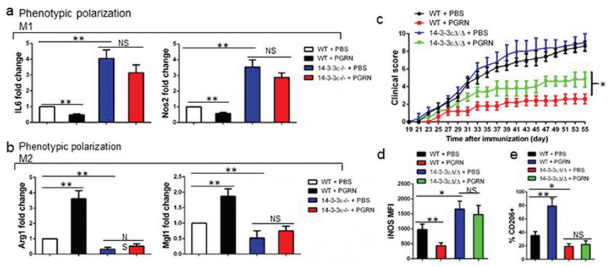

Abstract THU0056 – Figure 1. 14–3–3ϵ is a critical mediator of PGRN' regulation of macrophage polarisation and contributes to PGRN's anti-inflammation action. (a, b) qPCR analysis of Il1b and Nos2 (a), or Arg1 and Mgl1 (b) mRNA expression in WT, or 14–3–3ϵ-/- macrophages which are polarised to M1 (a) or M2 (b) in the the absence or presence of PGRN (200ng/ml). (c) Clinical arthritis score of WT or 14–3–3$\epsilon\Delta/\Delta$ CIA mice treated with or without PGRN. n=8 (d, e) CD45+CD11b+ cells were analysed for MFL of iNOS (d) and percentage of CD206+ cells (e). * p<0.05, ** p<0.01, NS=no significance

Conclusions: Both *in vitro* and *in vivo* results indicate that 14–3–3ϵ is a key molecule regulating macrophage polarisation which plays an important role in inflammatory arthritis, and it is an essential component for PGRN/TNFR2 mediated protective effect against inflammatory arthritis.
Disclosure of Interest: None declared
DOI: 10.1136/annrheumdis-2018-eular.4729

THU0057 MECHANICAL STRAIN DETERMINES THE SITE-SPECIFIC DIRECTION OF INFLAMMATION AND TISSUE DAMAGE IN ARTHRITIS

I. Cambré[1], D. Gaublomme[1], A. Burssens[1], P. Jacques[2], L. Meuris[3], S. Lambrecht[2], S. Carter[4], A. De Muynck[5], N. Callewaert[3], G. Kollias[6], R. Lories[4], G. Schett[7], D. Elewaut[1]. [1]*Rheumatology, UGENT/VIB*; [2]*Rheumatology, UZ Gent*; [3]*Biochemestry and Microbiology, UGENT/VIB, Ghent*; [4]*Development and Regeneration, KUL, Leuven*; [5]*Physics and astronomy, UGent*; [6]*Experimental Physiology, Biomedical Sciences Research Center 'Alexander Fleming'*; [7]*Rheumatology and Immunology, Friedrich Alexander University of Erlangen-Nuremberg and Universitatsklinikum, Ghent, Belgium*

Background: Many pro-inflammatory pathways leading to arthritis act systemically on the immune system rather than locally in the joint. However, the reason behind the regional and patchy distribution of arthritis represents a longstanding paradox.
Objectives: To explore the relation between mechanical strain and joint inflammation and to understand the underlying basis of joint pattern involvement in inflammatory rheumatic diseases.
Methods: Arthritis was induced by collagen-induced arthritis (CIA) and passive collagen antibody induced arthritis (CAIA) in respectively C57BL/6 and RAG2-/- (T- and B-cell deficient) mice. Animals were subjected to different regimens of mechanical strain. Increased strain occurred in voluntary running mice whereas tail suspension (unloading) abolished mechanical strain; both were compared to control housing conditions. The impact of different loading conditions was measured on clinical disease score, histology, micro-CT images and erosion quantification, gene induction in tendon and synovial tissue, immune cell recruitment *in situ*, development of anti-collagen antibodies and their pattern of siaylation and galactosylation.
Results: Voluntary running of CIA in C57BL/6 mice markedly induced an early onset and increased progression whereas no disease onset could be observed in the hind paws from animals in unloaded conditions. CAIA in running RAG2-/- mice also induced early arthritic symptoms and severe progression. Intriguingly, running conditions were sufficient to induce arthritis without the need of LPS as an inflammatory trigger. Mechanical strain did not alter however IgG autoantibody levels nor their levels of galactosylation and sialylation. Furthermore, we demonstrate that mechanical strain on stromal cells results in recruitment of classical monocytes into specialised mechano-sensitive regions characterised by a unique microanatomy. This promotes local inflammation and differentiation into local osteoclasts which induce regional erosions. A striking similarity was observed in the pattern of joint erosions in human patients with RA and SpA which were also confined to these mechanosensitive regions.
Conclusions: This study provides the first evidence that mechanical strain controls the transition from systemic autoimmunity into site-specific joint inflammation. Homing of inflammation and development of erosions was confined to specific mechano-sensitive regions, characterised by a high number of attachment- and contact points for tendons. This represents a novel paradigm and explains why arthritis in mice and humans is characterised by a regional and patchy distribution. Curiously, this pathway does not rely on adaptive immunity but rather on stromal cells. Mechano-stimulation of mesenchymal cells induced CXCL1 and CCL2 permitting recruitment of classical monocytes which can differentiate into bone-resorbing osteoclasts. Thus, mechanical strain controls the site-specific direction of inflammation and tissue damage in arthritis.
Acknowledgements:
Disclosure of Interest: None declared
DOI: 10.1136/annrheumdis-2018-eular.4736

THU0058 TAS8274, A HIGHLY SELECTIVE JANUS KINASE 3 INHIBITOR, SHOWS POTENT EFFICACY, BUT DOES NOT AFFECT HOST DEFENSE, IN PRECLINICAL MOUSE MODELS

H. Hayashi, S. Demizu, K. Tanaka, M. Mitsuya, A. Saito, T. Utsugi, E. Sasaki, Y. Iwasawa. *Taiho Pharmaceutical co., LTD., Tsukuba, Ibaraki, Japan*

Background: The family of Janus kinases (JAKs) plays important roles in signalling pathway mediated by various cytokine receptors. An aberrant activation of JAK-STAT signalling has been reported to be involved in the pathogenesis of autoimmune diseases[1]. Pan-JAK inhibitors have shown a good efficacy in patient with rheumatoid arthritis (RA)[2]. However, their use is limited due to safety concerns, including severe herpes zoster infection, by inhibiting JAK1-mediated interferon signaling[3]. Therefore, a selective JAK3 inhibitor would provide a better balance between efficacy and safety than pan-JAK inhibitors.
Objectives: We identified the characteristics of TAS8274, a novel highly selective inhibitor of JAK3, using *in vitro* assays, a mouse model of collagen-induced arthritis (CIA), and a mouse model of herpes simplex virus (HSV)−1 infection.
Methods : *In vitro* biochemical assay was performed using available kinase assay panels. The effects on anti-inflammatory responses were assessed by examining cytokine productions. IL-2, IL-3, and IFN-α–induced phosphorylation of STAT proteins in peripheral blood mononuclear cells (PBMCs) were analysed by a flow cytometry method. NK cell cytotoxicity in the presence of IFN-α was evaluated by Cr^{51} release assay. In a mouse skin HSV-1 infection model, TAS8274 and tacrolimus were administered for 7 days before inoculation of the virus on the back skin, and then were administered for another ten consecutive days. At the end of this experiment, the number of papules on the back was counted. To evaluate the therapeutic efficacy using mouse CIA model, TAS8274 was orally administered to CIA mice after the disease onset. Disease severity was evaluated by clinical score of paw swelling, and the scores of inflammation, pannus, cartilage, and bone damage were performed using a modified Mankin score system.
Results: TAS8274 inhibited the enzymatic activity of JAK3 (IC_{50}=0.16 nM), and showed more than 1000-fold selectivity against other JAK kinases. In the cell-based assays, TAS8274 strongly inhibited IL-17 production from differentiated Th17 cells. TAS8274 also suppressed the IL-2-induced STAT5 phosphorylation in PBMCs, but had much lower inhibitory effects on the IFN-α-induced STAT1 phosphorylation. In contrast, Tofacitinib and Baricitinib had robust inhibitory effects on the IFN-α-induced STAT1 phosphorylation. Furthermore, Tofacitinib and Baricitinib dose-dependently reduced the NK cell cytotoxicity, while TAS8274 had little effect on that. Tacrolimus-treated group significantly increased the number of papules compared with vehicle-treated group in a mouse HSV-1 infection model, but TAS8274-treated group did not increase the number of papules. In an established mouse CIA model, TAS8274 dose-dependently reduced the severity of arthritis and histopathological scores compared with vehicle-treated mice.
Conclusions: TAS8274 did not inhibit the JAK3-independent STAT signalling pathway *in vitro* and showed potent efficacy at dose range without exacerbation of the risk of HSV-1 infection. Our study demonstrates that TAS8274 would be an attractive therapeutic agent with excellent balance between efficacy and safety.

REFERENCES:
[1] Immunity 2012;36,542–50.
[2] Ann Rheum Dis. 2013;72,111–5.
[3] Arthritis Rheumatol 2014;66:2675–84.

Disclosure of Interest: None declared
DOI: 10.1136/annrheumdis-2018-eular.1865