arthritis 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 functions and loss of phenotype.

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 micromasses, (3) RA-SCID transplantation studies, and/or (4) a biobank for corresponding mRNA and IHC profiling. For explant culture, 3mm biopsies were cultured for 24hr w/o various inhibitors, and cytokine production was analyzed by Luminex. 3D-micromasses were generated from primary RA FLS and CD14+ PBMCs, stimulated for 3 weeks with 10 ng/ml TNF α or TGF β and analyzed by histology, IHC and QPCR. For target validation and preclinical imaging, 6mm biopsies were engrafted SC into SCID mice. Radionuclide- and fluorescently-labelled anti-CD64 antibodies were injected IV, and targeting was determined by biodistribution, μ SPECT/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 TNF α , TLR4, p38 and the JAK-pathway, resulting in significantly reduced production of proinflammatory mediators after 24hr of culture.

In contrast to the explant cultures, our 3D synovial micromasses could be followed for weeks. In this second translational model, lining formation was observed at day 7 and the micromasses could be stimulated to mimic RA- or OA-like features of synovial hyperplasia or fibrosis respectively. Long-term exposure to the RA-related cytokine TNF α lead to hyperplasia of the lining and an altered macrophage phenotype characterized by reduced CD163 expression. Conversely, the repair-related growth factor TGF β induced fibrosis-like changes in the micromass lining, a hallmark of OA. This was accompanied by an increased expression of *PLOD2*, *COL1A1* and α SMA.

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 *FCGR1* (*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 ^{111}In -DTPA-IrDye800CW-anti-CD64 antibody showed high uptake in the synovial transplants of the SCID mice, and specifically visualized the subcutaneous synovial grafts by both μ SPECT/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 micromass 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.

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OP0078

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 FlexImaging 4.1 software. Identifications were based on tandem mass spectrometry analyses in comparison to LIPID MAPS Structure Database.

Figure 1. A) PCA-DA analysis separates control and OA samples according to lipid profile. B) Loading plot of PCA-DA analysis representing the lipid masses characteristic to OA (negative side) and control (positive side) samples given by MALDI-MSI. C) MALDI-MSI images showing the differences in the spatial distribution of two phosphatidylcholines in OA synovium.

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%), phosphatidylinositols (26%), phosphatidylserines (14%) and lysophosphatidylcholines (6%). Some of them showed a specific localization within tissue. For instance, the phosphatidylcholine (PC) m/z 734.55 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). The PCA-DA analysis also showed a higher presence of phosphatidylinositols (PIs) and phosphatidylethanolamines specifically in OA samples, whereas lysophosphatidylcholines were more abundant in control samples compared to OA. Most of these molecules, mainly PIs, were also spatially distributed in the lining layer of the OA synovium.

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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WEDNESDAY, 12 JUNE 2019

Rehabilitation; opening Pandora's Box

OP0079-HPR

NON-PHARMACOLOGICAL CARE IN SYSTEMIC SCLEROSIS: OPENING THE BLACK BOX

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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. **Objectives:** To describe non-pharmacological care in SSc from the perspective of Dutch HPs, including referral reasons, diagnostic focus, interventions used and alignment in the communication between HPs and rheumatologists.

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 based on the Consumer Quality Index (CQI) (rheumatoid arthritis, version 2.0). Referral reasons and treatment targets were examined by means of open questions, and then linked to the ICF (International Classification of Functioning, Disability and Health) following the refined ICF Linking Rules (Cieza, 2016).

Results: 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). All in all 133 different referral reasons were reported that yielded 58 different ICF codes, of which 70.7% (N = 41) could be linked to the ICF domain "body structures and functions". The reported interventions focus on body functions and structures, training of daily activities, education and advices and psychosocial interventions (Table 1). The quality of communication between HPs and rheumatologists as perceived by the HPs is shown in Table 2.

Table 1. Interventions applied by the 79 health professionals, top 4 per topic

Interventions	N (%)
Treatments focus on bodily functions and/or structures	
Physical activity promotion	38 (48.3)
Training of body functions (e.g. muscular strength, range of motion)	34 (43.0)
Aerobic capacity training	25 (31.7)
Balance/coordination training	14 (17.7)
Training of activities	
Walking/biking	45 (57.0)
Movement activities/ sports	45 (57.0)
Leisure	19 (24.3)
Household	16 (20.3)
Education/advise/instruction	
Graded activity	44 (55.7)
Physical activity	42 (53.2)
Lifestyle (e.g. smoking, cold, silver gloves)	14 (17.7)
Energy conservation	12 (15.2)
Psychosocial interventions	
Self-management/ self-monitoring	52 (67.3)
Relaxation strategies/ stress management/ biofeedback therapy	23 (29.1)
Motivational Interviewing	13 (16.5)
Problem-solving training	10 (12.7)

Table 2. Quality of communication between HPs and rheumatologists, N (%)

	always/ mostly	sometimes/ never	N/A	don't know
Do you think that the treatments for SSc patients were well coordinated between you and the rheumatologist?	32 (42.7%)	20 (26.7%)	14 (18.7%)	9 (12.0%)
Do you think that the advice you and the rheumatologist gave to the SSc patients were well coordinated?	39 (52.0%)	16 (21.3%)	13 (17.3%)	7 (9.3%)
Did you and the rheumatologist, in your opinion, make good agreements with each other?	19 (25.4%)	26 (34.7%)	26 (34.7%)	4 (5.3%)
Did you inform the rheumatologist about the goals, progress and outcomes of your treatment?	31 (41.4%)	29 (38.6%)	14 (18.7%)	1 (1.3%)

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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Osteoporosis

OP0080

EFFECT OF DENOSUMAB VERSUS RISEDRONATE ON CORTICAL AND TRABECULAR BONE MICROARCHITECTURE BY HIGH RESOLUTION PERIPHERAL QUANTITATIVE COMPUTED TOMOGRAPHY (HR-pQCT) IN GLUCOCORTICOID-TREATED INDIVIDUALS

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Background: In a study of patients initiating or continuing GC, 12 and 24 months gains in lumbar spine and total hip areal bone mineral density (aBMD) were greater with DMB vs RIS.^{1,2}

Objectives: Evaluate the effects of DMB vs RIS on cortical and trabecular bone.

Methods: Phase 3, double-blind, double-dummy, active-controlled study randomised women and men ≥ 18 years, receiving GC (≥ 7.5 mg prednisone daily or equivalent) for <3 (GC-initiating [GC-I]) or ≥ 3 months (GC-continuing [GC-C]), to DMB 60 mg every 6 months or RIS 5 mg daily for 24 months. Subjects <50 years had a history of osteoporosis (OP) fracture. GC-C subjects ≥ 50 years had lumbar spine, total hip or femoral neck BMD T-score ≤ -2.0 ; or T-score ≤ -1.0 with history of OP fracture. All subjects were to receive daily calcium (≥ 1000 mg) and vitamin D (≥ 800 IU). In a subset, HR-pQCT scans of the distal radius and distal tibia were performed at baseline and Months 12 and 24. Treatment differences (DMB-RIS) were estimated using analysis of covariance (ANCOVA).

Results: The substudy enrolled 111 subjects (57 DMB, 54 RIS). DMB was associated with significantly greater increases than RIS in cortical thickness, total volumetric BMD (vBMD) and cortical vBMD at the radius and tibia at 12 and 24 months, and in trabecular vBMD at the radius at 12 months and tibia at 24 months (Table). Change in cortical porosity did not differ between DMB and RIS (Table). Percentage Change From Baseline and Treatment Difference in vBMD and Cortical Microarchitecture

		Distal Radius		Distal Tibia	
		Month 12	Month 24	Month 12	Month 24
Total vBMD	DMAb	1.8 (0.7, 2.8)	4.1 (2.6, 5.6)	1.3 (0.4, 2.2)	2.2 (1.2, 3.1)
	RIS	-1.1 (-2.2, 0.1)	-1.7 (-3.3, 0.1)	-0.8 (-1.8, 0.1)	-1.4 (-2.4, 0.4)
Cortical vBMD	DMAb-RIS	2.9 (1.4, 4.4)†	5.8 (3.6, 7.9)†	2.2 (0.9, 3.5)†	3.6 (2.2, 5.0)†
	DMAb	0.2 (-0.4, 0.8)	1.2 (0.4, 1.9)	0.5 (-0.1, 1.1)	1.0 (0.4, 1.5)
Trabecular vBMD	RIS	-0.7 (-1.3, 0.1)	-1.4 (-2.2, 0.6)	-0.7 (-1.3, 0.1)	-1.3 (-1.8, 0.7)
	DMAb-RIS	0.9 (0.1, 1.8)	2.6 (1.5, 3.6)†	1.2 (0.4, 2.1)	2.2 (1.4, 3.1)†
Cortical porosity	DMAb	2.3 (0.2, 4.3)	9.4 (1.4, 17.3)	0.8 (-0.3, 1.8)	1.7 (0.7, 2.8)
	RIS	-0.9 (-3.0, 1.1)	-0.7 (-9.0, 7.6)	-0.3 (-1.3, 0.7)	-0.4 (-1.5, 0.6)
Cortical thickness	DMAb-RIS	3.2 (0.3, 6.1)	10.1 (-1.4, 21.6)	1.1 (-0.4, 2.5)	2.1 (0.7, 3.6)
	DMAb	2.3 (-2.9, 7.5)	8.5 (1.1, 15.9)	1.3 (-2.5, 5.2)	3.0 (-0.7, 6.6)
	RIS	2.2 (-3.1, 7.6)	10.2 (2.5, 18.0)	2.0 (-1.9, 5.9)	1.7 (-2.1, 5.5)
	DMAb-RIS	0.1 (-7.3, 7.5)	-1.7 (-12.4, 9.0)	-0.7 (-6.1, 4.8)	1.3 (-4.0, 6.6)
	DMAb-RIS	5.2 (2.9, 7.4)†	8.6 (5.4, 11.8)†	3.5 (1.7, 5.2)†	6.0 (3.5, 8.5)†

Reported as LS mean (95% CI); p-value based on ANCOVA that included treatment, baseline value, and duration of prior GC use (<12 vs ≥ 12 months) as covariates. N = no. of subjects enrolled in substudy; n = no. of subjects with observed data p-value for treatment difference: *p<0.05; †p≤0.001