Prospects for drug discovery in osteoarthritis

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It is generally agreed that there is a need for a systematic plan to develop disease-modifying drugs for osteoarthritis (DMODs) [1]. To that end, there is a wealth of persuasive evidence that exists to support such a need; it is now a certainty that development of signs and symptoms of osteoarthritis (OA) is associated with aging, and in view of this parameter alone, OA will remain clinically relevant in the future as people live longer [1]. Thus, the burden of OA on the worldwide healthcare delivery system will be tested, and in that respect, it is likely that if DMODs are not developed within the next 5 years, the cost to patients for the treatment of their OA could significantly increase.

At present, most cases of OA remain indolent in the beginning and only become clinically relevant when nonimmune and immune-mediated inflammatory events begin to dominate the disease process [1]. Therefore, unless specific therapies are initiated to forestall the progression of OA to synovial joint failure, the current main recourse available to the patient is invasive joint replacement surgery. Reflecting on that scenario, we could theoretically be satisfied with such a clinical outcome. The impressive development of joint replacement prostheses has fulfilled the notion that – indeed – there is a ‘cure’ for OA and it is now available. However, recent advances stemming from laboratory-based studies, including the use of validated animal models of OA [2], that monitor the progress of experimental OA-like lesions as well as testing of various drug formulations [3] and cell-based therapies [4], should result in the successful development of new and clinically effective DMODs.

Although there is an ample agreement among investigators and physicians alike as to which OA animal model best suits the testing of new drug formulations, Cope *et al.* [2] asserted that a ‘more reliable’ OA model will be required that best reflects the natural history of human OA. For example, in my experience an OA model in the rabbit, successfully initiated by partial resection of the medial meniscus, resulted in articular cartilage surface fibrillation and osteophyte formation but failed to replicate subchondral bone sclerosis and the chronic inflammatory response that drives human OA to joint failure.

We can begin by asking, what is the state of development of DMODs in 2019? Many of the DMOD initiatives have focused on pain pathways [5], biological components of OA such as Wntless and the name Int-1 (Wnt) signaling, catabolic enzymes including aggrecanases [6], cathepsin K and, anabolic stimulators such as FGF-18 and cell-based therapies [7]. In that regard, it was asserted by Jones *et al.* [4] that high-grade evidence for the utility and efficacy of the so-called ‘stem cell’ therapies is lacking, as it is for intra-articular administration of platelet-rich plasma and bone marrow aspirate for treating OA. There are also other less recognized modalities for treating symptomatic knee OA. One of these involves strontium renelate, a strontium II salt of ranelic acid. Recently, administration of a strontium renelate formulation was shown to delay the loss of cartilage, as measured by the criterion known as joint space narrowing [8]. This formulation was also shown to increase osteoblast-mediated deposition of new bone while blocking osteoclast activity.

So, let's examine the multitude of pros and cons of some of these approaches for treating symptomatic OA. One aspect of any treatment approach is how to address the positive and/or negative results of experimental therapies using noninvasive measurements of OA disease progression, such as magnetic resonance imaging (MRI) [9]. Since MRI would likely have to be employed in a longitudinal long-term treatment modality, the cost – and exposure of – patients to MRI radiation must be a serious consideration.

Next up is the aggressive pursuit of agents that are designed to dampen or eliminate the chronic pain associated with OA [10–12]. Certainly there will always be issues involved with employing new and old drugs that merely target various pain pathways associated with symptomatic OA. Of note, these drugs may not show specific activity towards those metabolic pathways that actually govern the pathogenesis of OA, or its pathophysiology or progression. Some of these medicines, exemplified by paracetamol – a strong analgesic – were shown to only minimally affect pain compared with placebo even though current clinical guidelines routinely have recommended paracetamol as a first-line pain medicine for hip or knee OA [11]. Conversely, tanezumab is a monoclonal antibody with reactivity against NGF. Tanezumab was shown to reduce pain and increase physical function, as well as improve the patient's global assessment when administered to patients with OA, including those OA subgroups with co-morbid diabetes, severe OA symptoms or to a population of elderly OA patients greater than 65 years of age [12].

There are also several initiatives that have focused on re-purposing older drugs, such as corticosteroids [13] that have been historically employed for treating OA [14,15]. These drugs, such as triamcinolone acetonide, have proven to be useful for reducing pain. New formulations, exemplified by FX006 captured on microspheres [14], have already demonstrated that they can reduce pain in patients with knee OA; whereas, extended release formulations of triamcinolone acetonide (e.g., Zilretta) have also significantly reduced the mean daily pain intensity in knee OA patients compared with placebo [15].

There are also some very exciting initiatives that have evolved from laboratory-based research targeting several components of OA progression. These include the development of selective matrix metalloproteinase (MMP) MMP-13 inhibitors [16]. MMP-13 plays an important role in OA because this enzyme efficiently degrades Type II collagen. MMP-13 is a component of articular cartilage extracellular matrix that is widely expressed in OA cartilage but significantly less in nonarthritic cartilage. The selectivity of this MMP-13 inhibitor is likely to avoid some of the adverse events seen previously with older versions of MMP-13 inhibitors when they were tested *in vivo*. These include painful and joint-stiffening side-effects known as musculoskeletal syndrome. Cell-based therapies may also be on the horizon [17]. Thus, in a recently published study, bone marrow-derived mesenchymal stromal cells (BM-MSCs) isolated from patients who were defined by the Kellgren–Lawrence scoring criteria as late-stage OA received benefit from a single intra-articular injection of BM-MSCs as measured by pain relief and reduced synovial inflammation [18]. Another interventional approach has led to a major effort directed towards identifying microRNAs (miRs) [19] that regulate the expression of specific genes known to be pertinent to the progression of OA. One of these miRs is miR-21-5p that targets FGF-18 [20]. Thus, intra-articular injection of the miR-21-5p antagomir that neutralizes the activity of miR-21-5p significantly attenuated the index of severity in an animal model of experimental OA [20].

Perhaps the view from here is not so daunting for developing drugs designed to halt the progression of OA. Thus, several of the drugs likely to be developed in the next period will stem directly from all of the collaborations now ongoing between academic basic researchers, translational research-oriented scientists and physicians who are moving forward with plans to have a few DMODs available for preclinical testing in validated OA animal models before moving on to Phase I clinical trials for the testing of their safety and tolerability.

However, I believe at this time that one thing is certain. It was previously proposed that since many of the cellular events characteristic of rheumatoid arthritis overlap at some time with those in OA patients, why not use those accumulated successes in the drug therapy of rheumatoid arthritis to treat OA? At this juncture it would be difficult to carry out this proposal because it is likely that whatever newer DMODs are developed they will be administered directly to the affected synovial joint rather than risk a systemic administration and potential adverse events.

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