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.

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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 leukocyte infiltration organised into tertiary lymphoid structures (TLS). The mechanisms regulating leukocyte 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), secreted in response to adiponectin, regulates T-cell trafficking during inflammation via sphingosine-1-phosphate activity on endothelial cells¹. Disruption of this pathway by downregulation of adiponectin receptors on circulating B cells has been demonstrated in type-1 diabetes and rheumatoid arthritis, suggesting a potential role for PEPITEM in the pathogenesis of autoimmune diseases, and indicating a role for adiponectin receptors as biomarkers in these conditions¹.

Objectives: We aimed to investigate the efficacy of PEPITEM as an inhibitor of T-cell trafficking in an inducible animal model of salivary gland inflammation that mimics the histological features of pSS, and to investigate the potential translatability of this pathway in patients with pSS.

Methods: Submandibular salivary glands of C57BL/6 mice were intra-ductally cannulated with luciferase-encoding replication-deficient adenovirus to induce TLS formation as previously described². Mice were administered daily either PBS or PEPITEM by intraperitoneal injection from day 0, and their salivary glands dissected at day 5 post cannulation. T-cell infiltration into salivary glands was assessed using a combination of flow cytometry, immunofluorescence, and qRT-PCR for inflammatory chemokines.

Results: B cells in sera from cannulated animals express lower levels of both adiponectin receptors 1 and 2 in comparison with non-inflamed control mice. In cannulated animals treated with PEPITEM, histological analysis of salivary glands revealed fewer, as well as less aggregated, infiltrating T cells. Both CD4⁺ and CD8⁺ numbers were significantly lower in the salivary glands of PEPITEM-treated animals. Furthermore, administration of PEPITEM also decreased mRNA transcripts for lymphotoxin beta, IL-7, lymphoid chemokines (CCL19 and CXCL13)

and T-cell chemokine receptor CCR7, cytokines and chemokines known to regulate ectopic lymphopoiesis in pSS. Samples from pSS patients are currently being assessed to validate the relevance of this pathway in pSS.

Conclusions: These results demonstrate that administration of exogenous PEPITEM can reduce T-cell influx into salivary glands. This may represent a rescue of the homeostatic regulation of leukocyte 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.

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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/C/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 tubuloreticular inclusions (TRI). 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 I/II (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 TRI (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 how an IL-1 receptor associated kinase 4 (IRAK-4) inhibitor I92 (ND-2158, Nimbus Discovery),¹ 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 , MIP1- α and MIP1- β 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 , MIP1- α and MIP1- β 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*, *IFIT2-3*, *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 IRAK4i 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.

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AB0160 LOSS OF LET-7 MICRORNA UPREGULATES IL-6 IN BONE MARROW-DERIVED MESENCHYMAL STEM CELLS TRIGGERING TREG/TH17 IMBALANCE IN PATIENTS WITH SYSTEMIC LUPUS ERYTHEMATOSUS

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Background: Systemic lupus erythematosus (SLE) patients exist an imbalance between CD4⁺CD25⁺FoxP3⁺ T regulatory (Treg) and IL-17-producing cells (Th17). Correction of this Treg/Th17 imbalance may have therapeutic impact for SLE patients. Our previous study demonstrated that bone marrow derived mesenchymal stem cells (BMSCs) from SLE patients are defective in immune modulation, which might be involved in Treg/Th17 imbalance and disease onset, but the mechanisms are not clear yet. The expression imbalance of microRNAs (miRNAs) can cause cell dysfunction, which participates in a variety of diseases development. As an important computer predicted target of let-7, interleukin-6 (IL-6) is an important negative immune regulatory factors secreted by BMSCs. Our previous experiments found that the expressions of let-7 are markedly down-regulated in SLE BMSCs by microRNA array analysis, and the synthesis of IL-6 is significantly higher in SLE BMSCs compared to normal controls.

Objectives: To investigate whether loss of let-7 could play its role in SLE BMSCs immune modulation defects by directly up-regulating IL-6 mRNA, which might contribute to Treg/Th17 imbalance in PBMCs from SLE patients, to further understand the pathogenesis of SLE.

Methods: BMSCs were isolated, cultured and expanded from iliac crest bone marrow of four healthy donors and four SLE patients. Real-time PCR was used to further determine the let-7 expression and IL-6 mRNA level in BMSCs from healthy controls and SLE patients. The important computer predicted target of let-7, IL-6 was determined using the luciferase reporter assay. Let-7-mimics, let-7-inhibitor, and let-7-negative control were transfected to BMSCs with using Lipofectamine 2000. BMSCs from healthy controls and SLE patients were co-cultured

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 lower synthesis of TGF- β 1 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 shown 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 *in vivo*.

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-Fas^{lpr} mice with mild and advanced disease were treated with lentiviral vector pLVX-IL-37b. The protein levels of IL-37b in serum and tissue, IL-17, IL-6, IL-10 and TGF β -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-Fas^{lpr} 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 TGF β -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: These results indicate the protective action of IL-37 in LN, and strengthen the support for IL-37 as a new target for therapy of SLE.

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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 CD56^{dim} and CD56^{bright}) 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 $\pm$ SD 37 $\pm$ 10.7 years, mean disease duration $\pm$ SD 10.5 $\pm$ 7.9 years) affected by SLE according to the 1997 ACR criteria, and 7 HS (7F, mean age $\pm$ SD 33 $\pm$ 5.5 years). Disease activity was measured by SLEDAI-2K. Peripheral blood mononuclear cells (PBMCs) were purified