formation and reduce bone resorption which could in part explain the positive impact on bone erosions by Tofacitinib. Thus, we hypothesize that it will be unnecessary to stop this medication in case of fracture and suggest that positive effects on osteoporosis are likely.

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OP0075 PAR2 ACCELERATES OSTEOARTHRITIS-LIKE JOINT CHANGES IN A MURINE MODEL OF POST-TRAUMATIC OSTEOARTHRITIS

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Background: Post-traumatic osteoarthritis (PTOA) is associated with articular cartilage damage and represents a major clinical challenge due to the poor regenerative capability of cartilage. We have recently developed a novel and robust dual injury murine model of PTOA, which combines destabilisation of the medial meniscus (DMM) and cartilage scratch[1]. This model results in accelerated OA-like symptoms including enhanced osteophyogenesis. Prior studies in the DMM model have demonstrated that absence of proteinase-activated receptor 2 (PAR2) in mice results in significant protection from early OA-like symptoms[2,3].

Objectives: To investigate if the absence of PAR2 confers protection in a dual injury PTOA murine model.

Methods: PTOA was induced in both male C57BL/6 wild-type (WT) and PAR2$^{-/-}$ mice, via combined destabilisation of the medial meniscus and cartilage scratch (DCS). Twenty-eight days post-surgery, osteophytogenesis and bone changes were monitored using microcomputed tomography. Dynamic weight bearing was assessed as an indirect measurement of pain at day 14.

Results: Evaluation of the presence and number of osteophyte revealed no significant differences between WT and PAR2$^{-/-}$ mice at day 28. However, quantification of osteophytes revealed that PAR2$^{-/-}$ mice had significantly smaller osteophytes (p=0.006) with less mineralised bone (p=0.003). Moreover, analysis of metaphyseal trabecular bone on the operated leg showed a significant decrease in% bone volume/tissue volume (BV/TV) (p=0.025). Assessment of pain-related behaviour, using dynamic weight bearing at day 14, demonstrated that PAR2$^{-/-}$ mice exerted less load on their front paws.

Conclusion: The findings in this study show that PAR2 plays a role in accelerated OA-like symptoms (i.e., osteophyte formation) in a dual injury model of OA, where both destabilisation of the medial meniscus and cartilage damage drive disease pathology. Furthermore, the loss of PAR2 decreases pain behaviour suggesting that PAR2 is involved in pain sensing. Taken together, these results support the future exploration of PAR2 as a therapeutic target for PTOA.

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OP0076 JAK-INHIBITORS TOFACITINIB AND BARICITINIB IMPROVE PATHOLOGICAL BONE LOSS IN VIVO

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Background: Targeting cytokines relevant to rheumatoid arthritis (RA) has proven efficient in clinical practice, but there is still demand for therapies that rebuild joint tissues which have been subjected to deterioration. Since many cytokines involved in RA rely on the intracellular janus kinase - signal transducer and activator of transcription (JAK-STAT) signaling pathway, targeting them presents itself as option. For this approach, JAK-inhibitors such as Tofacitinib and Baricitinib, targeting JAK1/JAK3 and JAK1/JAK2 respectively, seem favorable, as they have been approved for the treatment of RA[1]. Moreover, preliminary data indicates an impact of JAK inhibition on local bone formation.

Objectives: To investigate the influence of JAK-inhibition on structural bone damage *in vivo* and its impact on osteoclast/osteoblast-mediated bone homeostasis *in vitro*.

Methods: *In vivo* analysis comprised unchallenged steady-state, the ovariectomy-induced mouse model of postmenopausal osteoporosis (OVX) and the serum-induced arthritis (SIA) mouse model. For steady-state analysis C57BL/6 (WT) mice obtained tofacitinib QD by oral gavage for 6 weeks. For OVX, WT mice received tofacitinib BID by oral gavage for 6 weeks. WT mice of the SIA model were fed tofacitinib or baricitinib BID for 14 days. Experimental readout included clinical parameters, ELISA (RANKL/OPG levels in serum), qPCR (mRNA expression in bone) and µCT. For *in vitro* analysis, murine osteoclasts (OC) were analyzed with TRAP staining (osteoclastogenesis) and von Kossa staining (Resorptive capacity). Murine osteoblasts (OB), derived from mesenchymal stem cells (MSC) and calvariae were assessed with qPCR (differentiation) and Alizarin red staining (mineralization capacity).

Results: In steady-state conditions, JAK-inhibition by tofacitinib enhanced tibial trabecular bone density and decreased RANKL/OPG fraction in blood serum. These findings, and increased trabeculae numbers, were also applicable to spinal bone of tofacitinib-treated OVX mice. In SIA, both baricitinib and tofacitinib improved clinical symptoms and halted trabecular and cortical bone loss. *In vitro* OC-differentiation and function were not affected by JAK-inhibition. However, tofacitinib and baricitinib amplified OCN expression in MSC-derived OBs at day 1 after osteogenic induction, together with reduced Igf1 and elevated Dkk1 levels at day 7. Moreover, as a result of JAK-inhibition RANKL expression was decreased in calvaria-derived OBs. Accordingly, both MSC- and calvaria-derived OBs showed increased mineralization when treated with JAK-inhibitors.

Conclusion: Our results suggest that JAK-inhibition by tofacitinib and baricitinib causes increased mineralization by osteoblasts, resulting in enhanced bone density *in vivo*, in both unchallenged and pathological mouse models.

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OP0077 INNOVATIVE TRANSLATIONAL MODELS TO STUDY HUMAN SYNOVIAL PATHOLOGY: TARGET VALIDATION AND PRECLINICAL IMAGING

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Background: Many experiments to study inflammation, hyperplasia, and fibrosis in the synovium have been performed in animal models of RA and OA. However, the predictive value of these models for the screening of potential drugs in RA is variable and for OA, none were sufficiently effective in clinical trials. Translational