its kinase activity. Inhibitors of PI3Kδ have been approved or are in clinical development for the treatment of B cell malignancies; their therapeutic potential in inflammatory and autoimmune disease is being explored. Seletalisib is a selective and potent PI3Kδ inhibitor that has been profiled in preclinical and early clinical studies.
Objectives: To assess the therapeutic potential of seletalisib in inflammatory and autoimmune disease.
Methods: *In vitro* cell-based studies were performed on blood samples taken from healthy volunteers (HV) or from patients with primary Sjogren's Syndrome (pSS) and/or psoriasis. In addition, samples were analysed from a single ascending dose study in HV (NCT02207595) and a multiple ascending dose study in HV and psoriasis patients (NCT02303509). T and B cell responses in the presence and absence of seletalisib were assessed by flow cytometry or a Meso-Scale discovery assay (Meso-Scale Diagnostics, MD, USA), following activation of the T cell- or B cell-receptor by receptor cross-linking or via stimulation with specific antigens. The functional selectivity of seletalisib was assessed in the BioMap system (DiscoverX, CA, USA). Translational studies used flow cytometry and/or immunofluorescence to demonstrate the presence of active PI3K signalling in diseased tissue, through expression of phosphorylated-AKT (pAKT) or -ribosomal protein S6 (pS6). The effect of seletalisib on PI3K signalling was determined by phospho-flow cytometry. Target engagement was determined through measurement of basophil degranulation in healthy subjects, and assessment of lesion severity score in skin biopsies from patients with psoriasis that were treated with seletalisib.
Results: Preclinical studies showed seletalisib potently inhibited T cell differentiation and function (IC_{50} range: 2–31 nM). Further, it blocked activation and proliferation of B cells (IC_{50} range: 16–49 nM). When profiled in a wide range of primary cell assay systems, including fibroblasts, epithelial, endothelial and vascular smooth muscle cells, seletalisib showed significant activity only in those systems containing lymphocytes, demonstrating its functional selectivity towards PI3Kδ-expressing cells. Expression of the PI3K pathway in lymphocytes was shown at the site of disease in clinical samples both from patients with psoriasis and pSS. Seletalisib inhibited PI3K signalling, measured by a reduction in pAKT and pS6 expression, in T cells derived from patients with psoriasis.
In first-in-man studies, mean seletalisib plasma concentration-time profiles increased with increasing dose after single and multiple dosing, with no major deviations from dose proportionality. There was no unexpected accumulation or loss of exposure after multiple dosing (time-independent pharmacokinetic (PK) profile) and apparent $t_{1/2}$ values (approx. 20h) were supportive of once-daily dosing. Inhibition of basophil degranulation in healthy subjects and effects on the cellular composition in lesional skin biopsies from patients with psoriasis, provided indications of target engagement, following treatment with seletalisib.
Conclusions: Seletalisib is a potent, selective PI3Kδ inhibitor with an attractive preclinical and human PK profile; clinical studies are ongoing.
Disclosure of Interest: A. Payne Shareholder of: UCB Pharma, Employee of: UCB Pharma, M. Juarez Shareholder of: UCB Pharma, Employee of: UCB Pharma, G. Johnston Shareholder of: UCB Pharma, Employee of: UCB Pharma, E. Helmer Shareholder of: UCB Pharma, Employee of: UCB Pharma, M. Thomson Shareholder of: UCB Pharma, Employee of: UCB Pharma
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THU0221 DOWNREGULATED EXPRESSION OF MIR200B-5P IN MINOR SALIVARY GLANDS (MSG) OF PATIENTS WITH SJÖGREN'S SYNDROME (SS) ASSOCIATED LYMPHOMA

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Background: The miRNAs of the miR-200 family are critical regulators of oncogene and tumor suppressor genes. Preliminary data from a limited number of patients with SS-associated lymphoma suggested that the expression of miR200b-5p in MSGs may be downregulated in lymphoma.
Objectives: To validate whether low miR200b-5p MSG-levels are associated with SS-related lymphomas and if they are deregulated before lymphoma development, suggesting a possible prognostic value.
Methods: miR200b-5p expression was analyzed by quantitative real-time PCR in total RNA from MSG tissues obtained from 77 SS patients and 9 patients with non-SS sialadenitis associated with sarcoidosis, HCV infection (4 each) or HBV (1 that was also diagnosed with MALT lymphoma). with chronic sialadenitis associated with sarcoidosis, HCV (4-each) or HBV infection (1 who was also diagnosed with MALT-lymphoma). SS-patients included 28 that did not develop lymphoma during follow-up (without lymphoma; median follow-up time since biopsy performance, range: 6yrs, 1–12.75yrs), 18 that developed lymphoma in the future (prelymphoma; median follow-up time till lymphoma diagnosis, range: 3.59yrs, 0.42–8.5yrs, 15-MALT, 2-NMZL, 1-DLCBL) and 32 with SS-associated lymphoma at the time of biopsy (lymphoma; 25-MALT, 2-NMZL, 2-DLCBL, 1-BALT, 1-LP and 1-SLL). In 15 cases, we had sequential MSG-samples from prelymphoma patients who transitioned to lymphoma (12-MALT, 2-NMZL, 1-DLCBL).
Results: Tukey's multiple comparison revealed that miR200b-5p levels were significantly down-regulated in MSG tissues of prelymphoma and lymphoma SS-patients (mean relative expression±SE: 0.37±0.10 and 0.26±0.06, respectively) compared to SS-patients without lymphoma (0.67±0.07; $p \leq 0.05$ and $p \leq 0.0001$ for pre- and lymphoma, respectively) or non-SS sialadenitis (0.85±0.28, $p \leq 0.05$ and $p \leq 0.01$, respectively). Interestingly, low miR200b-5p levels were detected in HBV patient that had MALT lymphoma (0.17). The expression of miR200b-5p was not found to differ between patients with SS without lymphoma and non-SS sialadenitis, or SS-associated pre-lymphoma and lymphoma. The analysis of the 15 cases of SS patients that had sequential samples before and on lymphoma diagnosis revealed that miR200b-5p levels do not significantly change over transition to lymphoma. The miR200b-5p expression levels were negatively correlated with the biopsy focus score (r:-0.6550, $p < 0.0001$), whereas they were not associated with the site or the number of involved sites, the type or the stage of lymphoma.
Conclusions: The significantly low levels of miR200b-5p in MSG tissues of patients with SS-associated prelymphomas and lymphomas suggest that miR200b-5p deregulation is implicated in SS-lymphomagenesis. The downregulation of miR200b-5p in prelymphoma samples and the lack of change over transition to lymphoma suggest that it can serve as a prognostic marker for future lymphoma development. The prognostic value of miR200b-5p in SS-associated lymphomas, the expressing cell types and affected molecular pathways are under investigation.
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THU0222 PROPHYLACTIC AND THERAPEUTIC ADMINISTRATION OF AN ANTI-CD40 ANTAGONIST ANTIBODY BLOCKS AND REVERSES PROTEINURIA AND NEPHRITIS IN NZB/W-F1 MICE

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Background: The CD40-CD40L pathway is a potential target for the treatment of autoimmune diseases, as CD40 is a costimulatory receptor on antigen presenting cells (APCs) critical for the induction and maintenance of an immune response through binding CD40L on T cells. In the absence of CD40, both humoral and cellular responses to foreign antigens are severely impaired. In particular, disruption of this pathway prevents the development of disease in lupus-prone mice.
Objectives: The objective of this work is to evaluate whether prophylactic and therapeutic treatment with an antagonistic anti-CD40 antibody prevents and reverses nephritis and other manifestations of lupus in lupus-prone mice.
Methods: NZB/W-F_1 mice were i.p. administered anti-CD40 prophylactically or therapeutically at various doses once or twice per week. Prophylactic treatment of NZB/W-F_1 mice began at 26 weeks of age and continued for 9 weeks, while therapeutic treatment was initiated in NZB/W-F_1 mice after they developed severe proteinuria (urine protein $\geq$300 mg/dL). Proteinuria was monitored weekly by urinalysis, and at study termination blood and spleen cells were analyzed by flow cytometry. Additionally, histological analysis of kidney, spleen, and salivary glands were performed, as well as gene transcription analysis of the kidney by microarray.
Results: As expected, prophylactic and therapeutic administration reduced the number of splenic germinal center (GC) B cells and T follicular helper cells (Tfh). Prophylactic treatment blocked development of proteinuria and extended survival in NZB/W-F_1 mice. Significantly, therapeutic anti-CD40 treatment reversed established, severe proteinuria in NZB/W-F_1 mice and extended their survival. In agreement, the kidneys and salivary glands of treated mice exhibited reduced inflammation compared to control mice, and the kidneys exhibited lower CD40, IFN-I and chemokine gene signatures compared to controls. Interestingly, anti-CD40 decreased expression of genes in kidney belonging to the "hepatic fibrosis" pathway, possibly explaining the improvement of kidney function.
Conclusions: Anti-CD40 treatment prevents the onset and reverses ongoing nephritis and sialadenitis in NZB/W-F_1 mice. Resolution of ongoing nephritis results in restoration of low or normal urine protein levels. Thus, treatment with an antagonistic anti-CD40 is a strong candidate for clinical study in SLE.
Disclosure of Interest: S. Perper Employee of: Abbvie, S. Westmoreland Employee of: Abbvie, Z. Liu Employee of: Abbvie, M. Duval Employee of: Abbvie, J. Seagal Employee of: Abbvie, B. McRae Employee of: Abbvie, S. Clarke Employee of: Abbvie
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THU0223 ELEVATED MTORC1 SIGNATURE IN B CELLS FROM SJÖGREN'S SYNDROME PATIENTS CORRELATES WITH B CELL HYPERACTIVITY THAT IS ABROGATED BY MTOR INHIBITION: A NOVEL THERAPEUTIC STRATEGY TO HALT B CELL HYPERACTIVITY IN PSS?

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Background: A hallmark feature of primary Sjögren's syndrome (pSS) is B cell hyperactivity, including presence of autoantibodies, aberrant presence of B cells and plasma cells in the salivary glands, elevated serum IgG levels and increased risk of lymphoma development. The mTOR pathway is essential for cell growth,