Background: Since the discovery of the sphingosine-1-phosphate (S1P) path- 
way and its potentially beneficial role of inducing lymphocyte retention and sub- 
sequent immunomodulation [1], several small molecule S1P receptor modulators 
have been approved for the treatment of diverse autoimmune diseases such as 
multiple sclerosis and ulcerative colitis. Cenerimod, a selective S1P1 receptor 
modulator, has shown efficacy in preclinical models of systemic lupus erythemato- 
sos (SLE), systemic sclerosis and Sjögren's syndrome [2-4] and is now enter- 
ing a Phase III clinical trial (OPUS; NCT05648500) in patients with moderate to 
severe SLE.

Objectives: We investigated the efficacy of cenerimod in modulating disease 
progression in preclinical models of rheumatoid arthritis (RA).

Methods: We analyzed the efficacy of cenerimod in several models of 
RA in mice and rats. Disease-relevant biomarkers such as autoantibody 
development and chemokine secretion were measured to gain a deeper 
understanding of the mode of action of S1P1 receptor modulation in these 
RA models.

Results: In mouse RA models, prophylactic treatment with cenerimod inhib- 
ited the acute inflammatory response post antigen challenge and prevented 
autoantibody formation, thus completely preventing the initiation of disease. 
Cenerimod treatment at disease onset further showed a strong reduction of 
joint inflammation and significantly delayed clinical symptoms and the secre- 
tion of several pro-inflammatory chemokines. Although corticosteroid treat- 
ment is frequently administered as an adjunct treatment for interventional 
disease management in RA, its systemic toxic effects do not permit long-term 
usage to control disease activity in patients with rheumatic diseases [5]. In 
rats, cenerimod treatment prevented disease development dose-dependently 
when given directly at initiation of disease, while treatment at disease onset 
stopped further exacerbation of the joints. Further, treatment with low-dose 
cenerimod limited joint inflammation to the same extent as low-dose corticos- 
teroid treatment while not having a similar negative impact on body weight 
over the duration of the experiment.

Conclusion: S1P receptor immunomodulation is a highly effective treatment 
option for murine models of RA with translational value for rheumatological 
idications. Combined with the published data on rheumatic diseases, we believe 
that S1P1 receptor modulation by cenerimod will benefit patients suffering from 
RA who are underserved by the current treatment landscape.

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POS1029 MACROPHAGE MARKERS FOLLOW RECEPTOR BETA 
AND CD206 ARE DIFFERENTIALLY EXPRESSED IN 
SYNOVIAL TISSUE OF RA PATIENTS WITH A DIFFUSE-
MYELOID, LYMPHO-MYELOID AND FIBROD-PAUCI 
IMMUNOPATHOTYPE

Keywords: Rheumatoid arthritis, Prognostic factors, Imaging

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Background: Three different synovial immunopathotypes of rheumatoid arthritis 
(RA) have been identified: Fibroid-Pauci immune (FP, fibroblast-rich), Diffuse-Mye- 
loid (DM, macrophage-rich) and Lympho-Myeloid (LM, lymphocyte- and 
macrophage-rich), and have been associated with treatment outcome to biologics 
[1]. Therefore, identification of the synovial immunopathotypes before the start 
of therapy could be supportive for development of individualized treatment strat- 
egies. However, this currently requires invasive synovial tissue sampling. Novel 
whole-body molecular imaging with positron emission tomography (PET) and the 
use of specific PET tracers can non-invasively detect and quantify the presence 
of immune cells in RA inflamed synovium. Folate-receptor beta (FRβ1) is a cell 
surface receptor on macrophages, shown clinical exploitation for high specific-
ity PET imaging of arthritis [2]. However, it remains to be elucidated whether 
FRβ1 is a suitable marker for RA immunopathotype stratification. Furthermore, it 
is unclear whether FRβ1 is expressed on macrophages with a pro-inflammatory 
(M1) or homeostatic (M2) phenotype in the 3 immunopathotypes.

OBJECTIVES:
(1) Investigate FRβ1 expression across the three distinct RA immunopathotypes.
(2) Investigate FRβ1 expression in relation to the general macrophage marker 
CD68 and the mannose receptor CD206 (which is associated with M2-type 
macrophages [3]).

Methods: Synovial biopsies of the RA-affected ankle or knee (N=28) were 
retrieved from RA patients with clinically active disease defined by ACR RA 
criteria [4]. Subsequently, biopsy sections were immunohistochemically stained 
in order to stratify each patient into one of three RA-immunopathotypes. Confocal 
microscopy was used to determine CD68, FRβ1 and CD206 expression (integ-
ated density), and co-expression (comparing fold-change average expression) 
for all patients within each immunopathotype (N=8-10/group).

Results: Out of 28 RA synovial biopsies 10 could be classified as FP, 9 DM and 9 
LM immunopathotype. Average expression of CD68, FRβ1 and CD206 was significantly 
increased in the DM and compared to the FP immunopathotype (#P <0.01). Quan-
titative CD68, FRβ1 and CD206 expression was highest in the DM immunopathotype. 
FRβ1 expression correlated significantly with CD206 expression in all three pathotypes 
(Spearman Rho= 0.67, P<0.001). On the contrary FRβ1 expression did not 
correlate with CD68 expression except in the DM pathotype (Spearman Rho= 0.46).

Conclusion: The results of the study put forward that FRβ1 is a potential target 
for delineation of RA immunopathotypes, to be explored for non-invasive molec-
ular imaging stratification. Furthermore, investigation of FRβ1 expression 
has an additive value over CD68 since it can be used to distinguish the presence of M2 
macrophages in the RA synovium specifically.

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POS1030 DNA-METHYLATION PROFILING IN THE BLOOD 
OF PATIENTS WITH RHEUMATOID ARTHRITIS-
ASSOCIATED INTERSTITIAL LUNG DISEASE

Keywords: Genetics/epigenetics, Lungs, Rheumatoid arthritis

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