compared to HLA-B15 patients. Accordingly, the genotype (presence of HLA-B27 or HLA-B15) and phenotype (axial or peripheral involvement) may help physicians when considering a targeted therapy of SpA patients with IL-17 inhibition in a context of personalized medicine

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THU0053 SELECTIVE ACTIVATION OF AN AMPK-CREB-NRF2-DEPENDENT PATHWAY BY CELECOXIB INDUCES VASCULOPROTECTIVE GENES AND MITIGATES AGAINST CARDIOVASCULAR RISK

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Background: Although concern remains about the athero-thrombotic risk posed by COX-2-selective inhibitors (COXIBs), the recent PRECISION trial demonstrated non-inferiority of moderate dose celecoxib when compared to naproxen and ibuprofen with respect to cardiovascular safety, with fewer actual CV events recorded for celecoxib. Moreover, celecoxib proved significantly safer than either comparator in regard to gastrointestinal events[1]. Given the markedly different cardiovascular risk associated with celecoxib and rofecoxib, we investigated the hypothesis that, in addition to cyclo-oxygenase inhibition, celecoxib specifically activates COX-2-independent AMP kinase (AMPK) signalling to exert protective effects in the vascular endothelium.

Objectives: To investigate COX-2-independent vasculoprotective signalling pathways activated by celecoxib in human endothelium.

Methods: *In vitro* studies of celecoxib, rofecoxib, ibuprofen and naproxen were performed on human umbilical vein and human aortic endothelial cells (HUVEC and HAEC). Inhibition of signalling pathways was achieved using siRNA. The vascular effects of celecoxib *in vivo* were studied in C57Bl/6 mice fed celecoxib (1000 ppm) or control chow (48 hrs). Aortic tissue was snap-frozen and sections studied by immunofluorescence confocal microscopy.

Results: At therapeutically relevant concentrations celecoxib (1–10μ M) induced the vasculoprotective protein heme oxygenase-1 (HO-1) in HUVEC and HAEC (EC) ($p<0.01$). In contrast, rofecoxib and the commonly used non-selective NSAIDs ibuprofen and naproxen failed to induce HO-1. Celecoxib derivative 2,5-dimethyl-celecoxib (DMC), which lacks COX-2 inhibition, also upregulated HO-1, implicating a COX-2-independent mechanism. Immunoblotting demonstrated that celecoxib and DMC induce AMPK$\alpha^{(Thr172)}$ and CREB-1$^{(Ser133)}$ phosphorylation leading to Nrf2 nuclear translocation ($p<0.05$). These responses were not seen with ibuprofen or naproxen, while siRNA depletion of AMPKα abrogated celecoxib-mediated CREB and Nrf2 activation ($p<0.05$). Acting via the same pathway, celecoxib induced additional cytoprotective genes including H-ferritin. *In vivo*, celecoxib similarly increased HO-1 and H-ferritin in murine aortic endothelium when compared to control-fed mice ($p<0.05$). Functionally, celecoxib treatment inhibited TNF-α-induced NF-κB p65$^{(Ser536)}$ phosphorylation by increasing AMPK activity. This attenuated VCAM-1 upregulation via induction of HO-1, as revealed by HO-1 siRNA ($p<0.05$). Similarly, celecoxib prevented the IL-1-mediated increase of IL-6 mRNA ($p<0.01$). These responses were not seen with ibuprofen or naproxen.

Conclusions: Celecoxib induces anti-inflammatory, anti-oxidant proteins HO-1 and H-ferritin in human vascular endothelium via a novel AMPK-CREB-Nrf2-dependent pathway. This mechanism may contribute to the important and marked differences in cardiovascular risk between celecoxib and rofecoxib. Understanding mechanisms underlying NSAID heterogeneity may ultimately lead to the development of safer anti-inflammatory drugs.

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THU0054 UTILITY OF SEROLOGICAL PARAMETERS IN GIANT CELL ARTERITIS FOR PREDICTING DISEASE COMPLICATIONS

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Background: Giant Cell Arteritis (GCA) is a systemic vasculitis affecting primarily large and medium sized arteries. Immediate high dose steroid treatment may prevent urgent complications, such as vision loss and cerebrovascular insults[1–3]. However, there is a clear lack of data on predicting serological markers and their association to clinical complications.

Objectives: To investigate serological parameters that support clinicians in predicting complications in a large, clinically well-characterized set of untreated GCA patients at time of diagnosis.

Methods: The study included 98 GCA patients (67% female) with a median (IQR) age 74.1 (67.3–78.8) years and a median (IQR) symptome duration time of 30 (20–90) days). Healthy blood donors (HDs, n=52, 61.5% female, median (IQR) age of 41.95 (20.4–63.1) years) served as controls. GCA complications studied were visual disturbances (including permanent loss of vision), relapses, peripheral artery involvement and claudication. Levels of 27 serum analytes were measured using Luminex xMAP Technology. Interleukin-6 (IL-6) and serum amyloid A (SAA) levels were tested using ELISA and nephelometry, respectively.

Results: The highest, significantly elevated analytes in GCA vs. HDs were SAA (85-fold > HDs mean values), IL-23 (63-fold) and IL-6 (11-fold). IL-13, α-fetoprotein and MMP-2 were significantly decreased in GCA, while levels of IL-2, IL-17A and TNF-α were unchanged. PCA analysis revealed a signature analyte profile positioning towards the HD cluster. SAA, CRP, haptoglobin, ESR, thrombocyte # and matrix metalloproteinase-1 (MMP-1) all negatively associated with visual disturbances, confirming our previous data. Age showed significant association to permanent visual loss, with older patients being more affected[3]. SAA, CRP and ESR at presentation were found to be predictive of relapsing disease, while MMP-2 negatively associated with relapse. VCAM-1, α-fetoprotein, MARCO and IL-27 were all negatively associated with peripheral artery involvement. MMP-2 and MARCO showed positive association with claudication, while IL-18 was negatively associated.

Conclusions: In our large study of untreated GCA patients we highlight the importance of using serological acute phase parameters, MMPs and other analytes for predicting complications.

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THU0055 LOW MOLECULAR WEIGHT BAFF SIGNALING INHIBITORS AMELIORATE IL-6, IL-10 AND IGG PRODUCTION IN VITRO AND IN VIVO MODELS OF AUTOIMMUNE DISEASES

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Background: In our previous study, we reported that soluble BAFF (sBAFF) robustly enhanced IL-6 production by peripheral monocytes of patients with primary Sjogren's syndrome (pSS) and that the expression level of a BAFF receptor (BR3) was significantly elevated in pSS monocytes. We also found that the proportion of BR3-positive monocytes to total monocytes was positively and significantly correlated with the serum IgG level of pSS patients. Investigation of the interaction of monocytes and B cells showed that IgG production by B cells was enhanced by sBAFF-stimulated monocytes. These data collectively suggest that the elevated expression of BR3 on monocytes is involved in IgG overproduction by B cells which is often observed in pSS, and that BAFF signaling via BR3 is a possible therapeutic target to treat pSS. A high throughput screening of a low molecular weight compound library successfully discovered two pyrrolopryimidine derivatives, BIK12 and BIK13, which inhibit sBAFF binding to BR3. We found that these compounds inhibited not only IL-6 production by BAFF-stimulated monocytes, but also IgG production by B cells co-cultured with the monocytes.

Objectives: To elucidate the mechanism of inhibitory activities of these compounds on BAFF signaling pathways, we measured production of IL-10 as well as IL-6 by monocytes *in vitro*, both of which work for B cell activation. In addition, we analyzed *in vivo* effects of the compounds on production of autoantibody and cytokines in autoimmune disease model mice.

Methods: Peripheral monocytes and B cells were prepared from healthy individuals. The monocytes were stimulated with sBAFF and cultured *in vitro* with or without peripheral B cells in the presence of BIK-12 or BIK-13. The amounts of IL-6, IL-10 and IgG were measured by ELISA. BIK-13 was administered intraperitoneally to MRL/lpr mice, an animal model of autoimmune diseases, three times a week for 6 months. Serum levels of an anti-ds DNA antibody, IL-6 and IL-10 were measured by ELISA.

Results: sBAFF enhanced the production of not only IL-6, but also IL-10 by peripheral monocytes *in vitro*. As expected, BIK12 and BIK-13 significantly suppressed production of IL-6 and IL-10 by BAFF-stimulated monocytes *in vitro* in a dose dependent manner. Notably, IgG production by B cells co-cultured *in vitro* with sBAFF-stimulated monocytes was significantly suppressed by these compounds. The compounds did not exhibit toxicities to the cells in the dose range. These data suggest that BAFF signaling via BR3 lead to production of IL-6 and IL-10 in monocytes, and the cytokines in turn mediates the signal to B cells resulting in IgG overproduction. Interestingly, serum levels of an anti-dsDNA antibody, IL-6 and IL-10 in MRL/lpr mice received BIK13 simultaneously declined as compared to control mice. These data collectively suggest that the compound was also efficacious *in vivo*.

Conclusions: BIK-13, a pyrrolopyrimidine derivative, suppressed IgG production