SAT0560

FROM A 2-YEAR MULTICENTRE CLINICAL TRIAL IN KNEE OSTEOARTHRITIS, A METABOLOMIC ANALYSIS REVEALS THAT OVER ACTIVATION OF THE CONVERSION PATHWAY OF PHOSPHATIDYLCHOLINE TO LYSPHOSPHATIDYLCHOLINE IS ASSOCIATED WITH KNEE CARTILAGE VOLUME LOSS OVER TIME

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Background: While progression of osteoarthritis (OA) is variable, no tools yet exist to predict disease course.

Objectives: To identify, using a metabolomic approach, serum marker(s) for predicting knee cartilage volume loss over time measured by magnetic resonance imaging (MRI) in a 24 month Phase III clinical trial in patients with symptomatic knee OA.

Methods: 139 knee OA patients who completed the clinical trial according to protocol were selected from a 24 month DMOAD trial studying the effect of licofelone versus naproxen. MRI was performed at baseline and 24 months. Targeted metabolomic profiling was performed on serum collected at baseline. Metabolite ratios as proxies for enzymatic reaction were calculated and used in the analysis. The levels of 186 metabolites were measured and 152 met the quality control requirements. The metabolite concentrations were standardised using the Z-score. 21 952 pair wise metabolite ratios were analysed. A metabolome-wide significance level of $\alpha=2.3 \times 10^{-5}$ was defined after correcting multiple testing with the Bonferroni method. Univariable and multivariable analyses adjusted for age, sex, BMI and medication were performed. Gene expression analysis of human OA articular cartilage (n=32) and subchondral bone (n=39) tissues from total joint replacement, and controls (non-OA) from individuals having a fracture (n=21; n=9, respectively) was done to further explore the potential metabolic pathway(s).

Results: Data revealed that the baseline ratio of the metabolite lysophosphatidylcholine 18:2 (lysoPC 18:2) to phosphatidylcholine 44:3 (PC44:3) was associated with the cartilage volume loss in the lateral compartment (univariable, $b=-0.21 \pm 0.04$, $p=8.53 \times 10^{-7}$; multivariable, $b=-0.18 \pm 0.04$, $p=9.5 \times 10^{-6}$). Further experiments demonstrated that the lysoPC 18:2/PC44:3 ratio was also significantly ($r=0.31$, $p=0.0002$) correlated with an articular degradation marker, COMP. The data of the increased lysoPC 18:2 to PC44:3 ratio involve a conversion pathway of PC to lysoPC which is catalysed by a phospholipase A2 (PLA2), suggesting a higher activity of PLA2. Data demonstrated that in both human cartilage and subchondral bone tissues, a PLA2, PLA2 group 5 (PLA2G5), was markedly over-expressed in OA cartilage and subchondral bone compared to these non-OA tissues (445% and 158% increase, respectively, all $p<0.02$). Interestingly, in these tissues TNF- α was also upregulated ($p=0.007$; $p=0.06$, respectively), and positively correlated with PLA2G5 ($r=0.71$, $p=0.02$).

Conclusions: Our data suggest that the ratio of lysoPC 18:2/PC44:3 is predictive of greater risk of cartilage loss in OA. We speculate that this specific conversion pathway may produce a bioactive molecule like oleoylethanolamide (OEA), which has been demonstrated to bind to a novel cannabinoid receptor, GPR119, thus could be a novel therapeutic target for OA treatment.

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SAT0561

MITOCHONDRIAL BACKGROUND INFLUENCES THE JOINT EVOLUTION IN A CONPLASTIC MOUSE MODEL OF AGEING

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Background: Several studies showed interesting associations between mtDNA haplogroups and different OA-related features, including prevalence, incidence or progression of the disease¹⁻³. The use of conplastic animals-individuals with the same nuclear genome but different mtDNA variants-provides an accurate tool to study the influence of the mitochondrial background in the ageing process⁴.

Objectives: To study the influence of mtDNA variation in the degree of joint deterioration of the knees of aged animals using a conplastic mouse model of ageing

Methods: mtDNAs from C57BL/6 and NZB/OlaHsd mice were used. These mtDNAs differ by 12 missense mutations, 4 tRNAs mutations, 8rRNAs mutations and 10 non-coding region mutations. Then, a conplastic mice strain was developed with the C57BL/6 nuclear genome and the NZB/OlaHsd mtDNA (BL/6^{NZB}) to compare with the original C57BL/6 strain (BL/6^{C57}) in animals of 25 and 75 weeks. A total of 38 limbs from 19 mice were processed to perform histologic analyses: 8 BL/6^{NZB}25 w, 10 BL/6^{NZB}75 w, 10 BL/6^{C57}25 w and 10 BL/6^{C57}75 w.

Results: Mankin score data showed significantly increased values in all knees from both strains at 75 w compared with 25 w ($p<0.001$), confirming the ageing of the joint. When 75 w mice were selected (table 1), the BL/6^{C57} strain showed a significantly increased score in whole joint ($p=0.038$), femoral condyles ($p=0.021$) and medial femoral condyle ($p=0.015$) than BL/6^{NZB} strain. Safranin-O/Fast-green ratio value at 75 w was higher in the medial compartment of BL/6^{NZB} compared with BL/6^{C57} (both tibial plateau and femoral condyle); however, only the differences detected in the medial compartment of the tibial plateau reached the statistical significance ($p<0.001$), whilst the differences detected in the femoral condyle borderline the statistical significance ($p=0.091$).

The width of the epiphyseal plate was analysed in both tibia and femur bones. The results showed significantly decreased values in BL/6^{C57} at 75 w compared with the same strain at 25 w in tibial plateau ($p<0.001$) and femoral condyle ($p=0.049$); however, these differences were not observed in animals belonging to BL/6^{NZB} strain. In addition, the BL/6^{C57}75 w strain also showed significantly lower values in tibial plateau than BL/6^{NZB} strain at the same age ($p=0.032$).

Abstract SAT0561 – Table 1. Mankin score grading of cartilage destruction in conplastic mice BL/6^{C57} and BL/6^{NZB} at 75 w

	LTP	LFC	MTP	MFC	TP	FC	Med comp	Lat comp	Whole joint
BL/	5,80	4,40	4,67	6,00	10,44	10,37	10,14	10,20	19,71
6 C57	$\pm 1,81$	$\pm 1,07$	$\pm 2,06$	$\pm 1,07$	$\pm 3,43$	$\pm 1,85$	$\pm 3,02$	$\pm 2,39$	$\pm 4,57$
BL/	5,00	4,38	4,40	4,44	9,40	8,71	8,44	9,13	17,43
6 ^{NZB}	$\pm 2,11$	$\pm 0,92$	$\pm 2,12$	$\pm 1,24^*$	$\pm 1,78$	$\pm 1,70^*$	$\pm 2,60$	$\pm 1,55$	$\pm 1,72^*$

LTP: lateral tibial plateau; LFC: lateral femoral condyle; MTP: medial tibial plateau; MFC: medial femoral condyle; TP: tibial plateau; FC: femoral condyle; Med comp: medial compartment; Lat comp: lateral compartment; * $p<0.05$ with respect to BL/6^{C57}

Conclusions: This study demonstrates the functional impact of mtDNA variation in the process of joint deterioration associated to ageing, leading to consider the mtDNA as a potential therapeutic target in osteoarthritis associated to ageing

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SAT0562

HIP SHAPE PREDICTS KNEE OSTEOARTHRITIS OUTCOMES OVER A DECADE IN OLDER-ADULTS

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Background: Various hip shapes may be important as a risk factor for development and progression of knee osteoarthritis, due to the biomechanical link between the two joints.

Objectives: This study aims to identify the relationship between hip morphology and structural and clinical osteoarthritis outcomes in the knee over 10.7 years, in older-adults.

Methods: 377 community-dwelling older-adults aged 50–80 years were studied. At baseline, dual-energy X-ray absorptiometry images of the left hip were obtained and hip shapes were described using mode scores from an 85-point statistical shape model. MRI scans were conducted at baseline and a mean follow-up of 10.7(SD:0.67) years later, to assess right knee tibial cartilage volume and bone-marrow lesions(BMLs). Knee pain was assessed using Western Ontario and McMaster Universities Osteoarthritis Index(WOMAC). Knee replacement(KR) data were obtained by data linkage to the Australian Orthopaedic Association National Joint Replacement Registry. Linear mixed-effects, log-binomial models