

## Bromodomain inhibitors are potent epigenetic regulators of catabolic gene expression in human osteoarthritic chondrocytes.

<sup>1</sup>María C. de Andrés, <sup>1</sup>Namrata Madhusudan, <sup>2</sup>Chas Bountra, <sup>2</sup>Udo Oppermann, <sup>1</sup>Richard O.C. Oreffo

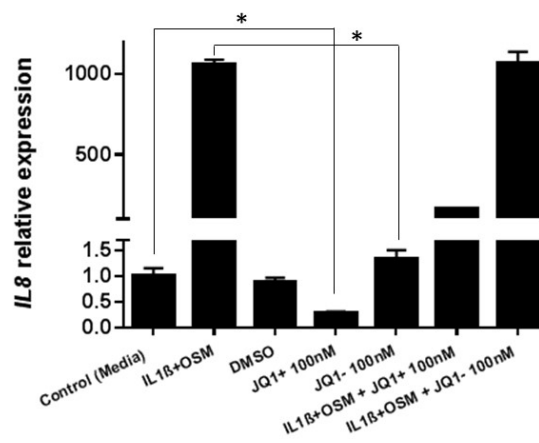
<sup>1</sup>Bone and Joint Research Group. Centre for Human Development, Stem Cells and Regeneration Human Development and Health, Institute of Developmental Sciences, University of Southampton, UK.

<sup>2</sup>Structural Genomics Consortium, University of Oxford, UK.

**Purpose:** Osteoarthritis (OA) is a complex disease of the articulation characterized by joint pain, functional limitation and reduced quality of life. An essential feature of the underlying pathogenesis of OA is an imbalance of anabolic and catabolic activity leading to progressive loss and destruction of extracellular matrix of articular cartilage. Genes involved in chromatin-mediated signalling constitute emerging target classes for future therapies. There is increasing evidence to support the role of DNA methylation in the pathogenesis of OA. However, few studies have investigated the effect of other epigenetic modifications in this debilitating disease. The current study has analysed the effects of three novel epigenetic modifiers: two bromodomains inhibitors (JQ-1, PFI-1) and a histone methyltransferase inhibitor (SGC707) on the catabolic gene expression involved in the pathogenesis of OA.

**Methods:** Chondrocytes extracted from OA femoral heads (n = 6) were cultured and subsequently incubated with increasing concentrations of the compounds. Interleukin 1-beta (IL-1 $\beta$ ) plus oncostatin M (OSM) alone or in combination with JQ-1, PFI-1 or SGC707, or media alone (control) were added to the incubated samples. After 6 and 24 hours, levels of *iNOS*, *COX2*, *IL8*, *IL1B*, matrix metalloproteinase-13 (*MMP13*), *RUNX2* and *COL9A1* gene expression were measured using qRT-PCR and expressed relative to GAPDH.

**Results:** The bromodomain inhibitors JQ-1 (100 and 800 nM) and PFI-1 (0.5 and 5  $\mu$ M) were able to suppress not only the expression of all the catabolic cytokines after co-stimulation with IL-1 $\beta$ +OSM but also the basal expression of OA chondrocytes without stimulation. Critically, preliminary results with JQ1 (see figure) and PFI-1 in OA chondrocytes show that this BET inhibitors are able to decrease catabolic gene expression (*iNOS*, *COX2*, *IL8*, *IL1B* and *MMP13*), *RUNX2* expression was also suppressed, and no effect was observed on the expression of the anabolic chondrocytic gene *COL9A1*. This data demonstrate these molecules are potent protective cytokine against cartilage degradation. Interestingly, the histone methyltransferase inhibitor SGC707 (0.1 and 1  $\mu$ M) did not induce any reduction in the expression of all the catabolic genes.



**Figure.** The bromodomain inhibitor JQ1 suppresses *IL8* expression in OA human articular chondrocytes. \*\*P<0.01.

**Conclusions:** This study demonstrates that inhibition of bromodomains by epigenetic modifiers modulates the expression of catabolic genes in OA chondrocytes. These results further substantiate the role of epigenetics in OA with implications for therapeutic intervention and our understanding of OA pathophysiology.