indicating that microglia cells may carry out the antigen presentation process seen in transcriptomic data. Low levels of serotonin and noradrenaline were observed at both 3 and 6 months of age in lupus mice; these aberrancies were mainly attributed to decreased serotonin synthesis as evidenced by intact serotonin metabolism (no differences were observed at its metabolite: 5-hydroxyindoleacetic acid). Analysis of the remaining regions of the brain combined with studies of metabolic activities of various brain regions by PET-CT scanning is in progress.

Conclusion: Immune cell trafficking from the periphery combined with marked inflammatory response in the hippocampus underlie the neuropsychiatric phenotype in NZW/B murine lupus. Our data indicate increased expression of activated myeloid cells -including microglia- in the hippocampus of lupus mice culminating in increased antigen presentation and decreased neurotransmitter levels.

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OP0041

SALIVA AND SERUM LEVELS OF CXCL13: ASSOCIATION WITH THE SEVERITY OF SALIVARY GLAND LESIONS AND LYMPHOMA IN PATIENTS WITH SJÖGREN'S SYNDROME (SS)

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Background: CXCL13 has been implicated in the formation of ectopic germinal centers (GC) in minor salivary gland (MSG) inflammatory lesions of SS patients. Recent studies suggest that serum CXCL13 levels associate with disease severity and risk for non-Hodgkin's lymphoma (NHL) development.

Objectives: To validate the clinical utility of CXCL13 by investigating potential associations of saliva and serum CXCL13 levels with various histopathologic (including severity of MSG autoimmune infiltrates and GC formation), serologic and clinical features of the disease, as well as NHL.

Methods: CXCL13 levels were measured by a commercially available ELISA (sensitivity: 1 pg/ml; Abcam, Cambridge, UK) in paired serum and saliva specimens from 25 SS patients (9 with NHL; SSL), 9 sicca controls (SC; sicca-complaining individuals with no infiltrates in diagnostic MSG biopsy and negative autoantibody profile) and 6 healthy controls (HC). From the 16 SS patients without evidence of NHL, 5 had mild, 6 intermediate and 5 severe lesions at MSGs, as arbitrarily defined by focus (FS) and Tarpley (TS) biopsy scores (mild: FS:1-1.7, TS:1, intermediate: FS:1.8-2.95, TS:2 and severe: FS: 3.0-11, TS: 3-4). Furthermore, the organization of the MSG infiltrates to GCs has been evaluated in 23 patients revealing 10 with GCs.

Results: Kruskal-Wallis analysis revealed that serum CXCL13 levels were significantly increased in SS patients without or with NHL (median: 94.83 pg/ml and 96.70 pg/ml, respectively), compared to SC and HC (35.44 and 40.92 pg/ml respectively; $p < 0.05$), whereas saliva levels were only marginally increased (76.47, 84.10, 55.98 and 65.30 pg/ml in SS, SSL, SC and HC, respectively, $p = 0.051$). Among SS patients with distinct MSG lesion severity, only those with severe lesions were found to express significantly higher serum CXCL13 levels (149.3 pg/ml) from SC and HC (p : 0.0051 and 0.0166, respectively). Spearman's Rank correlation analysis showed that both serum and saliva levels correlated with SG biopsy focus score (r : 0.6889, $p = 0.0001$ and r : 0.4222, $p = 0.01$, respectively). Mann-Whitney test revealed that serum CXCL13 levels were significantly elevated in patients with GCs at MSG lesions (156.1 vs 69.64 pg/ml, p : 0.0015), rheumatoid factor (105.0 vs 53.72 pg/ml, p : 0.015) and marginally with anti-Ro/La antibodies (121.8 vs 65.05 pg/ml, p : 0.06) compared to those without. Furthermore, CXCL13 levels were significantly increased in SS patients at high risk to develop NHL compared to low risk (149.3 vs 71.54 pg/ml, respectively, p : 0.0275). Saliva levels were not found to associate with the studied features.

Conclusion: Serum and to a lesser extend saliva CXCL13 levels are increased in SS and SSL patients and associate with the degree of MSG infiltration, as assessed by focus score. Serum, but not saliva, CXCL13 associates with various disease features, including GC formation, and may have a clinical utility in identifying SS patients at high risk to develop lymphoma.

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OP0042

BLOCKING OF CD103+ TISSUE RESIDENT MEMORY T CELLS (TRM) AS A THERAPEUTIC STRATEGY IN SJÖGREN'S SYNDROME

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Background: Tissue-resident memory T cells (TRM), are a recently identified T cells population featuring tissue localization and expression of markers of tissue homing, CD69 and CD103. Recently, the expansion of CD4+ TRMs and their involvement in the sialadenitis was described in a murine model of SS. However, CD4+ and CD8+ TRM's functional relevance in pSS is still not fully understood, and the TRM therapeutic targeting unexplored.

Objectives: The study aimed to address the role of CD4+ and CD8+ TRMs in the pathogenesis of pSS and to explore the therapeutic targeting of the tissue residency marker of TRM CD103.

Methods: An animal model of experimental (ESS) obtained by immunization of female C57BL/6 mice ($n=10$) with salivary glands (SG) protein extract and Freund's complete adjuvant used to investigate the dynamic of infiltration of SG by CD4+ and CD8+ TRMs, their frequency, and the impact of CD103 blockade. For the therapeutic intervention, at 10-weeks post-immunization, the salivary gland was cannulated via Wharton's duct, and an anti-CD103 neutralizing antibody or vehicle-injected. The mice's saliva flow rate was assessed, and SGs were analyzed by Flow-cytometry and immunohistochemistry (IHC).

The frequency and localization of TRMs was analyzed in minor SG of sicca syndrome (nSS) and pSS patients ($n=39$) by flow cytometry and IHC. The expression of genes involved in the tissue retention of TRMs was assessed in SG by RT-PCR.

Results: Upon the ESS progression, a significant progressive increase in CD45+CD103+ cells frequency was observed from 5wk to 20wk post-immunization ($p < 0.001$), where the CD8+ were the most abundant, followed by CD4+. Consistently, CD103+CD8+ T cells were detected within the lymphocytic infiltration of SG from ESS mice. Sorted purified SG CD103+CD3+CD8+ T cells showed higher Granzyme B, TNF-alpha expression compared to CD103+CD3+CD8+ at both mRNA and protein levels. Notably, ESS mice treated with anti-CD103 showed improvement in salivary function ($p < 0.05$) and reduced lymphocytic infiltrations measured as focus score (FS) ($p < 0.01$) and area-fraction ($p < 0.01$). Consistently, anti-CD103 treatment consistently reduced CD103+ cells and IFN-gamma+, Granzyme B+ and TNFa+ CD8+ cells. We next performed phenotypic analysis of CD45+CD103+ immune cells in the SG of pSS patients observing an increase in both with CD8+CD103+CD69+ and CD4+CD103+CD69+ ($p < 0.05$). Finally, IHC showed that the expansion of TRMs in pSS salivary glands was accompanied by a down-regulation of E-cadherin glandular expression and their migration outside the epithelium in the context of inflammatory infiltrates. SG of patients with pSS showed a significant up-regulation of BLIMP1, KLF-2, and S1PR1 and down-regulation of ITGB2. CXCL9 and CXCL10, and IL-15 involved in the tissue recruitment and long-term survival of TRMs were significantly modulated in pSS salivary glands.

Conclusion: TRM are expanded and activated in the SG of pSS and ESS, participating in the organization of tissue inflammation. Although the mechanisms behind this expansion are still not fully understood, CD103 could be a valuable novel therapeutic target to prevent lymphocytic infiltrations and glandular destruction in Sjogren syndrome.

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OP0043

INCREASED RISK OF SEVERE INFECTIONS AND MORTALITY IN PATIENTS WITH NEWLY DIAGNOSED SYSTEMIC LUPUS ERYTHEMATOSUS: A POPULATION-BASED STUDY

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Background: Systemic lupus erythematosus (SLE) is a chronic disease with a broad spectrum of autoantibodies and clinical manifestations. As much as 45%

of SLE patients were reported to suffer from severe infections^{1,2}. However, due to the high cost of recruiting patients, we still do not have a holistic picture of the SLE-infection association. Administrative data which encompass all provincially funded healthcare service data shows promising opportunities to advance the knowledge and management of the SLE patients which cannot be evaluated by the conventional clinical setting with small sample size and selective samples^{3,4,5}.

Objectives: To evaluate the risk of severe infection and infection-related mortality among patients with newly diagnosed systemic lupus erythematosus.

Methods: We conducted an age- and gender- matched cohort study of all patients with incident SLE between January 1, 1997 and March 31, 2015 using administrative health data from British Columbia, Canada. Primary outcome was the first severe infection after SLE onset necessitating hospitalization or occurring during hospitalization. Secondary outcomes were total number of severe infections and infection-related mortality.

Results: We identified 5,169 SLE patients and matched them with 25,845 non-SLE individuals from the general population, yielding 955 and 1,986 first severe infections during 48,367 and 260,712 person-years follow-up, respectively. The crude incidence rate ratios for first severe infection and infection-related mortality were 2.59 (95% CI, 2.39-2.80) and 2.20 (95% CI, 1.76-2.73), respectively. The corresponding adjusted hazard ratios were 1.82 (95% CI 1.66-1.99) and 1.61 (95% CI, 1.24-2.08). SLE patients had an increased risk of a greater total number of severe infections with crude rate ratio of 3.24 (95% CI, 3.06-3.43) and adjusted rate ratio of 2.07 (95% CI, 1.82-2.36).

Conclusion: SLE is associated with increased risks of first severe infection (1.8-fold), a greater total number of severe infections (2.1-fold) and infection-related mortality (1.6-fold).

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OP0044

ANA POSITIVITY IS ASSOCIATED WITH COMPLEX IMMUNE DISTURBANCE EVEN IN INDIVIDUALS WHO DO NOT DEVELOP CLINICAL AUTOIMMUNE DISEASE

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Background: Study of pre-clinical autoimmunity can reveal immune changes that initiate or prevent clinical disease. We previously reported an At Risk cohort of ANA positive individuals referred to secondary care, of whom 16% progressed to SLE or Sjogren's syndrome during follow up[1]. Recently, we also reported that even ANA positive individuals who do not develop clinical autoimmunity, have defective pDC function and non-haematopoietic interferon-production[2].

Objectives: To describe the immunophenotype of ANA-positive progressors and non-progressors compared to healthy controls.

Methods: We conducted a prospective observational longitudinal study of At-Risk individuals in Leeds (n=150) over 3 years with annual follow up. Those who met classification criteria for autoimmune connective tissue disease (AI-CTD) during follow up were termed progressors and others; non-progressors. Among the non-progressors, those with no clinical diagnostic criteria at any time point were called absolute non-progressors (ANP).

At baseline we analysed two IFN-stimulated gene expression scores previously described[3] and flow cytometry performed for major circulating subsets. Association between progression group and biomarkers were tested using independent samples t-test.

Results: 3 year follow up data were available in 148/150 patients. Outcomes were: progressors: 30/148 (20%) [SLE=25; pSS=5] and non-progressors: 118/148 (80%). Within the non-progressors, 69/148 (47%) were ANP.

A detailed analysis of baseline biomarkers is included in Table 1. Despite not developing clinically significant disease, non-progressors had significant alterations in several biomarkers. This was also evident in the ANP sub-group.

Table 1.

Biomarker	Healthy Controls	Non-progressors	Difference from healthy controls	Absolute non-progressors	Difference from healthy controls	Progressors	Difference from healthy controls
	Mean (95% CI)	Mean (95% CI)	p	Mean (95% CI)	p	Mean (95% CI)	p
IFN score A	-6.27 (-6.88, -5.65)	-5.22 (-5.64, -4.80)	0.016	-5.11 (-5.91, -4.32)	0.120	-4.14 (-5.11, -3.18)	0.001
IFN score B	-5.43 (-6.00, -4.85)	-5.30 (-5.62, -4.98)	0.193	-4.96 (-5.45, -4.47)	0.949	-4.27 (-4.90, -3.65)	0.136
% Mono-cytes	14.80 (10.50, 19.11)	15.46 (12.96, 17.97)	0.187	14.94 (11.42, 18.47)	0.738	10.36 (7.42, 13.30)	0.227
% CD4	62.90 (57.75, 68.05)	64.89 (60.86, 68.92)	0.001	68.72 (62.97, 74.47)	0.267	60.93 (53.64, 68.21)	0.001
T cells	32.18 (27.47, 36.90)	28.60 (25.12, 32.09)	0.135	25.02 (20.28, 29.77)	0.044	31.51 (25.63, 37.40)	0.875
% Naive	65.59 (56.56, 74.61)	73.74 (70.02, 77.46)	0.001	76.86 (72.21, 81.51)	0.128	60.93 (53.64, 68.21)	0.173
% Memory	29.56 (20.42, 38.72)	19.72 (15.84, 23.61)	<0.000	23.13 (16.65, 29.61)	0.054	25.57 (17.18, 33.96)	0.163
% B cells	1.12 (0.81, 1.43)	0.91 (0.58, 1.24)	0.964	1.01 (0.44, 1.58)	0.457	0.81 (0.53, 1.10)	0.112
% NK cells	13.65 (9.65, 17.65)	12.30 (8.90, 15.71)	0.480	12.35 (6.65, 18.05)	0.781	11.90 (8.65, 15.14)	0.195

Conclusion: Clinically benign ANA positivity is a complex immune state with many features seen in active SLE, including pDC exhaustion, keratinocyte interferon production and strong skin interferon score, increased blood interferon score, and disturbance of B cell subsets. These findings suggest that other factors are necessary for clinical disease, or that regulatory mechanisms stabilise autoimmunity. Further work in this cohort will address these questions.

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OP0045

NLRP12 INVOLVES IN THE LUPUS WITH POSITIVE INTERFERON SIGNATURE

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Background: Systemic lupus erythematosus (SLE) is a systemic autoimmune disease with diverse etiological factors. It was recognized that interferon (IFN) signature involved in the progress of SLE. NLRP12 (NOD-like receptor family (NLR) pyrin domain containing 12) is a pyrin containing NLR protein that we had linked its new biological function to the cross-regulation of Toll like receptor (TLRs) and Rig-I like receptor (RIG-I) pathways. NLRP12 acts as an innate immune check-point in regulating type I IFNs expression during TLRs and RIG-I activation. The importance of NLRP12 in lupus disease activity remained to be elucidated.

Objectives: To clarify the role of NLRP12 in regulating the interferon signature.

Methods: Peripheral blood mononuclear cells (PBMCs) were collected from SLE patients and healthy donors for analysis of NLRP12 and IFN- α gene expression by RT-QPCR. PBMCs were applied for Chromatin immunoprecipitation (ChIP) assay and electrical mobility shift assay (EMSA) to determine the putative transcription factor that regulates NLRP12 expression. An involvement of epigenetic regulation of NLRP12 expression in SLE patients was also analyzed. Bone marrow derived dendritic cells (BMDCs) were collected from wild type mouse and Nlrp12 knocked-out mice. Another CD14+ monocytes were isolated from 10 cases of lupus patients and 8 cases of healthy control, following by stimulating different type of nucleic acids, and IFN- α and IL-6 were measured with ELISA assay. CD14+ monocytes in lupus patients were also pre-treated with IFNAR2 antibody for further nucleic acid stimulation. Two mice models were applied for evaluation the role of Nlrp12: intraperitoneal injection of TMPD (2,6,10,14-tetramethylpentadecane, or pristane) in C57BL/6 mice and Fas^{lpr} mice. Both models were conducted with and without Nlrp12 knockout.