therapies for SS patients are still lacking. Polysaccharides derived from *Dendrobium officinale* (DOP) have been shown to possess immunomodulatory functions in various animal models. However, it remains unclear whether DOP can modulate immune responses and have potential therapeutic effects on SS.

**Objectives:** To investigate the immune modulatory and therapeutic effects of DOP on experimental SS (ESS) in mice.

**Methods:** Polysaccharides were extracted from *Dendrobium officinale* with removal of endotoxin. C57BL/6 mice were immunized with SG-derived proteins for ESS induction, followed by daily oral treatment of vehicle and different dosages of DOP. SG functions were assessed by monitoring saliva flow rates whereas lymphocytic infiltration and tissue destruction in SG were examined by histological analysis. Both T and B cell populations in peripheral lymphoid organs were analyzed by flow cytometry. The effects of DOP on IL-10-producing B cell (B10 cell) induction and Th17 cell differentiation were examined in culture. Moreover, TLR4 and TLR9 inhibitors were used to identify the function of TLR4/TLR9 in DOP-mediated effects.

**Results:** ESS mice with DOP treatment displayed significantly higher saliva flow rates than vehicle-treated ESS mice. DOP treatment ameliorated SG tissue destruction accompanied with profoundly reduced lymphocytic infiltration in ESS mice when compared with vehicle-treated counterparts. Moreover, DOP treatment markedly increased the numbers of B10 cells but decreased numbers of Th17 cells in peripheral lymphoid organs of ESS mice. Notably, DOP markedly increased frequencies and numbers of B10 cells but did not affect Th17 cells generation in culture. Moreover, TLR4 inhibitor, but not TLR9 inhibitor, significantly suppressed DOP-induced IL-10 production in B cells.

**Conclusions:** The results show that DOP treatment ameliorates ESS disease development by inducing regulatory B10 cells, suggesting that DOP might be a promising candidate for treating SS.

**REFERENCES:**

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**AB0157**

**TARGETING T-CELL TRAFFICKING IN A MURINE MODEL OF SJÖGREN’S SYNDROME**

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**Background:** Salivary glands of primary Sjögren’s syndrome (pSS) are characterised by complex lymphocyte infiltration organised into tertiary lymphoid structures (TLS). The mechanisms regulating lymphocyte trafficking into inflamed salivary glands are poorly described, but dysregulated T-cell recruitment during inflammation is believed to contribute to disease onset and chronicity. We recently described a homeostatic pathway in which a B cell-derived peptide (PEPITEM) is secreted in response to adiponectin, regulates T-cell trafficking during inflammation. Our work suggests that PEPITEM should be considered to address therapeutic needs in chronic inflammatory conditions, and that the detection of decreased levels of adiponectin receptors could serve as a biomarker in pSS.

**Objectives:** To investigate the homeostatic regulation of lymphocyte trafficking which is disrupted in inflammation. Our work suggests that PEPITEM should be considered to address therapeutic needs in chronic inflammatory conditions, and that the detection of decreased levels of adiponectin receptors could serve as a biomarker in pSS.

**Methods:** Polysaccharides were extracted from *Dendrobium officinale* with removal of endotoxin. C57BL/6 mice were immunized with SG-derived proteins for ESS induction, followed by daily oral treatment of vehicle and different dosages of DOP. SG functions were assessed by monitoring saliva flow rates whereas lymphocytic infiltration and tissue destruction in SG were examined by histological analysis. Both T and B cell populations in peripheral lymphoid organs were analyzed by flow cytometry. The effects of DOP on IL-10-producing B cell (B10 cell) induction and Th17 cell differentiation were examined in culture. Moreover, TLR4 and TLR9 inhibitors were used to identify the function of TLR4/TLR9 in DOP-mediated effects.

**Results:** ESS mice with DOP treatment displayed significantly higher saliva flow rates than vehicle-treated ESS mice. DOP treatment ameliorated SG tissue destruction accompanied with profoundly reduced lymphocytic infiltration in ESS mice when compared with vehicle-treated counterparts. Moreover, DOP treatment markedly increased the numbers of B10 cells but decreased numbers of Th17 cells in peripheral lymphoid organs of ESS mice. Notably, DOP markedly increased frequencies and numbers of B10 cells but did not affect Th17 cells generation in culture. Moreover, TLR4 inhibitor, but not TLR9 inhibitor, significantly suppressed DOP-induced IL-10 production in B cells.

**Conclusions:** The results show that DOP treatment ameliorates ESS disease development by inducing regulatory B10 cells, suggesting that DOP might be a promising candidate for treating SS.

**REFERENCES:**

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**AB0158**

**HISTOLOGICAL AND SEROLOGICAL CHARACTERISTICS CONTRIBUTE TO DIVERGENT OUTCOMES FOR INDIGENOUS PATIENTS WITH LUPUS NEPHRITIS**

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**Background:** Renal outcomes for Indigenous Australians (IA) with Lupus Nephritis (LN) are worse than for other ethnic groups.

**Objectives:** To investigate whether differences in renal biopsy findings can explain the worse renal outcome in Indigenous patients

**Methods:** A single centre cohort study of 83 SLE patients undergoing a first renal biopsy at our institution for LN evaluation. Histological assessment included review of ISN classification, A/AC/C sub classification, NIH tubulointerstitial activity and chronicity indices, tubulointerstitial index, semiquantitative IF scores for IgG, IgM, IgA, C3 and C1q deposits, localisation of electron dense deposits (EDD) and presence of thrombosis, vasculitis and tubulointeruclcular infections (TIR). Differences in histological and routine clinical findings including autoantibody profiles between IA patients (n=11) and the pooled data from Asian (n=29) and Caucasian (n=43) patients were analysed by non-parametric statistical methods.

**Results:** IA patients were younger at diagnosis (31 vs 38.5 years, p=0.08) and their biopsies contained fewer glomeruli (11 vs 21, p=0.01), more class III/IV (28 vs 15%) and no class V lesions (0 vs 21%) (p=0.06 for overall comparison). IA patients were less likely to have cellular crescents (0 vs. 25%, p=0.03), more likely to have fibrous crescents and a low tubulointerstitial index (p=0.08). The overall AI (5.1 vs 4.9) and CI scores (1.1 vs. 1.3) or presence of full house IF deposits (67 vs 71%), renal thrombosis (0 vs 4%) or TIR (55 vs. 39%) was similar across groups (all p>0.3). IA patients had lower eGFR (43 vs 65, p=0.025), more often carried anti-SSA52kd Ab (73 vs 33%, p=0.02) and during a mean follow-up of almost nine years, had a higher proportion of patients developing ESRD (18 vs 3%, p=0.02).

**Conclusions:** IA patients with SLE who develop LN have fewer glomeruli, an increased frequency of mesangial abnormalities with absence of cellular crescents and membranous nephropathy and a high prevalence of anti-SSA 52KD Ab. Although based on small numbers, this suggests that lower nephron mass and immunological pathways involving IFN-inducible anti-SSA expression may contribute to LN development and worse renal outcome in Indigenous patients.

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**AB0159**

**CYTOKINE PRODUCTION BY ACTIVATED PLASMACYTOID DENDRITIC CELLS AND NK CELLS IS SUPPRESSED BY AN IRAK4 INHIBITOR**

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**Background:** In SLE, immune complexes containing self-derived DNA or RNA (RNA-IC) trigger the synthesis of several pro-inflammatory cytokines by immune cells. Treatment with anti-malarials, such as hydroxychloroquine (HCQ), which
through endosomal TLR inhibition effectively blocks IFN-α, is standard of care. However, few patients experience complete remission.

**Objectives:** We asked whether an IL-1 receptor associated kinase 4 (IRAK-4) inhibitor for I92 (ND-2158, Nimbus Discovery), acting downstream of TLR 7/9, affects RNA-IC-induced cytokine production compared to hydroxychloroquine (HCQ).

**Methods:** Plasmacytoid dendritic cells (pDCs) and natural killer (NK) cells were isolated from peripheral blood mononuclear cells (PBMCs) of healthy individuals. PBMCs from 15 SLE patients were depleted of monocytes. Cells were stimulated with RNA-IC consisting of IgG from SLE patient sera and U1snRNP particles, in the presence or absence of I92 or HCQ. Cytokines were measured by immunoassays or flow cytometry. RNA-sequencing was performed on RNA-IC stimulated pDCs from four healthy individuals and the effect of I92 and HCQ was assessed.

**Results:** RNA-IC induced IFN-α, TNF-α, IL-6, IL-8, IFN-γ, MIP-1α and MIP-1β production in pDC and NK cell co-cultures. I92 reduced the pDC and NK cell derived cytokine production by 74.95%. HCQ interfered with cytokine production in pDCs, but not in NK cells. In monocyte-depleted SLE PBMCs I92 blocked TNF-α, IFN-γ, MIP-1α and MIP-1β production more efficiently than HCQ. IL-8 production was high in monocyte depleted PBMC from SLE patients, and not blocked by neither drug, despite significant inhibition of IL-8 in pDC-NK co-cultures from healthy individuals. Following RNA-IC activation of pDCs, 975 differentially expressed genes were observed (FDR<0.05), many connected to cytokine pathways, cell regulation and apoptosis. The IRAK4 inhibitor significantly changed more RNA-IC induced genes than HCQ (492 vs. 65 genes). Several top upregulated genes were reversed by both I92 and HCQ, including IFNA2, IFIT3-2, OASL, CXCL10, CD274, TNFSF10, APOL6. Genes such as DKK4, LAD1 and EAF2 were significantly more downregulated by I92 than by HCQ.

**Conclusions:** Whereas both HCQ and the IRAK4 inhibitor block important pro-inflammatory cytokines, the IRAK4 inhibitor I92 exhibits a broader inhibitory effect than HCQ on pathways triggered by RNA-IC, which suggests that IRAK4 inhibition could be a future therapeutic option in SLE and possibly other systemic autoimmune diseases characterized by the presence of ICs containing nucleic acid.

**REFERENCE:**

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**AB0160**

**LOSS OF LET-7 MICRORNA UPREGULATES IL-6 IN BONE MARROW-DERIVED MESENCHYMAL STEM CELLS IN PATIENTS WITH SYSTEMIC LUPUS ERYTHEMATOSUS**

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**Background:** Systemic lupus erythematosus (SLE) is a serious and noticed autoimmune disease, and lupus nephritis (LN) as one of its major complications without effective treatment. IL-37 has been identified as a natural inhibitor of innate immunity. Although increasing evidence showed that serum IL-37 correlated with SLEDAI and nephritis activity, However, it is still unclear that the therapeutic effect of IL-37 on lupus mice.

**Objectives:** This study aims to determine the inhibitory effect of IL-37 in lupus mice and lupus nephritis in vivo, and to expose the IL-37 related mechanisms of cell and molecules that inhibits the inflammation in lupus nephritis.

**Methods:** MRL-Fasβ/β mice with mild and advanced disease were treated with lentiviral vector pLVX-IL-37β. The protein levels of IL-37 in serum and tissue, IL-17, IL-6, IL-10 and TGFβ-3 produced by cell culture from spleen and kidney of mice were measured by ELISA, the relative mRNA expression of these cytokines in PBMCs was detected by RT-PCR, and the frequency of Th17 and Treg cells in splenocyte were determined by FACS.

**Results:** Our results show that IL-37 was highly effective in prolonging survival, alleviating the pathologic characteristics of lupus nephritis (LN) in MRL-Fasβ/β mice by reducing the autoimmune complex deposition such as IgM, IgG and C3, decreasing the production of inflammatory cytokines such as IL-17, IL-6 and promoting the anti-inflammatory cytokines IL-10 and TGFβ-3. We also found that IL-37 protect lupus mice from LN associated with increasing the frequency of Treg cells and reducing the frequency of Th17 cells.

**Conclusions:** This research indicated the protective action of IL-37 in LN, and strengthen the support for IL-37 as a new target for therapy for SLE.

**Disclosure of Interest:** None declared

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**AB0162**

**KLRG1 EXPRESSION IS REDUCED ON NK CELLS FROM SLE PATIENTS AND INVERSELY CORRELATES WITH DISEASE ACTIVITY AND CLINICAL FEATURES**

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**Background:** Systemic Lupus Erythematosus (SLE) is a multifactorial autoimmune disease, with different immunological alterations and clinical phenotypes. Natural killer (NK) cells participate in the regulation of several immune responses but their function in SLE is not well understood. 1 KLRG1 (killer cell lectin like receptor G1) is a trans-membrane protein expressed in humans especially on NK cells, working as an inhibitory receptor of their cytotoxic activity. Thus, KLRG1-mediated signal might have a role in preventing autoimmunity, increasing the activation threshold of NK cells. 2 KLRG1 gene also emerged as a disease susceptibility gene for SLE in four different ethnic groups. 3

**Objectives:** The aim of this study was to characterize KLRG1 expression on NK cells (both CD56dim and CD56bright) from SLE patients compared to healthy subjects (HS) and to investigate its possible correlations with clinical features, including SLE disease activity.

**Methods:** We enrolled 14 patients (14F, mean age±SD 37±10.7 years, mean disease duration ±SD 10.5±7.9 years) affected by SLE according to the 1997 ACR criteria, and 7 HS (7F, mean age±SD 33±5.5 years). Disease activity was measured by SLEDAI-2K. Peripheral blood mononuclear cells (PBMCs) were purified with PBMCs from SLE patients for 72 hours to detect their effect on the ratio of Treg/Th17.

**Results:** Compared to normal controls, the expression of let-7 was markedly down-regulated in BMSCs from SLE patients by RT-PCR, and the synthesis of IL-6 mRNA and protein levels were significantly higher in BMSCs from SLE patients. Compared to let-7-negative controls, transfection of BMSCs with let-7-mimics markedly lowered synthesis of TGF-β1 mRNA, and let-7-inhibitor led to an opposite effect. The mean value of Treg/Th17 was significantly decreased in PBMCs from SLE patients compared to normal controls. Transfection of normal BMSCs with let-7-inhibitor caused significant downregulation of Treg/Th17 compared to let-7-negative controls, while transfection with let-7-mimics led to an opposite effect.

**Conclusions:** SLE patients exist an imbalance between Treg and Th17 cells, which might be associated with up-regulation of IL-6 secretion of BMSCs by loss of let-7.

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**AB0161**

**INTERLEUKIN-37: A THERAPEUTIC FOR LUPUS NEPHRITIS IN MRL-FASLPR MICE**

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**Background:** Systemic lupus erythematosus (SLE) is a serious and noticed autoimmune disease, and lupus nephritis (LN) as one of its major complications without effective treatment. IL-37 has been identified as a natural inhibitor of innate immunity. Although increasing evidence showed that serum IL-37 correlated with SLEDAI and nephritis activity, However, it is still unclear that the therapeutic effect of IL-37 on lupus mice.

**Objectives:** This study aims to determine the inhibitory effect of IL-37 in lupus mice and lupus nephritis in vivo, and to expose the IL-37 related mechanisms of cell and molecules that inhibits the inflammation in lupus nephritis.

**Methods:** MRL-Fasβ/β mice with mild and advanced disease were treated with lentiviral vector pLVX-IL-37β. The protein levels of IL-37 in serum and tissue, IL-17, IL-6, IL-10 and TGFβ-3 produced by cell culture from spleen and kidney of mice were measured by ELISA, the relative mRNA expression of these cytokines in PBMCs was detected by RT-PCR, and the frequency of Th17 and Treg cells in splenocyte were determined by FACS.

**Results:** Our results show that IL-37 was highly effective in prolonging survival, alleviating the pathologic characteristics of lupus nephritis (LN) in MRL-Fasβ/β mice by reducing the autoimmune complex deposition such as IgM, IgG and C3, decreasing the production of inflammatory cytokines such as IL-17, IL-6 and promoting the anti-inflammatory cytokines IL-10 and TGFβ-3. We also found that IL-37 protect lupus mice from LN associated with increasing the frequency of Treg cells and reducing the frequency of Th17 cells.

**Conclusions:** This research indicated the protective action of IL-37 in LN, and strengthen the support for IL-37 as a new target for therapy for SLE.

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