a therapeutic target in RA and OA. To date, there are no published data on the functionally distinct VEGF-A splice variants in either RA or OA.

Objectives: To determine the patterns of, and relationships between, VEGF-A, SRPK1, and SRSF1 expression and activation and synovial inflammation in human RA and OA.

Methods: The study was approved by the Nottingham Research Ethics Committee 1 (05/Q2403/24) and Derby Research Ethics Committee 1 (11/H0405/2). Tissues were selected from age- and sex-matched cases in the University of Nottingham joint tissue repository. Post-mortem (PM) samples of healthy knee synovium (n=14, no history of arthritis or knee pain in the 12 months prior to death, no significant articular or synovial pathology) and arthroplasty-derived synovium samples from OA (n=35) or RA (n=14) patients were compared. OA samples were selected to represent the variety of inflammation levels, from low to high grade (0-3, Haywood et al., 2003). 8µm thick sections were stained for SRSF1, SRPK1, total VEGF-A and VEGF-A_{xxx}b via immunohistochemistry. Expression was estimated as fractional area, relative staining intensity (VEGF-A_{xxx}b), and SRSF1 activation quantified by the degree of nuclear localisation. Statistical analyses were performed using Kruskal-Wallis followed by Dunn's tests and Spearman's rank correlations.

Results: SRPK1 expression was similar across all conditions. SRSF1 showed significantly higher expression in the OA tissue compared to PM (H(2)= 11.29, p=0.002; OA median=0.2, IQR(0.15, 0.28); PM median=0.09, IQR(0.07, 0.16)), and significantly higher nuclear localisation (indicating activation) in RA vs. OA, and in both RA and OA vs PM (H(2)=37.65, p<0.0001 RA cf. PM; p=0.007 OA cf. PM; RA median=89, IQR(83, 93); OA median=36.1, IQR(29, 42); PM median=19.8, IQR(14,21)). Nuclear SRSF1 was significantly correlated with inflammation score (r= 0.52, p<0.05). Total VEGF-A expression was significantly increased in RA compared to PM and OA (H(2)=23.3, p<0.001 RA cf. PM; RA median=0.4, IQR(0.37,0.59); PM median=0.18, IQR(0.15,0.2)) and was also correlated with the severity of inflammation (r=0.47 p<0.05). VEGF-A_{xxx}b showed no change in expression in OA or RA, although VEGF-A_{xxx}b staining intensity was significantly higher in RA samples, compared to controls (H(2)=7.2 p=0.02; RA median=2.3(1, 4); PM median=0.9 (0.7, 1.4)).

Conclusion: Increased levels of SRSF1 activation, and the association of total VEGF-A expression with inflammation score, support the hypothesis that there is activation of alternative splicing in inflamed synovium in RA and OA. Targeting this pathway could be a novel therapeutic strategy in OA & RA.

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Both companies have with a focus on development of alternative RNA splicing control for therapeutic application in a number of different conditions, including ophthalmology (www.exonate.com), analgesia and arthritis (www.emendatherapeutics.com)., Consultant of:

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AB0067

CHONDROCALCINOSIS IS ASSOCIATED WITH A SPECIFIC EFFECT ON THE CHONDROCYTE PHENOTYPE THAT MARKEDLY DIFFERS FROM OA

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Background: Calcification of cartilage with BCP crystals is a common finding during osteoarthritis (OA) and is directly linked to the severity of the disease and hypertrophic differentiation of chondrocytes. Chondrocalcinosis (CC) is associated with CPPD crystal formation. There is only little knowledge about the effect of CPPD crystals on chondrocytes.

Objectives: The aim of this study was to investigate the chondrocyte phenotype in CC cartilage and the effect of CPPD crystals on chondrocytes.

Methods: Cartilage samples of patients with CC were used and compared with samples of severe OA patients without chondrocalcinosis and healthy cartilage samples served as control. Radiological presence of chondrocalcinosis was evaluated using standard X-ray pictures, as well as macroscopically inspection. The cartilage samples were stained using von Kossa/Safranin-orange staining. These stainings were used for OA severity scoring using the Chambers-Score. FTIR analyses were performed to distinguish CPPD and BCP crystals in cartilage. Chondrocyte differentiation markers were evaluated using Collagen 2 and X, as well as Sox9 and aggrecan as markers for chondrocyte hypertrophic differentiation in immunohistochemistry and qRT-PCR. TUNEL staining was performed to investigate cell death. In vivo results were validated using qRT-PCR for the expression of the respective genes after stimulation of C28 chondrocytes with CPPD and BCP crystals.

Results: Radiologically detectable cartilage calcifications were evident in chondrocalcinosis patients, but absent in OA patients without CC. CPPD crystals were detected on the cartilage surface, whereas BCP crystals were detected in the pericellular matrix of hypertrophic chondrocytes. CC cartilage exhibited an increased collagen X expression compared to healthy cartilage, as well as to severe OA cartilage containing BCP calcification. Interestingly, aggrecan and collagen 2 were not reduced in CC cartilage, but markedly reduced in OA cartilage. TUNEL positive cells were significantly increased in CPPD cartilage compared to OA cartilage, although the histological OA severity was lower. qRT-PCR indicated no relevant influence of CPPD crystals on hypertrophic marker genes, whereas BCP crystals significantly induced hypertrophic differentiation.

Conclusion: BCP and CPPD crystals seem to trigger differential effects on the chondrocyte phenotype. BCP crystals induce hypertrophic differentiation, which is not induced by CPPD crystals.

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AB0068

NOVEL CHONDROPROTECTIVE AND ANTI-INFLAMMATORY EFFECTS OF THE SELECTIVE HUMAN MELANOCORTIN MC3 RECEPTOR AGONIST PG-990 ON SNAP ACTIVATED CHONDROCYTES

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Background: Osteoarthritis (OA) is a degenerative joint disease that affects over 250 million people worldwide [1] with treatments focussing on the symptoms rather than the cause of the pathology [2, 3]. Thus, this degenerative joint disease requires novel treatment options [3, 4].

Therefore, the melanocortin system [4] could provide a novel avenue to explore given its ability to exert anti-inflammatory effects and chondroprotection [5], although the receptor subtype involved is unclear.