Methods: UST data were derived from the ACCEPT study (NCT00454584, n=85), in which PsO patients received either 45 mg or 90 mg of UST at weeks (wks) 0 and 4, and GUS data were from the first-in-human study (NCT00925574, n=24) that tested single subcutaneous doses of GUS. Skin biopsies were collected at baseline (BL), and wks 1 and 12 post-treatment from each study to evaluate 1) histologic improvement via epithelial thickness, T cells (CD3), and myeloid DCs (CD11c) counts and 2) molecular response to drug via microarray. Biopsies from healthy subjects served as controls. GUS 100 mg and 300 mg groups were combined to increase analytic power. The IC₅₀ of each drug was evaluated by cell-based bioassays.

Results: The two cohorts are comparable in BL demographics, disease characteristics, skin histopathology, PsO lesional molecular expression profiles, and significantly enriched canonical pathways. Blockade of IL-23 with GUS resulted in a significantly greater reduction in CD3 and CD11c counts in the skin at wk12 relative to BL when compared to UST blockade (>90% vs ~70%). In pts who achieved >50% improvement in PASI score, GUS (n=9) showed a larger impact on the PsO transcriptomic profile than UST 90 mg (n=12) by wk1 and greater enhancement was achieved by wk12. GUS neutralised 74% of the PsO disease profile by >80%, while UST resolved only 21% at wk12. Expression of PsO disease markers such as defensin Beta 4A and lipocalin 2 were fully resolved by GUS beyond the level observed in non-lesional skin of PsO pts, while UST only resolved these markers by 32% and 63%, respectively. *In vitro*, GUS showed higher potency (2–14 fold) than UST in inhibiting IL-23 activity, which may contribute to stronger neutralisation of PsO disease markers by GUS.

Conclusions: In conclusion, this comparative study demonstrates that GUS inhibits psoriasis-associated pathology and resolves the skin transcriptomic PsO disease profile more strongly than UST.

REFERENCE:

- [1] Langley RG, Tsai TF, Flavin S, Song M, Randazzo B, Wasfi Y, et al. Efficacy and safety of guselkumab in patients with psoriasis who have an inadequate response to ustekinumab: Results of the randomized, double-blind, Phase 3 NAVIGATE trial. *Br J Dermatol* 2017 Jun 21. doi:10.1111/bjd.15750

Disclosure of Interest: K. Li Shareholder of: Johnson and Johnson, LLC, Employee of: Janssen Research and Development, LLC, K. Campbell Shareholder of: Johnson and Johnson, LLC, Employee of: Janssen Research and Development, LLC, S. Garcet Grant/research support from: Janssen Research and Development, LLC, C. Brodmerkel Shareholder of: Johnson and Johnson, LLC, Employee of: Janssen Research and Development, LLC, J. Krueger Grant/research support from: Janssen Research and Development, LLC
DOI: 10.1136/annrheumdis-2018-eular.1978

OP0167

A LOW MOLECULAR WEIGHT BAFF SIGNALLING INHIBITOR, BIK-13, AMELIORATES B CELL ACTIVATION IN VITRO AND IN VIVO AUTOIMMUNE MODELS AND CONSEQUENTLY SUPPRESSES PRODUCTION OF IGG AND CYTOKINES

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Background: We reported that BAFF robustly increases IL-6 production by peripheral monocytes of patients with primary Sjögren's syndrome (pSS) and that the BAFF-induced IL-6 production and serum IgG levels of the patients were positively correlated with the expression level of a BAFF receptor (BR3) in pSS monocytes. Moreover, we found that IgG production by pSS B cells *in vitro* was significantly enhanced by BAFF-stimulated monocytes. These results collectively suggest that BAFF signalling via BR3 is involved in IgG overproduction and that is a possible therapeutic target to treat autoimmune diseases, such as pSS. We successfully discovered a pyrrolopyrimidine derivative, BIK-13, which inhibits BAFF binding to BR3 by our original high throughput screening.

Objectives: To explore the possibility of BIK-13 as a drug to treat autoimmune diseases.

Methods: Human PBMC were stimulated *in vitro* with a mixture of soluble BAFF (sBAFF), recombinant human IL-21, and anti-IgM and anti-CD40 antibodies ('multiple stimulation') to differentiate B cells into plasma blasts and/or plasma cells. BIK-13 was added to the culture and the differentiation of B cells was monitored by the expression levels of CD19/CD38/IgD and Activation-induced cytidine deaminase (AID) analysed by FACS and quantitative RT-PCR, respectively. The amounts of IL-6, IL-10 and IgG in the culture supernatants were measured by ELISA. BIK-13 was administered intraperitoneally to MRL/lpr mice and serum levels of an anti-dsDNA antibody, IL-6 and IL-10 were measured by ELISA. The proportion of B cells among splenic lymphocytes of the mice was analysed by FACS. Production of cytokines *in vitro* by stimulated splenic lymphocytes was measured

by ELISA. Infiltration of lymphocytes into organs was analysed by immunohistochemistry.

Results: FACS analysis of multiple-stimulated human PBMC indicated that differentiation of B cells into plasma blasts and/or plasma cells was inhibited by BIK-13 in a dose dependent manner. Interestingly, increased IgG, IL-6 and IL-10 production by the stimulated PBMC were concomitantly and significantly suppressed by BIK-13. In addition, the expression level of AID in the cells was also suppressed by BIK-13, suggesting that an IgG class switching was impaired. Administration of BIK-13 to MRL/lpr mice for 16 weeks decreased the serum levels of an anti-dsDNA antibody, IL-6 and IL-10 as compared to the control. Notably, immunohistochemical analysis revealed that infiltration of B cells into salivary and lacrimal glands was remarkably suppressed in BIK-13-treated mice. Moreover, the proportion of B cells among splenic lymphocytes was also decreased in BIK-13-treated mice as compared to the control. In addition, production of IL-6 and IL-10 by activated splenic lymphocytes of the BIK-13-treated mice was also remarkably suppressed as compared to control mice.

Conclusions: Our data collectively suggest that BIK-13, a low molecular weight BAFF-signalling inhibitor, suppresses B cell activation/differentiation *in vitro* and consequently inhibits production of IgG and cytokines, such as IL-6 and IL-10, by the cells. The compound inhibited infiltration of B cells into organs of model mice of autoimmune diseases. These data suggest that the compound is a promising drug candidate to treat autoimmune diseases, such as pSS.

Disclosure of Interest: K. Yoshimoto: None declared, N. Seki Employee of: Mitsubishi Tanabe Pharma Corporation, K. Suzuki: None declared, K. Sugahara Employee of: Mitsubishi Tanabe Pharma Corporation, K. Chiba Employee of: Mitsubishi Tanabe Pharma Corporation, T. Takeuchi Grant/research support from: Mitsubishi Tanabe Pharma Corporation
DOI: 10.1136/annrheumdis-2018-eular.4132

OP0168

NIK-IKK COMPLEX INTERACTION CONTROLS NF-KB DEPENDENT INFLAMMATORY ACTIVATION OF THE ENDOTHELIUM IN RESPONSE TO LTBR LIGATION

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Background: Sites of chronic inflammation, such as rheumatoid arthritis (RA) synovial tissue, are characterised by neovascularization and often contain tertiary lymphoid structures with characteristic features of lymphoid organs such as high endothelial venules (HEV), and sometimes even true germinal centres. Ligation of the lymphotoxin (LT)- β receptor (LT β R) results in activation of both canonical and NF- κ B-Inducing Kinase (NIK)-dependent noncanonical NF- κ B signalling in endothelial cells (EC) and plays a crucial role in lymphoid neogenesis. Noncanonical NF- κ B signalling in EC promotes inflammation-induced angiogenesis and triggers the development of the cuboidal HEV appearance. However, the relative contribution of the individual pathways to the acquisition of leukocyte traffic-regulating properties by EC is less well understood.

Objectives: To identify the molecular pathways by which LT β R drives inflammatory activation of EC to promote interactions with leukocytes.

Methods: Primary human EC were treated with LT β or LIGHT to activate LT β R, followed by analysis of downstream NF- κ B signalling pathways and expression of inflammatory cytokines and adhesion molecules. To repress canonical NF- κ B signalling pathway, a small molecule inhibitor of IKK β was used, and noncanonical NF- κ B signalling was repressed with siRNA targeting NF κ B2. The role of NIK in LT β R signalling was investigated using small molecule inhibitors and siRNA targeting NIK, as well as adenoviral overexpression of NIK. The role of NF- κ B signalling in RA was measured by stimulating EC with RA synovial fluid (RASf) followed by analysis of inflammatory mediators.

Results: LT β R triggering in EC resulted in activation of both canonical and non-canonical NF- κ B signalling pathways and induced inflammatory cytokine expression and immune cell adhesion. IKK β inhibition completely repressed LT β R-induced inflammatory activation of EC, indicating that this process was mediated through canonical NF- κ B signalling. Interestingly, inactivation of NIK with small molecule inhibitors and siRNAs significantly decreased LT β R-induced expression of inflammatory cytokines and adhesion of immune cells to endothelium, whereas silencing of NF κ B2 had no effect. This suggests that the noncanonical pathway is dispensable for NIK-dependent activation of EC through the canonical NF- κ B pathway. Further analyses, including silencing of NIK and NIK overexpression, demonstrated a role for NIK in activation of the canonical NF- κ B pathway by amplifying IKK complex activity. RASf stimulation of EC resulted in activation of canonical and noncanonical NF- κ B signalling, and increased the expression of inflammatory cytokines and adhesion molecules, which could be blocked by targeting NIK.

Conclusions: These findings suggest that in addition to regulating noncanonical signalling, NIK can serve as an amplifier of canonical NF- κ B signalling and associated inflammatory responses in EC, which may play a role in development and

maintenance of chronic inflammation. Consequently, NIK may be an attractive therapeutic target.

Disclosure of Interest: K. Jeucken: None declared, P. Kucharzewska Employee of: AstraZeneca, C. Maracle: None declared, J. P. van Hamburg: None declared, H. Olsson Employee of: AstraZeneca, S. Tas: None declared
DOI: 10.1136/annrheumdis-2018-eular.3413

OP0169 A COMBINATION OF PROTEINS AS MEASURED WITHIN THE MULTI-BIOMARKER DISEASE ACTIVITY SCORE AT PRESENTATION OF RA IDENTIFIES A GROUP OF ACPA-NEGATIVE RA PATIENTS WITH HIGH LIKELIHOOD OF DEVELOPING DMARD-FREE SUSTAINED REMISSION

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Background: Rheumatoid arthritis (RA) typically requires lifelong treatment. However, some RA patients achieve sustained disease-modifying antirheumatic drug (DMARD)-free remission, which is a proxy for cure of RA that has become increasingly achievable, as reported previously. DMARD-free sustained remission has been reported mostly in autoantibody-negative RA, yet the underlying mechanism is unknown. The multi-biomarker disease activity (MBDA) score combines 12 serum biomarkers and is developed to measure RA disease activity. We hypothesise that the subgroup of RA patients that is most likely to achieve DMARD-free sustained remission is identifiable at disease presentation by cytokines such as those combined in the MBDA score.

Objectives: To evaluate whether the MBDA score or its component cytokines at the presentation of RA are associated with ability to later achieve DMARD-free sustained remission.

Methods: 300 patients with RA (by the 1987 and/or 2010 criteria) who had been consecutively enrolled in the Leiden Early Arthritis Clinic between 2010 and 2015 were studied. At time of diagnosis, before DMARD treatment was started, the MBDA score, with a scale of 1–100, was determined from the serum concentrations of 12 biomarkers (VCAM-1, EGF, VEGF-A, IL-6, TNF-RI, MMP-1, MMP-3, YKL-40, Leptin, Resistin, CRP, SAA) with a pre-specified, validated algorithm. Patients were categorised as having a low (<30), moderate (30–44) or high (>44) MBDA score. DMARD-free sustained remission was defined as the absence of synovitis (by physical examination) that sustained after discontinuation of all DMARD therapy (including biologics and systemic and intra-articular corticosteroids) for the entire follow-up period, but had to extend to at least one year after DMARD withdrawal. Analyses were stratified for ACPA and restricted to 5 years follow-up as thereafter the number of patients became small. The median follow-up duration of all patients was 4.3 years.

Results: A total of 54 RA patients (18%) had achieved DMARD-free sustained remission. For the total group of RA patients, baseline MBDA category ($p=0.03$) and ACPA-negativity ($p<0.001$) were associated with achieving DMARD-free sustained remission. For ACPA-positive RA patients, the MBDA category at baseline was not associated with achieving DMARD-free sustained remission ($p=0.89$, figure 1). By contrast, among ACPA-negative RA patients, none of those with low MBDA score achieved DMARD-free sustained remission during 5 years follow-up, whereas the estimated rate of remission was 50% for those with moderate or high MBDA scores ($p=0.009$, figure 1). Of the 12 biomarkers in the MBDA test, only SAA showed a significant difference between ACPA-negative patients with and without DMARD-free sustained remission ($p=0.01$).

Conclusions: ACPA-negative RA patients who achieved DMARD-free sustained

remission were characterised by moderate to high MBDA scores at disease presentation. This is the first evidence that a cytokine profile at disease onset can identify a subgroup of ACPA-negative RA patients with a high likelihood of maintaining clinical remission after treatment withdrawal.

Disclosure of Interest: None declared

DOI: 10.1136/annrheumdis-2018-eular.6209

OP0170 HUMAN IL-38 REDUCES JOINT INFLAMMATION IN A MOUSE MODEL OF GOUTY ARTHRITIS

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Background: Interleukin-38 (IL-38) is the last member of the IL-1 family of cytokines to be fully investigated for its functions. IL-38 is proposed as an anti-inflammatory cytokine in various auto-inflammatory diseases, such as psoriasis and rheumatoid arthritis. For example, IL-38 knockout mice have exacerbated autoantibody-induced arthritis. Current understanding of the capacity of IL-38 in gout, a prototype IL-1 β driven auto-inflammatory disease, is unknown.

Objectives: We hypothesised that *in vivo* treatment with human recombinant IL-38 results in a reduction in joint inflammation in a mouse model of gouty arthritis.

Methods: We treated C57/Bl6 mice with 1 μ g recombinant IL-38 (3–152 AA) intraperitoneally at 24, 12 and 2 hours before induction of gouty arthritis with intra-articular injection of albumin-opsonized monosodium urate crystals (300 μ g) and palmitic acid (200 μ M) in 10 μ L PBS. Joint inflammation was scored after 4 hours. The synovial lining was cultured in RPMI for 2 hours to allow cytokines to be secreted, and cytokines in the synovium were extracted with Triton-X 100 to obtain total cytokines (membrane and intracellular). In the synovial culture fluid and extract, IL-1 β , IL-6 and KC were measured by ELISA. Data

Results: Mice treated with recombinant IL-38 exhibited significantly reduced joint swelling and redness on a three-point macroscopic inflammation scale: Vehicle-treated 1.5 ± 0.25 vs IL-38 Treated 0.75 ± 0.25 ($n=10$, $p<0.0001$, Mann Whitney-U test). The 2 hour synovial membrane culture fluid contained significantly lower levels of IL-1 β (1207 ± 480 vs 379 ± 184 pg/mL, $p<0.05$), IL-6 (10783 ± 2490 vs 5321 ± 2935 pg/mL, $p<0.05$) and KC (4390 ± 931 vs 1081 ± 750 pg/mL, $p<0.05$). In extract of the synovial membrane, there is a reduction in IL-1 β (1505 ± 397 vs 624 ± 509 pg/mL, $p<0.05$), IL-6 (11059 ± 2299 vs 3597 ± 2509 pg/mL, $p<0.01$) and KC (1505 ± 397 vs 624 ± 509 pg/mL, $p<0.05$).

Conclusions: Human recombinant IL-38 reduces swelling and redness of the joint, and pro-inflammatory cytokines secreted by and contained in the synovial membrane in a mouse model of gouty arthritis. These data reveal that recombinant IL-38 has therapeutic benefit in an IL-1 β mediated model of inflammation.

Disclosure of Interest: None declared

DOI: 10.1136/annrheumdis-2018-eular.5599

OP0171 LEPTIN LEVELS, OVERWEIGHT AND P GINGIVALIS PRESENCE CONTRIBUTE TO THE MECHANISM OF SYSTEMIC INFLAMMATION IN FIRST-DEGREE RELATIVES OF RHEUMATOID ARTHRITIS INDIVIDUALS

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Background: Association studies in rheumatoid arthritis (RA) have been focused in the pre-clinical phases of the disease in first-degree relatives (FDR). Data has shown that obesity, ACPA and the periodontal condition may modulate the severity and the clinical presentation of RA

Objectives: To investigate the levels of adipokines in FDR and establish their association with the state of rheumatic and periodontal condition

Methods: 124 FDR individuals and 124 healthy controls matched by age and gender were included. Rheumatologic (clinical and serological markers) and periodontal assessment was performed. It was quantified the adiponectin, leptin, IL6 levels. HLA-DRB1 was determined. Serum markers of RA (rheumatoid factor, erythrocyte sedimentation rate, C reactive protein (CRP), and ACPA. *P gingivalis* and IgG1/IgG2 *P gingivalis* were measured. Radiographs of hands and feet were evaluated the Sharp-van der Heijde score. An association analysis was made to evaluate the relationship between adipokines and periodontal, rheumatologic conditions using X2 test, and logistic regression model was performed to confirm this associations

Results: In FDR group, 71.77% were women with a mean age of 39.24 ± 12.22 years. 37.09% had overweight and 4.83% had obesity. Among the controls, 70.97% were women, with an average age of 39.31 ± 12.30 years. 27.41% had overweight and 4.83% had obesity. Leptin levels were found in 37.66% vs 18.42% in controls ($p=0.002$). In FDR, 60.48% had periodontal disease of which 62.66% moderate, *P gingivalis* in 62.10%. In controls, 55.64% had periodontal disease, of which 63.76% moderate with 42.74% *P gingivalis* positive ($p=0.002$). In the FDR, radiography of hands and feet showed in 25.28% of them had some alteration, 68.18% had ≥ 1 erosion, 45.45% had ≥ 1 joint space narrowing and in 6.89% juxta-articular osteopenia. An association of leptin levels with the low economic level was found $p=0.006$ and high levels of leptin in individuals with BMI ≥ 30 $p=0.031$.