weeks later. STP938 was administered to mice developing signs of arthritis from Day 28 to 45 orally daily b.i.d.

Results: STP938 inhibited *in vitro* proliferation of HEK_{wt} but not HEK-CTPS1_{KO} cells as well as Jurkat and human PBMCs. STP938 demonstrated a significant and dose-dependent inhibition of KLH-specific T and B cell responses *in vivo*. STP938 significantly reduced the disease severity in the CIA model in a dose-dependent manner as determined by clinical and histopathological readouts.

Conclusion: Our preliminary *in vitro* and *in vivo* results indicate that inhibition of CTPS1 specifically blocks proliferation of cells derived from the lymphocyte lineage and reduces the T cell driven inflammatory response. These data highlight the therapeutic potential of STP938 in treating patients with autoimmune diseases such as rheumatoid arthritis.

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OP0035

ASSESSMENT OF THE INTESTINAL PERMEABILITY IN PATIENTS WITH RHEUMATOID ARTHRITIS USING COLONIC TISSUES AND SERA

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Background: Patients with rheumatoid arthritis (RA) have an altered gut microbiota (dysbiosis) (1-3). This microbiota interacts with intestinal epithelium which can lead to an increased intestinal permeability, responsible for the passage of antigens and inflammatory molecules, and can therefore promote systemic inflammation. Gut microbiota tends to normalize with disease control (2), suggesting that systemic inflammation may directly influence the composition of microbiota and the gut barrier. It was shown in many inflammatory diseases that intestinal permeability is impaired, but to date there is very little data in RA.

Objectives: In the present study, we evaluate the intestinal permeability in RA patients by analyzing tight junctions in colonic biopsies and serum markers.

Methods: Colonic biopsies from 20 RA patients who underwent colonoscopy for screening with normal histology were compared with those from 20 age and sex matched controls. ZO-1, occludin and claudin 2 junction proteins were evaluated by immunohistochemistry. The staining intensity was assessed by two blinded independent readers. The serum concentrations of LPS-binding protein (LBP), CD14s and zonulin were evaluated by ELISA in 25 patients naive of DMARDs, 41 patients before and after introduction of a DMARDs and 21 controls. Elevated zonulin in serum indicates an increase in intestinal permeability while LBP and CD14s indicate bacterial translocation.

Results: ZO-1 expression was significantly lower in biopsies from patients with RA than controls (mean score $\pm$ SD of 1.6 ± 0.56 vs 2.0 ± 0.43 ; $p = 0.01$). Age, sex, disease duration and immunological status did not significantly influence the expression of colonic junction proteins. LBP and CD14s were higher in serum from RA patients naive of DMARDs than controls ($p = 0.002$ and $p = 0.003$). LBP, CD14s and zonulin levels significantly correlated with DAS28 ($r = 0.61$, $p = 0.005$; $r = 0.51$, $p = 0.030$ and $r = 0.46$, $p = 0.049$, respectively). After treatment, unlike non-responders, LBP and CD14s were significantly reduced in DMARD responders and variations in LBP and CD14s significantly correlated with changes in DAS28 ($r = 0.46$, $p = 0.002$ and $r = 0$, $p = 0.030$, respectively).

Conclusion: This work is one of the first to explore intestinal permeability in RA and to show altered tight junction in colonic tissue from RA. This increased intestinal permeability appears to be related to the systemic inflammation. Improving the gut microbiota through food or probiotics could enhance the effect of treatments by limiting this amplification loop of inflammation.

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OP0036

IL-6 ACTIVATES YES-ASSOCIATED PROTEIN (YAP) IN FIBROBLASTS AND INDUCES YAP-SNAIL COMPLEX FORMATION TO DRIVE SYNOVIAL LINING PATHOLOGY IN INFLAMMATORY ARTHRITIS

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Background: In rheumatoid arthritis (RA), the fibroblast-like synoviocytes (FLS) in synovial lining become invasive and cause joint destruction. The molecular mechanisms underpinning this pathogenic FLS phenotype are incompletely understood. The FLS descend from *Growth differentiation factor 5* (*Gdf5*)-expressing joint interzone cells in the embryo, and we showed that conditional ablation of the transcriptional co-activator Yes associated protein (Yap) in *Gdf5*-lineage cells prevents synovial lining hyperplasia after traumatic cartilage injury in mice [1].

Objectives: Here, we investigated a potential role for Yap in pathogenic FLS in immune-mediated inflammatory arthritis.

Methods: Immunohistochemistry was used to detect Yap in human RA synovium and Yap, Snail and Ctcf in mouse synovium following antigen-induced arthritis (AIA). To determine the effect of Yap knockout (KO) in synovial stromal cells, AIA was induced in *Gdf5-Cre;tdTomato;Yap^{fl/fl}* (Yap cKO) and *Gdf5-Cre;tdTomato;Yap^{wt/wt}* (control) mice, or in *Pdgfra-CreER;Yap^{fl/fl}* (Yap cKO, targeting *Pdgfra*-expressing fibroblasts) and *Yap^{fl/fl}* or *Yap^{wt/wt}* (control) mice after adult tamoxifen induction. Yap KO in both models was confirmed by immunohistochemistry. After nine days, arthritis severity was determined by histological scoring of synovial lining hyperplasia, immune infiltrates, cellular exudate, and marginal erosions. *TdTomato+ Gdf5*-lineage cells in synovium were quantified. *In vitro*, Yap reporter cells were treated with inflammatory cytokines to evaluate their ability to stimulate Yap-induced GFP expression by flow cytometry. Snail overexpression, siRNA-mediated Yap knockdown, and IL-6/sIL-6R stimulation were performed on normal mouse FLS, AIA-FLS or human RA-FLS, and cell invasion through a matrigel-coated transwell was quantified. A proximity ligation assay was utilised to detect Yap/Snail complex formation.

Results: Average expression levels of Yap ($p < 0.0001$), its transcription factor partner Snail ($p = 0.002$), and their downstream target Ctcf ($p = 0.0003$), were increased in mouse synovium after AIA ($n = 5$), and Yap was highly expressed by FLS in human RA synovium. Yap cKO mice ($n = 24$) showed a significantly decreased arthritis severity ($p = 0.002$) after AIA compared to controls ($n = 22$), with significant reductions in synovial lining hyperplasia ($p < 0.001$), synovial immune cell infiltrates ($p = 0.026$) and marginal erosions ($p = 0.002$). Similarly, Yap cKO mice ($n = 6$) showed a significant decrease in arthritis score ($p = 0.039$) after AIA compared to controls ($n = 9$). However, both control mice ($p < 0.001$) and Yap cKO mice ($p < 0.001$) showed an extensive expansion of *tdTomato+ Gdf5*-lineage synovial cells after AIA, with no significant difference between control and Yap cKO mice. *In vitro*, Yap knockdown prevented IL-6/sIL-6R-induced invasion of normal mouse FLS ($p = 0.037$) and decreased the invasiveness of AIA-FLS ($p = 0.0057$). Using Yap reporter cells, we found that Yap was activated by IL-6/sIL-6R ($p = 0.016$), but not TNF α or IL-1 β . Finally, IL-6/sIL-6R treatment of normal mouse FLS ($p = 0.033$) or human RA-FLS ($p = 0.036$) induced Yap-Snail complex formation, and Yap knockdown prevented FLS invasion induced by Snail overexpression ($p = 0.027$).

Conclusion: These data demonstrate that via activation by IL-6, and co-operation with the transcription factor Snail, Yap acts as a key modulator of the invasive and destructive phenotype of FLS in inflammatory arthritis. Therapeutic targeting of Yap could reduce joint destruction in RA.

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