in UST-NR or PBO patients. IGS levels were elevated in 67% of patients at baseline versus healthy controls. Serum IFN- α levels and IGS levels in blood were not modulated by UST treatment through week 24. Baseline IFN-I signature status did not associate with response to UST, as the treatment effect size (UST vs PBO) was similar in IGS low ($\Delta=27\%$) and high ($\Delta=28\%$) patients.

Conclusion: Response to UST was associated with reductions in IFN- γ levels, whereas IL-17A, IL-17F, IL-22 and IFN-I remained largely unchanged. While these findings require confirmation in an ongoing Phase 3 study, these data implicate the involvement of the IL-12 pathway and suggest a novel mechanism of action for UST-R in SLE.

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OP0279

A UNIQUE IL-21 SIGNATURE CHARACTERIZES LESIONAL AND CIRCULATING T-FOLLICULAR HELPER CELLS IN SJÖGREN'S SYNDROME PATIENTS WITH ECTOPIC GERMINAL CENTRES AND MALT LYMPHOMA

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Background: B/T cell aggregates in the salivary glands (SG) of Sjögren's syndrome (SS) can form ectopic lymphoid structures (ELS) with germinal centers (GC), which are linked to MALT lymphoma (MALT-L) development. T follicular-helper cells (Tfh), main producers of IL21, are crucial for affinity maturation and class-switching of GC B cells, and may be responsible for onset of autoimmunity.

Objectives: To characterize the cytokine production in circulating T cells alongside the Tfh infiltration and the expression of IL21/IL21 receptor (IL21R) in the SGs of SS patients, in the context of ectopic GCs and MALT-L.

Methods: SG biopsies with matching histology and RNA from 37 SS and 38 non-specific chronic sialadenitis (NSCS) patients were stratified as ELS-/ELS+ based on CD3/CD20/CD21/CD138 immunostaining (IHC). Histological samples and mRNA from 12 parotid MALT-L were also analyzed. Gene expression was measured by Taqman RT-PCR. Multicolor immunofluorescence/confocal microscopy for CD3, CD4, CD45RO, ICOS, PD1, BCL6 identify Tfh cells in SG and MALT-L tissues. FACS analysis for CD4, CD8, INF γ , IL17, IL21, Granzyme-B, IL10, CD25, Foxp3, CXCR5, ICOS, PD1, was performed on peripheral blood mononuclear cells from 20 SS and 10 NSCS patients with matched SG histology for the characterization of T CD4+ cells cytokines production.

Results: IL21 and IL21R expression, together with CD4⁺CD45RO⁺PD1⁺ICOS⁺ Tfh cells were strongly enriched in ELS+ vs ELS- SS SGs. Tfh cells densely infiltrated B cell rich areas and, within ectopic GC, acquired BCL6 expression, both in ELS+ and MALT-L. Tfh infiltration significantly correlated with SG IL21 mRNA level, which in turn was associated with high T (CD3+), B (CD20+) and plasma cells (CD138+) IHC scores and significantly correlated with CXCL13, LT β , BAFF, AID and Pax5 gene expression. MALT-L samples displayed 10-fold higher IL21 mRNA and twice as much PD1⁺ICOS⁺BCL6⁺ Tfh-cells/field in comparison to ELS+ SS samples. Within the SGs, IL21 and INF γ were the most abundant cytokines produced by infiltrating CD4 T cells and CXCR5+ Tfh cells frequently displayed double IL21/INF γ production. Similarly, IL21, IL17 and INF γ producing ICOS⁺CXCR5⁺ circulating Tfh cells were significantly increased in the peripheral blood of SS patients compared to sicca, but only IL21+ Tfh cells were associated with the presence of ectopic GC in SG. IL21, IL17 and INF γ production by Tfh in the peripheral compartment showed a positive correlation with IgG serum levels.

Conclusion: Within the SG of SS patients Tfh cells closely segregate with lesional IL21 expression, localize within ELS and are strongly enriched during MALT-L development, which is supporting their role in sustaining B cell activation and malignant transformation. High production of IL21 by Tfh in peripheral blood selectively identifies SS patient with ectopic GC in the SG, suggesting a role for IL21+ Tfh cells as surrogate markers of SG histopathology in SS.

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OP0280

THE SELECTIVE JAK1 INHIBITOR INCB054707 AMELIORATES CUTANEOUS LESIONS IN A SPONTANEOUS MURINE MODEL OF SYSTEMIC LUPUS ERYTHEMATOSUS

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Background: Systemic lupus erythematosus (SLE) is an autoimmune disease that can affect multiple organs, including the skin, joints and kidneys. The disease is characterized by the development of skin lesions, autoantibody production and inflammation-induced glomerulonephritis. The skin is involved in up to 85% of SLE cases¹. In the MRL/lpr spontaneous mouse model of SLE, disease symptoms also include lymphocyte hyper-proliferation, resulting in lymphadenopathy and splenomegaly. The evolutionary conserved Janus kinase-signal transducer of activators of transcription (JAK-STAT) pathway constitutes a rapid membrane to nucleus signaling modality that affects key biological aspects of the mammalian immune system². Janus kinase 1 (JAK1) is involved in the downstream signaling pathway of type I interferons (IFNs), and high levels of type I IFNs are associated with SLE³. INCB054707 is an oral small molecule JAK1 selective inhibitor currently being evaluated in clinical trials for the dermatological disease hidradenitis suppurativa (NCT03569371 & NCT03607487). We hypothesized that INCB054707 should reduce IFN signaling and ameliorate cutaneous lesions in SLE.

Objectives: To determine the effectiveness of INCB054707, a selective JAK1 inhibitor, in a preclinical model of cutaneous lupus erythematosus.

Methods: Female MRL/lpr mice were randomized to treatment groups at 11 weeks old to receive twice daily oral doses of vehicle (0.5% methyl cellulose) or INCB054707 at 10, 30, or 90 mg/kg for 10 weeks. Efficacy was determined by weekly scoring of the changes in skin, lymph node size, and proteinuria. At study termination (week 21), inguinal lymph nodes and spleens were excised and weighed, skin lesions and kidneys were excised and fixed for histopathologic analysis, and serum was collected for pharmacokinetic analysis and ELISA. Autoantibody presence in the serum was detected using a commercial anti-dsDNA ELISA kit.

Results: In vitro enzymatic selectivity screening of INCB054707 revealed JAK1 IC50 = 8.9 nM versus JAK2 IC50 = 463 nM, resulting in a JAK1/JAK2 selectivity

ratio of approximately 52-fold. Spontaneous skin lesions were observed in 90%+ of vehicle treated mice by 18 weeks of age, with the majority located around the head and nape of the neck. Histologically, lesions were characterized by combined lymphocyte infiltration and epidermal thickening. In contrast, therapeutic INCB054707 treatment dose-dependently reduced the incidence and severity of cutaneous lesions ($p < 0.05$). In addition, INCB054707 treatment abrogated lymphoid tissue and spleen enlargement ($p < 0.0001$) in a dose-dependent manner. Kidney damage was only partially improved by INCB054707 at the highest (90 mg/kg) dose. Quantification of anti-dsDNA antibodies by ELISA revealed a profound, statistically significant reduction of antigen-specific autoreactive IgG immunoglobulins in the serum ($p < 0.0001$). Total immunoglobulin titers were not reduced.

Conclusion: These data are consistent with immunomodulation and show that oral INCB054707 treatment, resulting in JAK1-specific inhibition, has the potential to modulate ongoing inflammatory (autoimmune) cutaneous skin disease.

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OP0281

ELEVATED EXPRESSION OF BAFF-RECEPTOR IN PERIPHERAL MONOCYTES PROMOTES B CELL ACTIVATION AND CORRELATES WITH CLINICAL MANIFESTATIONS OF PRIMARY SJÖGREN'S SYNDROME

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Background: Primary Sjögren's syndrome (pSS) is an idiopathic autoimmune disease whose major clinical manifestations are xerostomia and keratoconjunctive sicca, and is often accompanied with hypergammaglobulinemia. Several lines of evidence suggest that a focal lymphocytic infiltrate of the exocrine glands is responsible for lesion formation, IgG production and subsequent dysfunction of the glands. It is well known that B cell activating factor (BAFF) and its receptor, BR3, are deeply involved in the pathogenesis of pSS, and hence BAFF and BR3 are promising targets to treat the disease. We have reported that the abnormally elevated expression of BR3 in monocytes is associated with overproduction of inflammatory cytokines, such as IL-6, by monocytes of pSS patients. Our in vitro experiments suggest that BAFF-stimulated monocytes contribute to IgG overproduction by pSS B cells. We also found that the population of a specific subset of B cells overexpressing BR3 was abnormally increased in pSS patients and that the proportion of the subset was positively and significantly correlated with serum levels of autoantibodies and total IgG as well as ESSDAI, one of the indicators of disease activity of pSS. Our results collectively suggest that the elevated expression

of BR3 in pSS monocytes results in B cell activation and subsequent overproduction of IgG. However, the relationship between the abnormalities of peripheral cells and clinical manifestations of pSS has not been fully understood.

Objectives: To elucidate possible roles of abnormal monocytes in the development of clinical manifestations of pSS.

Methods: The expression level of BR3 in peripheral monocytes of patients with pSS ($n = 65$) and healthy controls (HC: $n = 38$) was analyzed by FACS. Peripheral B cells were cultured with BAFF-stimulated monocytes in the presence or absence of an anti-IL-6 receptor antibody, and the proportion of CD38^{high}IgD^{low} cells among CD19⁺ cells, and IgG production were analyzed by FACS and ELISA, respectively. The serological data and focus scores by lip biopsy of the patients were collected by clinical records.

Results: FACS analysis revealed that the expression level of BR3 in pSS monocytes was significantly higher than that of HC ($p < 0.001$). Moreover, the expression level of BR3 in peripheral monocytes was positively and significantly correlated with serum levels of IgG ($p = 0.01$) and IgM ($p = 0.02$) of the patients. Notably, BR3 expression in monocytes from focus score-positive pSS patients was significantly higher than that from negative patients ($p = 0.006$). In addition, BR3 expression in pSS monocytes was elevated in anti-SS-A and/or anti-SS-B positive patients as compared to negative patients. When B cells prepared from pSS patients were mixed with autologous monocytes and co-cultured in vitro in the presence of BAFF, 1) the proportion of CD38^{high}IgD^{low} cells, which are plasmablasts and/or plasma cells, among CD19 positive cells and 2) the amounts of IgG produced by the cells were drastically enhanced by BAFF-stimulation, whereas the stimulation showed only marginal effects when B cells were solely cultured in vitro. In addition, an anti-human sIL-6R antibody significantly inhibited the proportion of CD38^{high}IgD^{low} cells and IgG production. These data strongly suggest that IL-6 produced by BAFF-stimulated monocyte plays a pivotal role in B cell differentiation and the IgG overproduction in pSS patients.

Conclusion: Our data strongly suggest that accelerated signal transduction through a BAFF-BR3 axis in monocytes is involved in the pathogenesis of pSS and associates with clinical manifestations of the disease. These results also suggest that BAFF and the BAFF signaling pathways through BR3 are the possible therapeutic targets for pSS.

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