failure to identify effective treatments in clinical trials in osteoarthritis (OA) and other conditions. The treatment response to placebos has been to linked to an effect on opioid receptors in the brain. In addition, placebo responses in trials have been explained by regression to the mean, in which patients enroll in trials when their condition is flaring and the natural history is for their flare to resolve, leading to a natural improvement in their symptoms. Also, positive expectations of a therapeutic effect contribute to placebo response. Higher placebo effects have been linked to reduced treatment effects where treatment effect is defined as (treatment effect - placebo effect). In meta-analyses of OA trials, investigators at the University of Nottingham showed that placebo (so-called contextual) effects of OA treatments often accounted for more than half of the total treatment effect (treatment effect + placebo effect) for pain reduction among proven treatments. Investigators from Tufts University showed that among different modes of administration, placebo responses were greater for injected and topical than for oral treatments. In OA and other painful conditions, variability in pain scoring and initial high pain scores may also be predictive of large placebo effects.
Given the high placebo (or contextual) effects seen in OA, what should be done? This depends on the goal of the enterprise. If the goal is to enhance the patient response to treatment, the best approach is to maximize this response by encouraging a positive expectation for treatment and by choosing treatment modalities likely to maximize this response, injected or topical treatments. Further, such advice may need to be incorporated into treatment guidelines. On the other hand, if the goal is to optimize the likelihood of detecting the efficacy of a treatment, then minimizing placebo responses is necessary. This can be accomplished by providing no positive expectations for treatment and by minimizing pain reporting variability.
Conclusions: Placebo responses to treatment are critical elements contributing to treatment response. We need to consider them in both clinical treatment approaches and in testing potential treatments in OA.

I-5
NON-CODING RNA SIGNATURE IN PAINFUL KNEE OA:

Lars Arendt-Nielsen.

Purpose: Environmental factors may change how our genes are operating - this is called epigenetic modifications. Epigenetic changes have received increasing traction in many areas of medicine e.g cancer where specific drugs have been developed to reset the disease driven epigenetic modifications. In recent years there has been an interest in exploring the possible role of epigenetic changes and the associated proteomic changes in chronic pain. Epigenetic changes and modifications processes include the action of transcription factors, chromatin modifying enzymes and chromatin-remodeling complexes and the action of noncoding RNAs. It has been suggested that epigenetic modifications, like the actions of noncoding RNAs (e.g. microRNAs, lncRNAs, siRNAs, circRNAs), might be highly related to the pathophysiology of OA, and this may pave the way for future treatments; in this regard several studies have illustrated the possible diagnostic potential of circulating noncoding RNAs (ncRNAs) in OA, indicating that this family of molecules may act as potential predictors for the onset and the clinical evolution of osteoarthritis. The purpose of this study was to investigate is epigenetic changes could be detected in patients with painful knee OA and if the possible changes were 1) associated with pain and if 2) they could predict the development of chronic pain 1 year after total knee replacement.
Methods: A total of 202 patients scheduled for total knee replacement were included and 39 matched controls. The following were assessed: Pain assessments pre- and post-operatively (1 year) and pre-operative serum samples. Real-time poly-chain reaction (RT-qPCR), quantitative and qualitative techniques allowed the evaluation of the circulating ncRNAs in serum samples, trough the isolation and retro-transcription of total RNAs. This methodology reduces nonspecific results and reduces the difficult handling of the big amount of data obtained through other molecular biology techniques. Furthermore, a new proteomic approach, i.e. the proximity extension assay (PEA), was been used which gives a specific and standardized overview of inflammatory markers involved in the pathology. The pain intensity was assessed on a visual analogue scale from zero to ten, where zero indicated the absence of pain, whereas ten was referring to the worst pain experienced.
Results: The following preoperative serum circulating microRNAs were upregulated: 146a-5p (miRNA associated with inflammation response, pain sensation and OA pathogenesis); 145-5p (miRNA associated with the expression of TNF-α and IL-1b and involved in OA pathogenesis); 130b-3p (miRNA involved in inflammatory cascade and in the maintenance of chondrogenesis). The 3 dysregulated miRNA were predictors for post-operative pain at 1 year. A total of 13 proteins involved in inflammatory process were differently expressed in OA patients vs healthy controls, and 4 of the proteins were found to predict post-operative pain. Patients with KOA showed ten cytokines with significantly lowered expression in the serum and five cytokines with higher expression levels when compared to healthy participants. Specifically, FGF-21 and 4E-BP1 were associated with pain in KOA, and TWEAK, FGF-21, CSF-1, IL6 were identified as independent predictors for post-operative pain intensity.
Conclusions: The data suggest that epigenetic profiling in association with proteomics could possibility be a new biomarkers approach for 1) understanding pain and disease progression in OA and 2) suggest new possible precautions to prevent the development of chronic post-operative pain after joint replacement.

I-6
REHABILITATION & OUTCOMES

Melanie Holden.

Purpose: This year in review will present key highlights from research relating to osteoarthritis rehabilitation published in the last year.
Methods: Studies focused on rehabilitation (defined as non-pharmacological, non-surgical treatments designed to optimize function and reduce disability) among adults with osteoarthritis will be identified from an electronic database search. The search will be carried out in Medline, Embase, and CINAHLPlus between April 2021 and March 2022. Studies of any type that are of perceived high clinical importance and quality or controversy in the field will be selected and summarised in the review. There will be a focus on core recommended treatments, adjunctive treatments, novel and emerging therapies/ research methods, and translation of evidence into practice.

I-7
OA BIOLOGY

Seungwoo Han.

Purpose: The field of osteoarthritis (OA) biology is rapidly evolving and brilliant progress has been made this year as well.
Methods: Landmark studies of OA biology published in 2021 and early 2022 were selected through PubMed searches and classified by their molecular mechanisms, and it was largely divided into the intra-cellular mechanisms and the inter-compartment or inter-cellular interaction in OA progression.
Results: The intra-cellular mechanisms involving OA progression included 1) Piezo1/TRPV4-mediated calcium signaling, 2) low grade inflammation by TLR-CD14-LBP complex and IKKβ-NFkB signaling, 3) PGRN/TNFR2/14-3-3ϵ/Elk-1 anabolic cascade, 4) G protein-coupled receptor (GPCR) signaling, 5) mechanical loading-cilia/Ift88-hedgehog signaling, 6) mitochondrial fission by ERK1/2-DRP1 pathway, and 7) hypoxia-DOT1L-H3K79 methylation pathway. The studies on inter-compartment or inter-cellular interaction in OA progression included the following subjects: 1) the anabolic role of Lubricin, a proteoglycan from superficial zone cells, 2) osteoclast-chondrocyte interaction via exosomal miRNA and sphingosine 1-phosphate (S1P), 3) αV integrin-mediated TGFβ activation by mechanical loading, 4) TGFβ-mediated suppression of sclerostin in osteocytes, 5) catabolic role of Flightless I as a DAMPs-triggering molecule, and 6) catabolic role of paracrine signaling from fat.
Conclusions: Despite the disastrous Covid-19 pandemic situation, many outstanding studies have expanded the boundary of OA biology. They give us not only critical insight on pathophysiology, but also clue for the treatment of OA.