arthritides research with human cells is often performed in monolayer culture where the absence of extracellular matrix and other cell types results in alterations of cell functionality.

**Objectives:** To improve the predictive value of preclinical arthritis research by developing and optimizing innovative translational models to study human synovial pathology in vitro and in vivo.

**Methods:** Synovial biopsies from RA patients were obtained during joint replacement surgery and processed for either (1) explant cultures, (2) 3D-synovial micro-masses, (3) RA-SCID transplantation studies, and/or (4) a biobank to study lipidomics and monitor disease progression. For explant culture, 3mm biopsies were cultured for 24h w/o various inhibitors, and cytokine production was analyzed by Luminex. 3D-micro-masses were generated from primary RA FLS and CD14+ PBMCs, stimulated for 3 weeks with 10 ng/ml TNFα or TGFβ3 and analyzed by histology, IHC and QPCR. For target validation and preclinical imaging, 6mm biopsies were engrafted into SCID mice. Radiolucine- and fluorescently-labelled anti-CD64 antibodies were injected IV, and targeting was determined by biodistribution, μSPECT/CT and IVIS imaging analysis.

**Results:** Our first assay with RA synovium explants demonstrated to be highly suitable to test the therapeutic efficacy of inhibitors for TNFα, TLR4, p38 and the JAK-pathway, resulting in significantly reduced production of proinflammatory mediators after 24h of culture.

In contrast to the explant cultures, our 3D synovial micro-masses could be followed for weeks. In this second translational model, lining formation was observed at day 7 and the micro-masses could be stimulated to mimic RA- or OA-like features of synovial hyperplasia or fibrosis respectively. Long-term exposure to the RA-related cytokine TNFα lead to hyperplasia of the lining and an altered macrophage phenotype characterized by reduced CD663 expression. Conversely, the repair-related growth factor TGFβ3 induced fibroblast-like changes in the micromass lining, a hallmark of OA. This was accompanied by an increased expression of PLOD2, COL1A1 and cSMa.

Our third preclinical model, the RA synovium SCID mouse, was previously validated using adalimumab, secukinumab, and rituximab, and was now used to study CD64 as a potential marker to image synovitis. Gene expression of FGFR1 (CD64) in synovial explants from RA patients was shown to correlate positively to gene expression of pro-inflammatory factors IL1B, TNFA, IL8, S100A8, MCP1, and with damage-associated genes MMP2 and MMP13. Interestingly, dual-labelled 111In-DTPA-IRye800CW-anti-CD64 antibody showed high uptake in the synovial transplants of the SCID mice, and specifically visualized the subcutaneous synovial grafts by both μSPECT/CT and IVIS imaging.

**Conclusion:** The development of these translational models allows us to bridge the gap between preclinical and clinical drug development research. Whereas our synovial explant assay is ideal for short-term interventions, and the RA-SCID mouse a great translational model for in vivo preclinical studies, donor variability and access to sufficient tissue may be challenging. In such cases, the 3D synovial micro-mass model may be an excellent alternative. Especially in combined setting, these 3 translational approaches will improve target validation and preclinical development of novel anti-rheumatic drugs.

**REFERENCE:**


**Disclosure of Interests:** None declared


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**LINKING LIPID MARKERS TO SYNOVIAL HYPERPLASIA AND VASCULARIZATION IN OSTEOARTHRITIS BY MALDI-MSI**

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**Background:** Synovial inflammation or synovitis causes severe histological changes in the tissue affecting its normal functioning. These morphological changes are one of the most characteristic events in the OA pathology. Additionally, lipid species are recognized as important key factors in the development and regulation of inflammatory processes. Therefore, the lipid signature of the synovial membrane can provide new markers involved in the synovitis process undergoing the OA disease.

**Objectives:** To define the specific lipid profile and distribution in human control and OA synovial membranes.

**Methods:** Human synovial membrane samples of OA patients (n=13) and controls (n=10) were compared by matrix-assisted laser desorption ionization mass spectrometry imaging (MALDI-MSI). Tissue sections at 10 μm thickness were mounted on conductive slides and coated with norharmane matrix (7mg/ml: 2.1 chloroform/methanol) for lipid extraction. MALDI images were acquired using a MALDI TOF-TOF instrument (Rapiflex MALDI TissueTyper, Bruker, Germany) in reflectron positive and negative ionization mode at a pixel size of 50 μm. Multivariate statistical analysis was used to search for the lipids with the highest differences between OA and control synovial membranes. Then, lipid spatial distribution was investigated with Flex Imaging 4.1 software. Identities were based on tandem mass spectrometry analyses in comparison to LIPID MAPS Structure Database.

**Results:** MALDI-MSI in combination with principal component analysis (PCA) and discriminant analysis (DA) revealed differential lipid profile between OA and control samples. Data acquired in positive ion mode showed a good separation of OA patients and controls (Figure 1A). OA tissues showed higher lipid content in the mass/charge (m/z) range 600-800, compared to controls (Figure 1B). Among identified lipid species, we found 35 phospholipids significant differentially expressed between OA and controls, mainly classified in phosphatidylcholines (30%), phosphatidylethanolamines (26%), phosphatidylinositol (26%), phosphatidylserines (14%) and lysophosphatidylcholines (6%). Some of them showed a specific localization within tissue. For instance, the phosphatidylcholine (PC) m/z 734.56 showed a specific localization in the lining layer of hyperplastic OA synovium, whereas PC m/z 768.56 were located in the sublining layer characterized by high vascularity and inflammatory cell infiltrations (Figure 1C).

**Conclusion:** OA synovial tissues were characterized by a higher content of phospholipids, mainly PCs and PIs, compared to control synovial biopsies. Specific phospholipids related to morphological features of the synovial membrane have been described for the first time by MALDI-MSI. These molecules could have an important role in the synovitis associated with the pathogenesis of OA and constitute relevant molecular disease classifiers for the OA diagnosis.

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Background: Although health professional (HP) treatments are considered to be a corner stone in the management of systemic sclerosis (SSc), little is known about the referral process to and the content of non-pharmacological care in SSc.

Methods: Dutch HPs were invited through their SSc patients to complete an anonymous online survey provided by the Dutch ARCH (Arthritis Research and Collaboration Hub) working group. The survey comprised multiple response and open questions covering six topics: sociodemographic questions, referral reasons, diagnostic focus, treatment targets, interventions and the assessment of quality of communication between HPs and rheumatologists. A total of 79 HPs, 65.8% women (N=52), with a mean age of 41.2 (SD=13.6) from 8 different professions completed the survey. Physiotherapists were the largest group represented (73%, N=58).

Results: Further, the results describe a suboptimal communication between rheumatologists and HPs and after referral to the needs of the individual patient. Viewed from this perspective, it is evident that the referral process to SSc patients is still fragmented and suboptimal. The results of this study show clear discrepancies between referral reasons and applied interventions, visible in the clear focus on body functions and structures on one hand and the broad spectrum of applied interventions on the other hand.

Conclusion: The results of this study show clear discrepancies between referral reasons and applied interventions, visible in the clear focus on body functions and structures on one hand and the broad spectrum of applied interventions on the other hand. It is possible that HPs make a translation of the reasons given for referral to the needs of the individual patient. Viewed from this perspective, it is questionable whether the referrals by the rheumatologists are sufficiently targeted. Further, the results describe a suboptimal communication between rheumatologists and HPs that should be targeted in practice and further research.

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