Introduction. Oncostatin M (OSM) is a member of the IL-6 cytokine family and is produced by T cells, neutrophils and macrophages. While OSM represents a potential biomarker for rheumatoid arthritis, its reported activity to enhance matrix degradation in combination with IL-1 or TNF alpha raises the possibility of its potential contribution to induce degradation in human cartilage.

Results: OSM represents a potential biomarker for rheumatoid arthritis, its mechanism of OSM and IL-1 synergy. In addition, we evaluated several human synovial fluids from patients suffering from sports injury and/or arthritis for levels of OSM.

Methods: Human articular cartilage was obtained from autopsy (National Disease Research Interchange, Philadelphia, PA, USA), and human SF were obtained with informed consent and used under the approval of the institutional review board. Cartilage was graded normal based on a modified Collin's score [3]. Cartilage explants were incubated with IL-1α (20-100 ng/ml), OSM (10-50 ng/ml), or the combination and analyzed for aggrecan degradation. Aggrecanase production was measured using a human articular chondrocyte cell-based enzymatic assay and a neopteptide ELISA [4]. Monolayer chondrocytes were used to examine the effects of IL-1α and OSM on gene expression of ADAMTS-4, ADAMTS-5, MMP-9, and MMP-13 by RT-PCR. OSM concentrations in OA SFs were analyzed using an ELISA developed at GSK and employing a monoclonal anti-human OSM.

Results: Human articular cartilage explants were treated with IL-1α, OSM, or a combination, in the absence or presence of a selective aggrecanase inhibitor, SB703704. The combination of IL-1α and OSM caused a synergistic stimulation of aggrecan degradation in a concentration dependent manner, compared to IL-1α treatment alone.

(figure 1) In a human chondrocyte-based assay, IL-1α or OSM alone had minimal effects on aggrecanase production, but the combination resulted in a synergistic stimulation of aggrecanase production (data not shown). The synergistic effects by IL-1α and OSM on both cartilage aggrecan degradation and aggrecanase production was completely blocked by the aggrecanase inhibitor.

To identify specific proteases impacted by IL-1α and OSM, we treated monolayer chondrocytes derived from four human donors with IL-1α, OSM, or a combination of IL-1α and OSM, and analyzed RNA expression by RT-PCR for ADAMTS4, ADAMTS5, MMP9, and MMP13 at 6 and 24 hours post-stimulation. Both IL-1α and OSM alone induced ADAMTS-4 and MMP-13 expression. IL-1α but not OSM induced MMP-9 expression, and neither had an appreciable impact on ADAMTS-5 expression either alone or in combination. The combination of IL-1α and OSM had an additive effect on MMP-9 and MMP-13, and caused a synergistic stimulation of ADAMTS4 expression (figure 1).

OSM concentrations in SFs from 46 OA subjects were analyzed using an ELISA (figure 3). Of these, 33 SF samples had detectable levels (limit of detection: 16 pg/ml) of OSM. Several SF samples contained OSM at high levels (> 2000pg/ml), and OSM concentrations of > 1000pg/ml were detected in three samples.

Conclusion: These results suggest that the synergistic stimulation of aggrecan degradation in human cartilage explants by IL-1α and OSM is associated with a specific and synergistic induction of ADAMTS-4. Although recent evidence suggests that ADAMTS5 is required for aggrecan degradation in mouse models, the data presented here would support the involvement of ADAMTS4 in aggrecan degradation in human articular cartilage. In addition, a role for OSM in OA is supported by our observation that significant levels of OSM were detected in several SF samples from patients with joint injury.