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

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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.

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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