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Osteoarthritis and Cartilage

Commentary

# Are pro-regenerative therapies the future of osteoarthritis disease modification?

Osteoarthritis (OA) has historically been regarded as a disease of imbalance between synthetic, anabolic responses in the joint tissues and catabolic, degradative ones. Since adult articular cartilage has always been thought to have the poor reparative capability, most research over the past two decades has focused on targeting inflammatory and degradative pathways in OA to halt progression. Despite gaining important mechanistic insights from human and preclinical molecular analyses, none of the randomized controlled trials targeting inflammatory cytokines or disease-relevant proteases has met its primary endpoints,[1] leaving many to question whether disease-modifying OA drugs are a realistic aspiration.

The recent publication by Gerwin et al. demonstrates the value of taking a different approach to disease modification in OA.[2] They employed a methodology in which small molecules were screened for their ability to promote chondrogenesis in mesenchymal stem cells (MSCs) in vitro.[3] In this recent paper, the screen input was a proprietary Novartis secretomics collection. From 6300 proteins screened, angiopoietin-like 3 was identified, and its chondrogenic activity mapped to the carboxy C-terminal domain. A truncated and proteolysis-resistant protein (LNA043) was generated for further testing. LNA043 was able to promote some chondrogenic genes in human MSCs (albeit not increasing type II collagen or aggrecan) and induced the Wnt inhibitor, DKK1, in a chondrocyte cell line. It was also able to suppress interleukin-6 after inflammatory (poly I:C) stimulation and partially reverse poly I:C-mediated suppression of chondrogenic genes after culture in the chondrogenic medium. The mechanism of action was shown to be through α5β1 integrin, although it was notable that all in vitro responses were only evident at very high (supramicromolar) concentrations of LNA043.

Importantly, in vivo, a single intraarticular (i.a.) dose of LNA043 given 1 week after joint destabilization surgery was able to modify structural damage in rat OA; protection that was still evident when weekly injections were initiated 4 weeks after surgery. Furthermore, using a minipig focal cartilage defect model, multiple i.a. injections of LNA043 were able to improve the repair score after 12 (but not 6) months of treatment. The authors concluded that LNA043 is a pro-regenerative agent that is able to promote the repair of cartilage even in the presence of inflammation.

In an experimental medicine study derived from their included phase I clinical trial, cartilage was collected at the time of planned arthroplasty in individuals who had received LNA043 i.a., injection up to 21 days prior to operation. RNA sequencing was performed, and key signatures were compared with existing OA datasets. Whilst this analysis was underpowered and used a historical control as a comparator, it was able to demonstrate penetration of LNA043 into the cartilage and showed some LNA043-dependent gene expression changes that, in part, mirrored the in vitro data, for example, in altering modulators of Wnt signaling. Such changes appeared to be sustained over the 21 days, despite the inability to detect LNA043 in the tissue beyond the first few days. Phase II clinical studies are underway.

The paper by Gerwin et al. is one of only a handful in which we are seeing a shift in the focus of OA target discovery toward those that promote intrinsic repair of the damaged cartilage. Some of these have only been demonstrated as yet in preclinical models,[3–5] while others have shown translational success. In the FGF-18 Osteoarthritis Randomized Trial with Administration of Repeated Doses (FORWARD) study of 549 individuals with moderate-to-severe OA, sprifermin, a truncated form of the growth factor FGF18, was able to arrest the loss of articular cartilage volume and increase the thickness of cartilage at 2 years after 18 months of cyclical i.a. treatment.[6] Whilst this change was not associated with an improvement in pain outcomes, a post hoc analysis of a subgroup at risk of progression (those with at least moderate pain and definite reduced radiographic joint space width at baseline) did show an analgesic response at Year 3.[7] A phase II study of 455 OA patients treated with i.a. lorecivivint, a Wnt inhibitor, failed to demonstrate significant slowing of radiographic progression, although the authors did report an increase in radiographic joint space width in a subgroup of individuals with predominantly unilateral symptoms.[8] Unfortunately, preliminary results recently reported from Phase III lorecivivint trial data did not meet primary or secondary endpoints, which included joint space width.[9] The data did, however, suggest a positive signal in a subgroup of patients with moderate rather than severe disease.

These studies align well with in vivo and human genetic data. There are now around 80 putative genes that are linked to polymorphic variants associated with OA risk in genome-wide association studies.[10] Of those putative genes that are recognizable, a strong growth factor/chondrogenic group emerges, which includes transforming growth factor-beta, transforming growth factor-alpha, fibroblast growth factor (FGF), and Wnt family members and pathways. Several of these have been shown to be pro-regenerative or chondroprotective in vivo.[11–13] Where validated, the data point toward hypomorphic variants in these factors being associated with the increased disease. These results suggest for the first time that genetic risk in OA is controlling the effectiveness of an individual's intrinsic repair mechanism and that OA may be better described as a disease of failed repair.

If the future of disease modification in OA is going to be through targeting regeneration, what additional considerations must we consider at this stage? It is possible that patient stratification will be required prior to selecting the right therapy for the right patient. Whether genetic risk variants increase or decrease an individual's response to treatment, or whether sex and age do, are unknown.

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There may be a need to combine different treatments to achieve structural and patient-relevant outcomes. Will we need to add anti-inflammatory therapies to reduce the commonly present joint inflammation before we can enhance cartilage repair? Will we need to correct the hostile biomechanical joint environment?

Studies of surgical joint distraction and high tibial osteotomy demonstrate the importance of mechanical offloading in promoting endogenous repair of cartilage and also indicate that even severely damaged joints can respond, so perhaps these should be combined with pharmaceutical approaches to improve efficacy.[14] It remains to be seen to what extent and how cartilage regrowth might affect pain in order to deliver symptom, as well as structure, modification. Nerve growth factor is the best-validated driver of OA pain, and this is made largely by damaged cartilage in the joint,[15] so regeneration of cartilage might suppress its production. This is yet to be proven.

Major trial design considerations include ensuring that our clinical endpoints and tools are appropriate. Proven loss of cartilage will be a minimal inclusion requirement to be able to demonstrate an improvement in the thickness of cartilage. How this will be measured, for instance, by magnetic resonance imaging (MRI) or time to arthroplasty, and over what time period, will need careful consideration. Irrespective of the remaining challenges, this change in direction is refreshing and, in view of emerging biology, has never appeared so well justified.

## Conflicts of interest

TLV has received research funding to support the STEpUP OA Consortium from UCB, Galapagos, Biosplice, Novartis, Fidia, and Pfizer. PGC has performed speakers bureaus or consultancies for AbbVie, AstraZeneca, Biosplice, BMS, Eli Lilly, Galapagos, Genascence, GSK, Janssen, Merck, Moebius Medical, Novartis, Pfizer, Regeneron, Stryker, and UCB.

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