Results: There were 43 members from 30 local associations in Oulu, Mikkeli, Helsinki and Turku in these geocaching trainings. All these members are suffering from rheumatic and other musculoskeletal diseases (RMDs) and work as volunteers for sport and physical activity, and now for geocaching. By 12 October 2018 there were 48 reumageocaches made by 13 local associations. The caches were logged 6593 times. So local associations earned 173-4303 euros each to be used for promoting sport and physical activity programmes and active lifestyles.

Conclusion: Promoting an active lifestyle is part of the health and wellbeing policy in The Finnish Rheumatism Association. The goal is to encourage people of all ages to stay healthy by getting enough exercise.

The geocaching project shows that it is easy to some of local associations to start projects like this. Some associations thought that it is too difficult to learn new methods especially when their members are elderly people. Geocaching is increasingly popular, inclusive, a fun and healthy pastime for individuals of all ages. It is also great for groups like local associations, families, friends, and youth groups working as teams. Those local associations that were involved in this project received a great budget for their local sport and physical activity programmes. It is great to see something evolving from the beginning and come into being.

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Cartilage, synovium and bone

OP0071

REVEALING THE LINK BETWEEN OSTEOARTHRITIS DEVELOPMENT AND MESENCHYMAL STEM CELL SENEESCENCE

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Background: Tissue accumulation of p16^{INK4A}-positive senescent cells is associated with age-related disorders such as osteoarthritis (OA). These senescent cells induce a tissue loss of function through a particular secretory phenotype called SASP (senescence-associated secretory phenotype).

Objectives: Links between OA onset and cellular senescence remain poorly detailed. We wanted to determine the localization of articular senescent cells in *in vivo* OA mouse models and study the involvement of mesenchymal stem cells (MSC) senescence in OA pathogenesis.

Methods: Wild-type mice C57BL/6, SAMP8/R1 (senescence accelerated mouse-prone and resistant), transgenic p16^{INK4A} +Luc and p16^{INK4A} Luc/Luc were used. Experimental OA was induced by intraarticular injections of collagenase (CIOA). Cartilage, synovial tissue and subchondral bone were analyzed by histology, RT-qPCR and micro-tomography. MSCs come from healthy human donors and primary chondrocytes from OA patients.

Results: (1) CIOA was induced in senescence-driven luciferase transgenic mice. Under CCD camera, a peak in luminescence was detected at day 24 post-injection revealing the presence of senescent cells in the joint. Remarkably, articular senescence is not only a marker of the pathology but contributes to OA onset: mice deficient in p16^{INK4A}, a main senescence-driving known cell cycle inhibitor, were partially protected against CIOA. These results were confirmed in C57BL/6 mice after CIOA by showing an increase in gene expression for senescence, catabolic and inflammatory markers in the synovial tissue preceding cartilage degradation.

(2) MSCs found in synovial, cartilage, fat pad and bone marrow participate in joint homeostasis. Because MSC are proposed to be at the root of OA development, we hypothesize that cellular senescence onset in these progenitor cells would be a possible etiological factor for OA. We have established an *in vitro* p16^{INK4A}-induced senescence model on human primary MSC: their intrinsic properties such as self-renewing are altered during senescence onset. Furthermore, in co-culture conditions with chondrocytes from OA patients, senescent MSC lost their extrinsic chondroprotective properties.

(3) To *in vivo* challenge these findings, we rely on the mouse model of accelerated senescence SAMP8, which develop spontaneous OA at the age of 6 months with cartilage degradation, synovial hypertrophy, osteophytosis and subchondral bone remodeling associated to meniscal calcification. Isolated MSC from these mice express senescence but non-inflammatory markers (p16^{INK4A}, p21waf1, MMP13, TGF-β1). Remarkably, intra-articular injection of these isolated SAMP8-derived MSC compared to SAMR1-derived control MSC, in young wild-type C57BL/6 mice, was sufficient by its own, to induce significant articular cartilage degradation (OA score of 12.2 ± 1.5 vs 6.1 ± 3.5 for SAMP8 and SAMR1 MSC respectively. p < 0.05).

Conclusion: p16^{INK4A}-induced cellular senescence in MSC played a causative role in cartilage loss of function and OA pathogenesis. *In vitro*, senescent MSC show

altered intrinsic and extrinsic supportive tissue functions. *In vivo*, intra-articular injection of senescent MSC was sufficient to induce cartilage degradation. Specific targeting of such deleterious senescent cells could be an innovating and promising treatment in OA.

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OP0072

INHIBITION OF CLK2 AND DYRK1A BY SM04690 AS A NOVEL MOLECULAR REGULATOR OF WNT SIGNALING, CHONDROGENESIS, AND INFLAMMATION, A POTENTIAL DISEASE-MODIFYING TREATMENT FOR KNEE OSTEOARTHRITIS

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Background: In the synovial joint, Wnt pathway upregulation contributes to osteoarthritis (OA) by increasing osteocyte differentiation, cartilage thinning, and inflammation. SM04690, a novel small molecule, has previously demonstrated potential OA disease-modifying effects through Wnt pathway inhibition *in vitro* and *in vivo*.

Objectives: To elucidate the novel mechanism of action for SM04690 on Wnt pathway inhibition, chondrocyte differentiation, and anti-inflammation.

Methods: Wnt pathway activity was measured using a cell-based TCF/LEF luciferase reporter in SW480 colon cancer cells. A kinome screen (318 kinases) was performed. The effects of SM04690 on protein phosphorylation of serine and arginine rich splicing factors (SRSF proteins), Sirt1, and FoxO1 in hMSCs, chondrocytes, and synovial fibroblasts were measured by Western blot. The effects of SM04690 and siRNA knockdown (KD) on chondrogenic and Wnt pathway gene expression were measured by NanoString gene expression panels and effects on LPS-induced inflammatory cytokines (IL-6, IL-8, TNF-α) in BEAS-2B cells were measured by qPCR and ELISA. *In vivo*, the pharmacodynamic effects of SM04690 were evaluated in monosodium iodoacetate injection-induced and anterior cruciate ligament transection with partial medial meniscectomy rat knee OA models in which a single intra-articular SM04690 (0.1 μg, 0.3 μg, 1.0 μg) or vehicle injection was administered. Cartilage was isolated at Day 10 and 35; phosphorylation and expression of SRSF proteins, Sirt1, FoxO1, STAT3, and NF-κB were measured by Western blot.

Results: SM04690 was a potent (EC₅₀ = 11 nM) inhibitor of Wnt signaling. Cdc-like kinases (CLKs) and dual-specificity tyrosine kinase (DYRK1A) were identified as molecular targets of SM04690. In hMSCs and chondrocytes, compared to DMSO, SM04690 potently inhibited CLK-mediated phosphorylation of SRSF proteins. SM04690 also inhibited DYRK1A-mediated Sirt1 and FoxO1 phosphorylation, thus increasing total and nuclear FoxO1 levels. Compared to siRNA control, DYRK1A/CLK2 dual KD increased expression of chondrogenic genes (*COL2A1*, *ACAN*, *COMP*, *CD44* [all *P* < 0.05]). CLK2 and DYRK1A KDs each inhibited Wnt pathway genes (*AXIN2*, *TCF7*, *TCF4*, *LRP5*, *FZD6*, *FZD7*, *PITX2* [all *P* < 0.05]) with no effects on β-catenin levels, compared to siRNA control. In synovial fibroblasts, compared to DMSO, SM04690 decreased phosphorylation of NF-κB and STAT3. In BEAS-2B cells, compared to siRNA control, DYRK1A KD inhibited inflammatory cytokine production (IL-6, IL-8, TNF-α [all *P* < 0.05]), while DYRK1A/CLK2 dual KD enhanced anti-inflammatory effects of DYRK1A KD. In cartilage from rat OA models, compared to vehicle, SM04690 inhibited phosphorylation of SRSF proteins, Sirt1, FoxO1, and STAT3, as well as expression of NF-κB.

Figure 1. Schematic representation of SM04690's proposed mechanism of action via CLK2 and DYRK1A inhibition in OA