**AB0043**

**EFFECT OF IN VIVO HYDROXYCHLOROQUINE AND EX VIVO ANTI-BDCA2 TREATMENT ON PDC IFNA PRODUCTION FROM PATIENTS AFFECTED WITH CUTANEOUS LUPUS ERYTHEMATOSUS**

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**Background:** BIIB059 (aka 24F4A) is a monoclonal antibody that targets BDCA2, an inhibitory receptor expressed on pDCs. Plasmacytoid dendritic cells (pDCs) are a major source of Type-I Interferon (IFN-I), which is considered to be a key pathogenic driver in Cutaneous Lupus Erythematosus (CLE). Recent results from a Phase I clinical trial suggest that BIIB059 may ameliorate skin lesions in CLE patients. BIIB059 is currently evaluated in Phase II clinical trial for CLE with or without SLE.

**Objectives:** Given that Hydroxychloroquine (HCQ), a widely-used CLE therapy, and BIIB059 are both able to inhibit pDC-derived IFN-I production; this study aimed to determine whether BIIB059 would show an additional inhibitory effect on pDCs response after ex vivo or in vivo treatment with HCQ.

**Methods:** The effect of BIIB059 on pDC-derived IFNα was measured from peripheral blood mononuclear cells (PBMC) either from healthy donors in presence or absence of HCQ or from CLE patients clinically exposed to various levels of HCQ. TLR7, TLR8, and TLR9 agonists (ssRNA, R848, and Cpg-A) were used for pDC stimulation.

**Results:** pDCs were the only producers of IFNα in response to Cpg-A, R848, and ssRNA stimulation in PBMC cultures. CLE patients with high blood HCQ levels showed lower ex-vivo pDC responses to Cpg-A, but not R848 or ssRNA. In contrast, BIIB059 reduced the amount of IFNα produced by pDCs from CLE patients in response to all TLR agonists, irrespective of the blood HCQ level. This effect was observed in patients with low or high blood IFNα signature and in patients with or without concomitant SLE diagnosis.

**Conclusion:** Clinically-relevant HCQ concentrations partially inhibit the pDC response to TLR9 and weakly affect the response to TLR7/8 stimulation. BIIB059 robustly inhibits pDC responses even in the presence of HCQ, highlighting its unique potential to disrupt pDC disease relevant biology, which could provide additional therapeutic benefit for CLE patients.


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**AB0044**

**PHARMACOLOGICAL MANIPULATION OF SIRTUIN 1 ACTIVITY IN EXPERIMENTALLY INDUCED ARTHRITIS**

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**Background:** Sirtuin 1 (Sirt1) is a member of the sirtuin family of NAD+ dependent protein deacylases. This nuclear enzyme with deacetylase activity serves as a metabolic sensor and transcriptional regulator, and exerts its beneficial effects by activation of sirtuins via an alternative mechanism, had a similar effect on IL-1beta expression in vitro. Finally, Parp1 cleavage, a marker for cell death, was reduced in purified BM neutrophils following Sirt1 activation.

**Conclusion:** Sirt1 activity modulation, whether activation or inhibition, improved clinical scores in arthritis. This corresponds to the mobilization of neutrophils from the BM to the periphery. The selective increase of IL-1beta following Sirt1 activation indicates that while activation or inhibition achieves a similar outcome, this is done through different molecular pathways. Our results underscore that systemic pharmacological modulation of Sirt1 activity for a complex disease, such as rheumatoid arthritis, is complicated and attention should be paid to the schedule and duration of treatment, as well as to the progressive involvement of various cell types, in order to maximize the beneficial effects.

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**AB0045**

**MESENCHYMAL STEM CELLS INHIBIT THE ACTIVATED COMPLEMENT C5 BY CLUSTERIN IN LUPUS NEPHRITIS**

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**Background:** Dysregulation of clusterin (CLU) and over-activated complement C5 were involved in the development and progression of lupus nephritis (LN). Allogeneic mesenchymal stem cells (MSCs) transplantation has achieved good clinical results for refractory LN, however, the exact mechanisms remain to be elucidated.

**Objectives:** To investigate the clinical effect of MSCs on SLE model mice (B6. lpr), and explore the mechanisms of MSCs inhibiting the activated complement C5 in vivo and in vitro.

**Methods:** 26-week-old female B6.lpr mice were randomly allocated in three groups, which were given the following treatments, CTX (200mg/kg), MSCs (1×10⁶), and an equal volume of PBS. 24 hours urine and peripheral blood were collected periodically. All mice were sacrificed at 40 weeks of age. Urine protein to creatinine ratio and plasma creatinine were quantified to evaluate renal disease. Levels of C3, soluble C5b-9 (SC5b-9), CLU, and anti-dsDNA antibody were determined in the plasma by ELISA. Histopathological evaluation of renal lesions was undertaken by HE, PAS, PASM and Masson staining under light microscopy. Podocyte foot processes were assayed by the transmission electron microscopy. Accumulation of immunocomplexes (IC), C3, C5b-9, and CLU were detected in renal specimens by immunofluorescence or immunohistochemistry. Expressions of CLU in MSCs were detected by real-time PCR and ELISA. MSCs-derived CLU was purified and functional analysis was performed accordingly.

**Results:** Compared to the control mice, both proteinuria and plasma creatinine were significantly improved in each treatment group. Plasma C3 was significantly elevated in mice of MSCs and CTX groups. There were decline trends in plasma levels of anti-dsDNA and SC5b-9 in treated mice when compared to the control mice. Notably, plasma CLU was only significantly elevated in MSCs treated mice. Pathological analysis showed that the proliferation of glomerular cells and foot process fusion were significantly alleviated in MSCs treated mice. Immunofluorescence and immunohistochemistry showed that depositions of IC, C1q, C3 and C5b-9 were significantly decreased in the MSCs group, although the expression of CLU was obviously increased in these mice. Mechanistically, interferon-α promoted the secretion of functional CLU by MSCs in vitro.

**Conclusion:** Allogeneic MSCs transplantation can effectively improve the clinical outcome of lupus mice. Possible mechanisms of MSCs might be related to inhibit the activated C5 via clusterin, which would be a potential treatment target in the future.

**REFERENCE**

¹ Harris CL, et al. Mol Immunol. 2018

**Disclosure of Interests:** None declared