secretion by patient-derived monocytes, a mechanism with translational potential in SpA.

**Conclusion:** Our detailed characterization of Tregs at an important inflammatory site illustrates the marked specialization of Treg subpopulations and identifies a broad transcriptional profile upregulated across all synovial regulatory cells. Our TCR analysis provides evidence of Treg clonal expansion, which may be driven by antigen, and confirms functional specialisation of individual clones. We also propose a new insight into a Treg functional mechanism through LAG-3 that suggests a novel therapeutic approach to immune-driven diseases.

**REFERENCES:**
[1] Penkava et al., Nature Communications, 2020

**Disclosure of Interests:** Davide Simone: None declared, Frank Penkava: None declared, Anna Ridley: None declared, Stephen Sansom: None declared, Hussein Al Mossawi Employee of: UCB, Paul Bowness Grant/research support from: Regeneron, Celgene/BMS and GSK.

**DOI:** 10.1136/annrheumdis-2021-eular.4278

**Figure 1.** Six month DAS28CRP remission versus pre-treatment median fluorescence of CD39 expression on CD4+ T-cells (A); CD25 High expressing CD4+ T-cells (B); and ROC curve of predictive utility of pre-treatment CD39 expression on CD25 High CD4+ T-cells (C).

**Conclusion:** These findings support the potential role of CD39 in the mechanism of methotrexate response. Expression of CD39 on circulating Tregs in treatment-naïve RA patients may have particular value in identifying early RA patients likely to respond to methotrexate, and hence add value to evolving multi-parametric discriminatory algorithms.

**REFERENCES:**

**Disclosure of Interests:** None declared

**DOI:** 10.1136/annrheumdis-2021-eular.2030
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 HEK293_p 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. We further demonstrated 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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2. Disclosure of Interests: Hélène Asli, Eli Lilly Company of: Step Pharma, Andrew Novar. None declared. Louise Birch Shareholder of: Step Pharma, Rebecca Lane: None declared. Norbert Minet Employee of: employee as Ph D student under CIFIRE grant, David Laughton: None declared, Pascal George Shareholder of: Step Pharma, Geoffroy de Ribains Shareholder of: as former employee of Step Pharma, Employee of: former employee of Step Pharma, Sylvain Latour: None declared, Alain Fischer: None declared, Tim Bourne Shareholder of: UCB, Step Pharma, Stryx Therapeutics, Consultant of: a range of biotech companies, Employee of: former employee of Step Pharma and Stryx Therapeutics, Andrew Parker Employee of: Step Pharma

**DOI:** 10.1136/annrheumdis-2021-eular.148

**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 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 Ctgf 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;Ya pfl/fl (Ya p cKO) and Gdf5-Cre;tdTomato;Ya pcre/cre (control) mice, or in Pdgfr-Cre;Yapfl/fl (Ya p cKO, targeting Pdgfr-expressing fibroblasts) and Yapcre/cre or Yapcre/cre (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 over-expression, 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 Ctgf (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=0.028) 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 expanded expression 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 human RA-FLS (p=0.057). Using Yap reporter cells, we found that Yap was activated by IL-6/sIL-6R (p=0.016), but not TNFα or IL-1β. 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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**Acknowledgements:** This work was funded by the Medical Research Council (MR/L020211/1 and MR/L022893/1) and Versus Arthritis (20775 and 21156).

**Disclosure of Interests:** None declared

**DOI:** 10.1136/annrheumdis-2021-eular.2530