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Review

The hallmarks of osteoarthritis and the potential to develop personalised disease-modifying pharmacological therapeutics

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SUMMARY

Osteoarthritis (OA) is an age-related condition and the leading cause of pain, disability and shortening of adult working life in the UK. The incidence of OA increases with age, with 25% of the over 50s population having OA of the knee. Despite promising preclinical data covering various molecule classes, there is regrettably at present no approved disease-modifying OA drugs (DMOADs). With the advent of next generation sequencing technologies, other therapeutic areas, in particular oncology, have experienced a paradigm shift towards defining disease by its molecular composition. This paradigm shift has enabled high resolution patient stratification and supported the emergence of personalised or precision medicines. In this review we evaluate the potential for the development of OA therapeutics to undergo a similar paradigm shift given that OA is increasingly being recognised as a heterogeneous disease affecting multiple joint tissues. We highlight the evidence for the role of these tissues in OA pathology as different "hallmarks" of OA biology and review the opportunities to identify and develop targeted disease-modifying pharmacological therapeutics. Finally, we consider whether it is feasible to expect the emergence of personalised disease-modifying medicines for patients with OA and how this might be achieved.

The unmet clinical need in OA for a personalised disease-modifying therapeutic

Osteoarthritis (OA) is an age-related condition and the leading cause of pain, disability and shortening of adult working life in the UK. The incidence of OA increases with age, with 25% of the over 50s population having OA of the knee[1]. Despite this prevalence, and in contrast to rheumatoid arthritis[2], there are currently no effective Disease-Modifying OA Drugs (DMOADs) which have met regulatory approval.

Clinical management of OA typically entails a limited combination of pharmacological and non-pharmacological treatment options to reduce pain and increase tolerance for functional activity[2]. Unfortunately, Non-Steroidal Anti-Inflammatory Drugs (NSAIDs) either do not modify the disease course or have been associated with serious renal and cardiovascular effects and gastrointestinal bleeding in the clinic[3]. Patients with knee OA can be offered intra-articular corticosteroid injections which can be effective in some patients in providing pain relief, but the benefit is short-lived and frequent injections can damage the articular cartilage. Recent studies have reported structural benefits with dietary Glucosamine supplementation in patients with knee OA[4]. Some of these supplements therefore hold great promise, and may in the future be part of a holistic treatment approach. However, currently they are not recommended by OARSI and ACR[5]. Ultimately therefore, many patients with knee or hip OA will undergo surgery to replace the diseased joint.

In stark contrast, our understanding and subsequent treatment of cancer has changed dramatically over the last 10–15 years. The emergence of molecular biology combined with next generation sequencing approaches has enabled a paradigm shift from labelling cancer by anatomical location and tissue type, to being defined by its molecular genetics phenotype. Importantly, this paradigm shift has facilitated the emergence of personalised therapeutics. The importance of developing personalised therapeutics was highlighted during the clinical studies of Iressa (Gefitinib), developed by AstraZeneca for patients with non-small cell lung cancer (NSCLC) to

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target the epidermal growth factor receptor (EGFR). Initial clinical trials with Gefitinib were conducted with a large mixed patient cohort and did not show overall efficacy. However, retrospective analysis revealed that the drug was efficacious in approximately 10% of patients whose lung cancer exhibited activating EGFR mutations[7]. This illustrates the importance of improved profiling of patient populations so that patients are stratified to find the right drug for the right patient. This personalised medicine approach also facilitates smaller, more targeted trial designs with a greater chance of meaningful outcomes.

Furthermore, because of our understanding of cancer biology as a multi-faceted disease, therapeutics have been developed which are designed to target different hallmarks of cancer biology, from tumour cell growth and apoptosis, tumour metabolism to anti-angiogenic drugs which target the tumour vasculature, for example the VEGF antibody Avastin (bevacizumab). These different therapeutic strategies offer a multitude of potential therapeutic targets and also are now opening the door to the study of combination therapeutics which will likely lead to a further step-change in drug efficacy[8].

In this review we evaluate the potential for the development of OA pharmacological disease-modifying therapeutics to undergo a similar paradigm shift given that OA is increasingly being recognised as a heterogeneous disease and one that involves the whole joint, encompassing multiple tissue types including cartilage, bone, adipose and skeletal muscle. We briefly highlight the evidence for the role of these tissues in OA pathology and review the opportunities within each of these tissues to identify and develop targeted disease-modifying therapeutics (Fig. 1 & Table I). We also consider whether it is feasible to expect the emergence of personalised disease-modifying medicines for patients with OA and how this might be achieved.

Biological effect areas in OA for identifying potential therapeutic targets

Targeting cartilage matrix degradation

OA is characterised by the degradation of cartilage matrix components, including cartilage specific type II collagen and the proteoglycan aggrecan[9], ultimately resulting in the loss of cartilage structure and function. Targeting cartilage matrix degeneration is a well explored area for drug target discovery, and therefore the majority of what could be termed “low-hanging fruit” have already been picked. However, given that there are thought to be several key anabolic and catabolic pathways enzymes that are dysregulated in OA cartilage[10], there remains the opportunity to identify and validate new drug targets. In addition, there are also the untapped opportunities to explore and identify novel combinations from combining existing known targets. For example by combining therapeutics that are anti-catabolic with those that activate anabolic signalling pathways. As in cancer drug discovery, these are areas which should be investigated to identify a novel efficacious combination from combining known targets.

Matrix metalloproteinases (MMPs), a diverse family of zinc-dependent proteolytic enzymes involved in the maintenance of the extracellular matrix[11], were initially seen as attractive drug targets for the treatment of OA[12] and indeed other therapeutic areas including cardiovascular disease and cancer[13–15]. However, despite several candidates showing good efficacy in preclinical

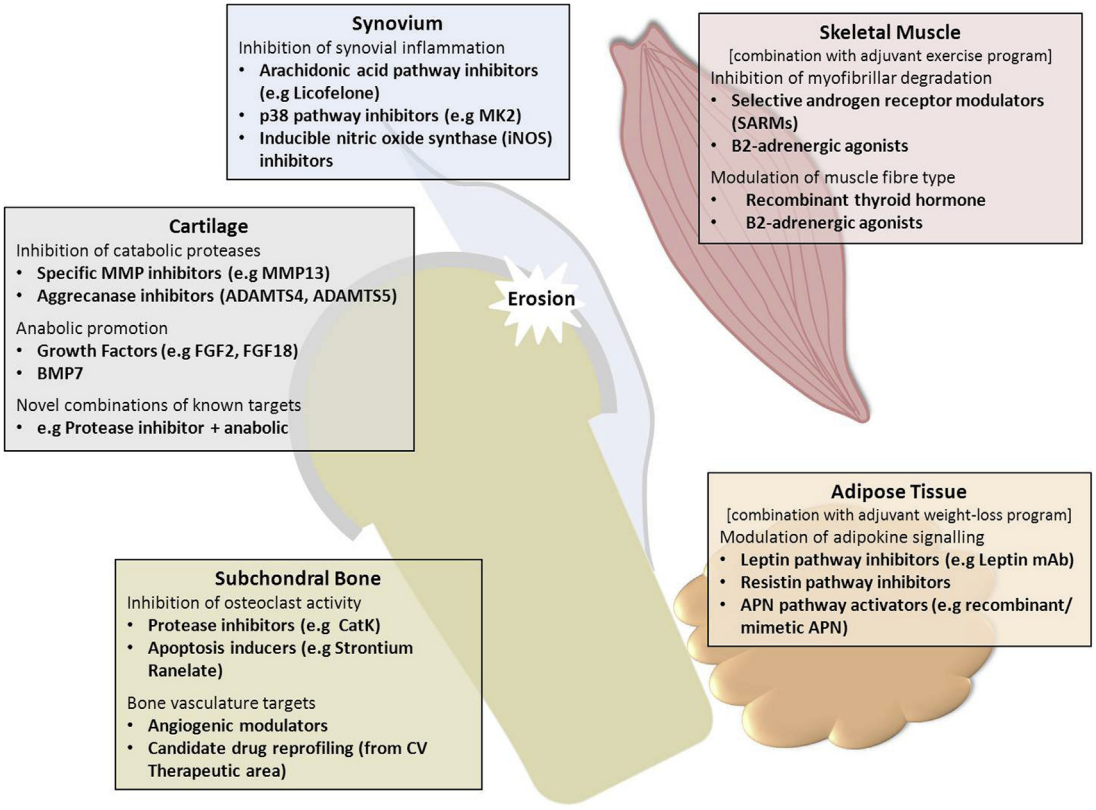

Fig. 1. Representation of the multiple biological effect areas within the OA joint and key pathways to exploit for the development of pharmacological DMOADs. OA is widely recognised as a disease of the whole joint (encompassing cartilage, subchondral bone, synovium, skeletal muscle and adipose tissue), offering new opportunities to identify new drug targets, new drug combinations and re-profiling old drugs from other therapeutic areas.