clinical utility. Epigenetic chromosomal conformational signatures (CCSs) represent a novel class of stable blood-based biomarkers, which reflect the primary early step in a cascade of gene dysregulation preceding epigenetic changes in DNA methylation, histone modifications and transcription initiation. Furthermore, the easily assessed binary readout of CCSs (i.e. the presence or absence of the defined loops) means this modality has several potential advantages as predictive biomarkers over other single modality techniques. In a recent study, we have evaluated a molecular prognostic biomarker in early RA patients and identified a CCS that can differentiate conventional DMARD (cDMARD) responders from non-

responders. We now plan to test if the same modality to can predict whether patients will or will not respond to their first bDMARD.

Aims

Our overall aim is to create prognostic biomarkers that can be used at multiple points during a patient's clinical journey to help choose the optimal therapy for that individual at that time. However, the specific focus of this project is to generate an epigenetic biomarker signature that can be used in a clinical laboratory-based test to predict whether or not patients who have failed a cDMARDs will respond to specific bDMARDs. Importantly, the development of these tests will enable clinicians to identify the most optimal treatment regime for their patients.

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

The PhD student will receive training in a range of the key skills, both 'Quantitative' and 'Interdisciplinary'. In brief, this project will require the student to become proficient in the interrogation of clinical outcomes in RA, and the generation and statistical evaluation of 'omic' data (transcriptional, epigenetic) entailing high order bioinformatics skills. Basic cellular and molecular pathology techniques will be attained; namely the functional characterization of the epigenetic motif upon immune cell function that will require large scale data analysis, building on the skills acquired trhought the studentship. Finally, and most importantly, at the end of this studentship, the student will have all of the necessary skills to seamlessly transition between biological, clinical, and computational elements of biomedical science.

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 high-impact publications. The data generated in these studies will form the basis for developing new precision medicine tests and approaches that can define the correct treatment for individual patients; a current area of unmet clinical need.

Key References

1. Porter D, van Melckebeke J, Dale J, Messow CM, McConnachie A, Walker A, et al. Tumour necrosis factor inhibition versus rituximab for patients with rheumatoid arthritis who require biological treatment (ORBIT): an open-label, randomised controlled, non-inferiority, trial. The Lancet. 2016 Jul 16;388(10041):239–47.
2. Carini C, Hunter E, Ramadass AS, Green J, Akoulitchev A, McInnes IB, et al. Chromosome conformation signatures define predictive markers of inadequate response to methotrexate in early rheumatoid arthritis. Journal of Translational Medicine. 2018 Jan 29;16(1).