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DOCTORAL SCHOOL

DOCTORAL THESIS

Personalised predictive medicine in the outcomes of biologic treatments in degenerative joint conditions

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INTRODUCTION: Monomeric C-reactive protein (mCRP), the subunit of pentameric CRP has been shown to be a critical molecule mediating many acute and chronic pathological responses to inflammation. Having a full understanding of the role of mCRP will have a huge impact on potential diagnostic and prognostic advances, as well as potential therapeutic benefits in Osteoarthritis. More recent cellular therapies such as Micro-Fragmented Adipose Tissue are gaining increasing interest to target and revert the underlying disease process. Artificial intelligence (AI) algorithms could improve clinical accuracy in deciding the most appropriate stratified treatment approach, increasing the percentage of individuals designed as “super responders”.

AIMS OF THE THESIS: Discuss the current perspectives of mCRP and their use in the prognosis of disease. To compare the efficacy of MFAT or MFAT combined with PRP for the treatment of Hip Osteoarthritis. To investigate an AI method (using traditional and quantum computing) to identify the most appropriate candidates for biological treatment for knee osteoarthritis

CHAPTER 1- MONOMERIC C-REACTIVE PROTEIN: The activity of mCRP was originally thought to be due to azide contamination but more recently it has been shown to be an important protein having a fundamental role in moderating pathobiological effects of inflammation. Here, the role of mCRP in pathological disease processes is described. We focus on the current opinions on potential diagnosis and prognosis based upon modulation of systemic blood levels of mCRP and aim to discuss the potential of small molecules as mCRP-blocking agents or inhibitors of dissociation.

Undoubtedly, a greater understanding of the role of mCRP in progression of disease will impact significantly on novel precision-based therapeutics.

CHAPTER 2 - MFAT IN HIP OSTEOARTHRITIS: Hip OA contributes significantly to reduced quality of life in association with lower mobility and is responsible for many person years loss of active work. Biological intra-articular injections have effectively been demonstrated to reduce pain, increase ability, and slow down tissue degeneration. In this work approximately 150 individuals with OA of the hip (grade 1 to 4), were given micronized micro-fragmented adipose tissue (MFAT), or in some cases a mixture of this with blood-derived platelet-rich plasma (PRP). A notable improvement in the OA visual analogue scale (VAS), in addition to the Oxford hip score (OHS) was found. Approximately 60% of participants had an increase in VAS more than 20 points in both treatments. Therefore, MFAT/PRP combination could play a positive role in the treatment of hip osteoarthritis. This may be crucial for patients with low BMIs, where the use of this combination of biologics may be able to compensate for the difficulty in acquiring enough MFAT for treatment.

CHAPTER 3 - PRECISION MEDICINE IN BIOLOGIC TREATMENT OF KNEE OA: OA biologicals are a new offering in the field and may be used as an adjunct to standard treatment. Identifying the most appropriate individuals, who will respond the best is of critical importance. 300 individuals received MFAT during a recruitment period of 24 months and full clinical information together with Oxford Knee Score (OKS; 1 year) were correlated and analysed in order to predict the 12-month outcome using standard regressors (random forest). This “algorithm” seems quite powerful and can predict response to OKS changes following 1 year in our patient group.

CHAPTER 4 - QUANTUM ENHANCED PRECISION MEDICINE IN KNEE OA: Quantum machine learning uses experimental medicine combined with digital technology hypothesising that it can support data-driven clinical determinations stratifying treatment for all stages of but particularly advanced osteoarthritis. We retrospectively trained and validated our application on a dataset of 170 patients eligible for knee arthroplasty which over the course of 2 years, micro-fragmented fat was injected one time. We trained a Quantum Neural Network Classifier to predict response from non-response in terms of pain and function. Our application showed high sensitivity but low specificity. Further research on Quantum Neural Networks and precision_KNEE_QNN is needed. We propose that this Quantum Machine Learning algorithm be tested on other therapies. Large unstructured datasets, such as those from national health systems, are best suited for Quantum Machine Learning. These real-world datasets require a new and novel approach so that they can be used for personalised precision medicine.

DISCUSSION: The use of biological treatments is of particular interest because of the global burden of OA. MFAT is an interesting candidate because it is accessible to majority of people. In our study of hip OA, both the MFAT and MFAT+PRP groups showed a significant improvement in joint function OHS after 12 months. These findings highlight the importance of using predictive models to identify the best candidates for biological cell-based therapies. We suggest that these models support clinical care so that both clinicians and patients can make good choices when navigating treatment pathways. The role of biomarkers in OA has been explored. This provides an opportunity to consider the use of predictive models in both diagnosis and treatment strategies. Although our precision medicine tools have both shown promising results, they need to be further validated.

This thesis and the articles included provide excellent opportunities for these precision medicine modelling tools to be applied to larger datasets to validate responder rates and target treatment more specifically towards individuals. Further research should also be directed towards the application of responses in regard to functional outcomes and quality of life assessments.