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 SRFS1 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/H04052/2). 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 arthritic or synovial pathology) and arthroplasty-derived synovium (n=14, no history of arthritis or knee pain in the 12 months prior to death, no significant arthritic 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 (0-3, Haywood et al., 2003). Bum thick sections were stained for SRFS1, SRPK1, total VEGF-A and VEGF-A_b via immunohistochemistry. Expression was estimated as fractional area, relative staining intensity (VEGF-A_a/b), and SRFS1 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. SRFS1 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(0.02, 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=19.6, IQR(14, 21)). Nuclear SRFS1 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, 0.23)) and was also correlated with the severity of inflammation (r=0.47, p<0.05). VEGF-A_b showed no change in expression in OA or RA, although VEGF-A_a_b staining intensity was significantly higher in RA samples, compared to controls (H(2)=7.2 p=0.02; RA median=3.3 (1, 4); PM median=0.9 (0.7, 1.4)).

Conclusion: Increased levels of SRFS1 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.

References:

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2017: Consultancy to Pfizer Ltd; personal financial disclosure
2017: Consultancy to Pfizer Ltd through Nottingham University; non-personal financial disclosure (payment to University).
L. Lucas: Shareholder of, LFD is a co-inventor on patents protecting alternative RNA splicing control and VEGF-A splice variants for therapeutic application in a number of different conditions. LFD is also a founder equity holder in, and consultant to, Exonate Ltd, and Emenda Therapeutics Ltd. 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:
LFD is also a founder equity holder in, and consultant to, Exonate Ltd, and Emenda Therapeutics Ltd.

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.

AB0067

CHONDROCALCINOSIS IS ASSOCIATED WITH A SPECIFIC EFFECT ON THE CHONDROCYTE PHENOTYPE THAT MARKER DIFFERENT FROM OA

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Background: Calcification of cartilage with BCP crystals is a common finding during osteoarthrits (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 is 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 Chambres-Score. qRT-PCR analyses was 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-890 ON SNAP ACTIVATED CHONDROCYTES

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Background: Osteoarthritis (OA) is a degenerative joint disease that affects 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.