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Highlights of the 14th International Symposium on Sjögren's Syndrome

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The theme of the 14th International Sjögren's Symposium (ISSS) held in Washington DC, between the 18th and the 21st of April, 2018 was "Paths to Precision Diagnosis and Therapy". Sjögren's syndrome (SS) is a common, complex and heterogeneous disease, still lacking precise diagnostic techniques as well as specific and effective therapeutic intervention (1, 2). It is therefore a significant public health problem as it is a potentially disabling condition, negatively affecting patients' quality of life, as highlighted by patients themselves in the Panel that opened the Meeting. The topics of the 14th ISSS focused on disease sub-setting through the use of biomarkers, genetic tests and molecular studies of the targeted tissue, clinical trial design and outcome measures, standardisation of salivary gland histopathological scoring, and identification of pathophysiologic pathways amenable to therapeutic targeting. Importantly, one of the primary objectives of the Symposium was to foster successful drug development and clinical trial design for SS.

The Symposium was co-chaired by Alan Baer (Baltimore, USA), Ilias Alevizos (Bethesda, USA) and Esen Akpek (Baltimore, USA). There were 384 participants from 33 different countries. Travel grants were awarded to 35 young investigators and postdoctoral fellows, enabling them to present their work, exchange ideas and network with more senior investigators. There were thirty-one oral and 189 poster presentations in addition to 37

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plenary lectures. The meeting was preceded by a pre-Conference Workshop on Salivary Gland Ultrasonography in SS that combined didactic and practical training sessions.

The *opening lecture* by Roland Jonsson (Bergen, Norway) included an overview of the life and scholarly work of Henrik Sjögren, and a tribute to three eminent Sjögren's researchers, Norman Talal, Rolf Manthorpe, Susumu Sugai, each of whom had died within the past 3 years.

The theme of the Symposium was introduced by Anthony Rosen (Baltimore, USA) who gave an outstanding lecture on the application of precision medicine to systemic autoimmune diseases, such as SS. More specifically, he specified how SS and other genetically heterogeneous systemic autoimmune diseases, may have a diverse spectrum and a complex, nuanced or overlapping phenotype. Moreover, these diseases may be driven by numerous environmental forces, displaying a marked kinetic complexity in their initiation, propagation and flares. He suggested that disease subsets can be defined phenotypically, biologically, and molecularly in an attempt to identify and discover hidden disease patterns of clinical relevance. Bringing three different examples, cancer in systemic sclerosis, amplification of the immune response in myositis fostered by autoantigen expression in muscle and the interferon signature in SS, Dr. Rosen concluded that in order to move towards proper subset phenotyping we have to carefully search for the "fuel" in autoimmunity: self sustaining processes, hubs where sustaining interactions occur and loops that may identify therapeutically relevant pathways, especially in the affected tissues.

The *first plenary session* of the Symposium was dedicated to the *"Definition and Epidemiology of SS"*. The leitmotiv of this session was the recognition of the different subtypes of the disease and their impact on SS diagnosis and treatment.

H. Scofield (Oklahoma City, USA) opened the session with a discussion of existing classification criteria and the recent development of the ACR/ EULAR criteria set (3). He emphasised the difficulties that remain in the diagnosis of SS, both in non-research contexts (*i.e.* distinguishing sicca from SS) and in dedicated rheumatology clinics (*i.e.* dealing with a multidisciplinary approach). For the future, he recommended refining classification criteria with the inclusion of novel biomarkers and novel diagnostic tools such as salivary gland ultrasonography, mass cytometry, and proteomics. Immunological research performed at the glandular level (*i.e.* $CD4^+$ $PD1^+$ effector regulatory T cells and $IL21^+$ effector conventional T cells) and in peripheral blood ($CD25^+$ T regulatory cells, follicular T cells, memory B cells, mucosal invariant T cells) also promises to provide distinctive disease signatures.

C. Shiboski (San Francisco, USA) summarised the efforts made by the Sjögren's International Collaborative Clinical Alliance (SICCA) registry for moving towards a better characterisation of the SS phenotype and genotype (4). The SICCA cohort included 3514 patients from 9 research centres; after two years of follow-up, 771 patients were recalled. The registry data provided information on the stability over time of the 3 categories of SS phenotypic features (serology, oral, ocular), with the percent unchanged, ranging from 78% (for Schirmer's test) to 97% (for anti-SSA/SSB). Among participants with focal lymphocytic sialadenitis (FLS) and focus score ≥1, 75% still had this histopathological

diagnosis after the 2–3-year follow-up, while 17% were not found to have FLS at follow-up. The total incidence of lymphoma was <1%. F. Barone (Birmingham, UK) focused on the current efforts of the Sjögren's community to re-define the histopathological assessment of minor salivary gland biopsies as diagnostic tools, predictors of disease severity and stratifiers in clinical trials. She highlighted the significant variability among different centres in the analysis of key histopathologic aspects, including the focus score and the definition of ectopic germinal centres. The current direction of the SS scientific community is to develop a consensus for the use of digital image analysis for the quantitative assessment of immune cell infiltration and to define a minimal set of immunohistochemical markers to identify germinal centres. Finally, she focused on the definition of surrogate biomarkers of salivary gland histopathology in the peripheral compartment and on preliminary data from multicentre analyses indicating that circulating CXCL13 levels are closely associated with the degree of immune cell infiltration and lymphoid organisation in the salivary glands.

Finally, C. Baldini (Pisa, Italy) highlighted the importance of defining disease subtypes in primary SS (pSS) in order to move from one-size-fits-all therapy towards personalised medicine based on individual genetics, clinical features, environment, comorbidities etc. Given the complexity and heterogeneity of SS, the definition of SS subgroups may be a prerequisite to get from phenotype to endotype, get better insights into the pathogenesis of the disease, discover novel therapeutic targets and drugs, and test their efficacy. Novel statistical methodologies such as machine learning/neural networks could be explored in parallel with conventional statistics in order to identify unknown, hidden and important information from large datasets.

J.O. Pers (Brest, France), presented extensive preliminary data from the PRECISESADS initiative aimed at redefining the taxonomy of autoimmunity via molecular profiling of patients with diverse autoimmune diseases, including SS. Data were presented for the first 385 SS patients enrolled in the cross-sectional cohort and 43 in the inception cohort. RNA-Seq analysis of peripheral immune cells in SS revealed 519 immune-related genes whose differential expression served to identify three main clusters of patients. Cluster 3 displayed the highest levels of circulating pro-inflammatory cytokines, including CXCL13 and IP10 with the latter closely correlated with a type 1 IFN signature. Interestingly both IP10 and CXCL13 expression levels were associated with disease severity based on ESSDAI. A parallel aim of the PRECISESADS initiative is to identify disease subsets through deep immunophenotyping of peripheral blood immune cells by flow cytometry, achieved through a multicentre harmonisation of protocols and reagents. With discriminant function analysis and Flock analysis approaches, SS patients could be discriminated from other systemic autoimmune diseases by a unique signature characterised by an increase in IgDhiC-D24hiCD38hiCD27-TACI-CD5hi transitional B cells and of $CD45RA^{+}$CD27-CD62Llo/-CD57hi effector $CD8^{+}$ T cells. This is an important refinement of previously reported increases in these subsets in SS patients.

Concurrent session A: Novel insights

This session of selected abstracts showcased novel findings in different aspects of SS pathogenesis, including molecular mechanisms of salivary hypofunction and fatigue as well

as clinical management of fatigue and ocular dryness. The Scofield group presented back-to-back communications on novel aspects of SS pathogenesis. S.M.S. Quadri (Oklahoma City, USA) generated recombinant monoclonal antibodies (MAbs) from single cell suspensions of CD3− CD4− CD8− $CD19^+$ CD27high CD38high IgG+ plasmablasts isolated from SS salivary glands. They screened the MAbs against multiple antigenic peptides of the 2nd (a.a. 213–228) and 3^{rd} (a.a. 514–527) extracellular domains of the muscarinic M3 Receptor (M3R), which mediates acetylcholine-induced secretion. Interestingly, 9/51 MAbs were positive to the 2nd domain and 5/51 to the 3^{rd} domain of M3R and 6 of these antibodies displayed inhibitory activity in a functional assay using muscarinic agonists. Overall, this work suggests that pathogenic antibodies are generated from locally-selected B cells.

From the same group, V. Harris (Oklahoma City, USA) described an interesting approach on defining the contribution of an X-chromosome gene dose effect to the observed sex bias in SS susceptibility. They focused on the dehydrogenase/reductase protein encoded by the gene Chromosome X open reading frame 21 (CXorf21), which escapes X inactivation and is known to increase susceptibility to lupus. Although the work presented was mostly focused on SLE, they confirmed that CXorf21 expression was restricted to $CD19^+$ B cells and monocytes. CXorf21 basal gene and protein expression was elevated 1.5-fold in female compared to male primary monocytes, suggesting an X chromosome gene dosage effect. Of relevance, CXorf21 expression could be induced in a concentration-dependent manner using TLR7 or NOD1 specific ligands, suggesting that this pathway is involved in pathogen sensing and could contribute to disease pathogenesis.

The next two presentations tackled basic science and clinical aspects of fatigue, one of the key SS-related clinical manifestations. I. Bodewes (Rotterdam, The Netherlands) used the SOMAscan proteomics approach in order to identify biomarkers and possible treatment targets. She and her research team identified 14 proteins (out of >1000 detectable proteins using this technology) differentially expressed in fatigued compared to non-fatigued pSS patients including complement factors (C4b, C3b, C3d, C3 and the C1 inhibitor, SERPING1), enolases (alpha and gamma), SNAP25, IL-36, BMP6 and UCH-L1. Fatigue remains an unmet clinical need in SS but promising data were also presented by K.L. Hackett (Newcastle upon Tyne, UK) using a multidisciplinary, biopsychosocial intervention addressing reversible causes of fatigue including autonomic dysfunction, comorbidities and medications. This combined approach involving occupational therapy, physiotherapy, health psychology and cognitive behavioural therapy resulted in a statistically significant and clinically meaningful improvement in fatigue.

Finally, V.Y. Bunya (Philadelphia, USA) presented a novel dry eye screening questionnaire developed with data from the SICCA cohort. In a univariate analysis of 87 questionnaire responses in the registry, 11 questions were best able to differentiate dry eye with SS versus dry eye without SS. Four of these questions independently associated with SS using a multivariate logistic regression model. The authors concluded that these 4 specific questions should be administered to patients with dry eye to help raise suspicion of underlying SS.

The session was concluded by D. Lucchesi (London, UK) who presented novel data indicating a negative regulatory role for IL-27 in the formation of ectopic germinal centres in

the salivary glands. His research team used a model of virally-induced sialadenitis in C57Bl/6 mice and showed that mice lacking IL-27RA displayed a significantly higher degree of B cell infiltration, forming larger and more abundant germinal centres in the submandibular glands compared to wild-type littermates. Intriguingly, the observed aberrant germinal centre response was due to an increased expression of IL-17 by infiltrating $CD4^+$ T cells, suggesting that IL-27 exerts a key role in regulating the magnitude of Th17 responses in the local salivary gland microenvironment with a direct impact on ectopic germinal centre formation.

Concurrent session B: Mechanisms of mucosal dryness

The concurrent session B, entitled “Mechanisms of mucosal dryness”, was specifically focused on oral and ocular surface chronic inflammation, imbalances in the regulatory and inflammatory immune responses and potential new therapeutic approaches designed to restore this balance either by inhibiting or blocking inflammatory effectors and their cytokines or by inducing regulatory effectors. The importance of goblet cells in secreting mucins and in maintaining ocular surface homeostasis is well established. In this meeting, data were presented on the novel role of goblet cell derived factors, other than soluble mucins, in immune regulation/homeostasis of the ocular surface. In particular, it was shown how conjunctival goblet cells have the ability to secrete TGF-beta 2 and activate it in a thrombospondin-1 (TSP-1)-dependent manner, allowing modulation of neighbouring dendritic cell phenotypes towards an immature or tolerogenic state. From this perspective, TSP-1-deficient mice spontaneously develop chronic ocular surface inflammation that resembles SS and a polymorphism in the gene encoding TSP-1 results in reduced TSP-1 expression that in turn correlates with susceptibility to chronic ocular surface inflammation in humans. The possibility of taking advantage of the immunomodulatory function of TSP-1 opens novel perspectives for the treatment of dry eyes in pSS. Another potential target for therapeutic interventions in SS-related dry eyes may be meibomian glands, sebaceous glands that preserve integrity of the lipid layer of the ocular film. Dysfunction of meibomian glands has been described in SS and other dry eye disorders leading to ocular surface dessication, ulceration, infection and visual impairment. Patients with primary and secondary SS have both aqueous-deficient and evaporative dry eye disease with significant alterations in their tear film, lid margin, cornea, and conjunctiva and a 10-fold increase in their dry eye symptoms relative to controls.

Regarding oral dryness pathogenesis, M. Julieta Gonzalez (Santiago, Chile) presented novel insights on mucin 5B (MUC5B) hyposulfation as a key factor for dryness symptoms in SS patients. She showed that Gal3-O-sulfotransferase activity was decreased in the acinar cells of minor salivary glands of SS patients without gene expression changes, suggesting that inflammation might be related to this decreased enzymatic activity. In cultured human submandibular gland cells, she also showed that mucins were capable of inducing the expression of pro-inflammatory cytokines via a TLR4-mediated mechanism. Two other presentations focused on potential pathogenic mechanisms that can lead to salivary gland dysfunction. The first one presented by Cortes Troncoso (Bethesda, USA) demonstrated the role of miR-142–3p in dysregulation of calcium signalling pathways in epithelial cells mediated by targeting the sarcoplasmic reticulum $Ca2^+$ ATPase (SERCA2b) and ryanodine

receptor type (2RyR2) genes. The authors demonstrated that miR-142–3p binds to the 3' untranslated region of SERCA2b and RyR2. Additionally, miR-142–3p-transfected cells showed a significant decrease in mRNA and protein levels, as well as a decrease in fluorescent intensity of SERCA2b, RyR2 and AC9 by in situ staining. The second one suggested an inflammatory-mediated impairment of the regenerative capacity of salivary gland stem cells (SGSCs) in pSS. Pringle S. (Groningen, The Netherlands) showed that proinflammatory cytokines (*i.e.* IFNα, TNF-α and IL-6) can modulate SGSC dynamics and potentially induce their senescence and exhaustion. The authors hypothesised new therapeutic interventions for hyposalivation in pSS such as generation of new SGSCs using iPS technology.

Getting novel insights into the pathogenesis of the disease is a crucial starting point for biomarker discovery and in turn for biologically-based diagnosis and disease stratification. *"Biomarker Discovery for Diagnosis and Stratification"* was the topic of the second plenary session. Over time, several clinical, serological, histopathological and molecular biomarkers have been implemented aiming at early diagnosis and identification of distinct clinical and prognostic phenotypes and concomitant comorbidities. In a comprehensive up-to-date overview, C. Mavragani (Athens, Greece) mentioned several traditional and novel biomarkers for SS, distinguishing those related to early disease, clinical heterogeneity, disease activity, outcomes (*e.g.* lymphoma and specific comorbidities such as atherosclerosis and cardiovascular disease), and therapeutic response. She mentioned typical SS autoantibodies, novel salivary proteins (*i.e.* salivary protein-1, carbonic anhydrase VI, cystatin S) and novel molecular biomarkers (*i.e.* calprotectin, IL-1). More specifically, she summarised the recent literature on novel peripheral biomarkers (including serum CXCL13 and type I IFN signature) and histology biomarkers (thymic stromal lymphopoietin, CCL21 and CXCL13) potentially related to disease activity (5–13). Among lymphoma predictors, she quoted the recent research on inflammasome activation, type I and II interferons, A20 protein mutations, defective immunosurveillance, B-cell activation and epigenetic alterations (*i.e.* methylating enzymes, miRNA). She concluded that validation of existing biomarkers and discovery of new ones are awaited in large multicentre collaborative studies. The identification of different subsets of SS patients using transcriptome profiling was the focus of the talk by F. Ng (Newcastle, UK). He first presented a comprehensive overview of the existing datasets which have been used to stratify SS patients based on the identification of unique molecular signatures using microarrays or RNASeq technology, either in whole blood or PBMCs, highlighting promises and pitfalls of this complex field of research in a multifactorial and highly heterogeneous disease such as SS. He then presented extremely interesting data obtained in the discovery cohort of the UKPSS registry and confirmed in independent validation cohorts (ASSESS and the Stavanger cohort) whereby SS patients were stratified into four main clinical subsets by cluster analysis of five key symptoms in SS, namely fatigue, dryness, pain, anxiety and depression; LSB (low symptom burden); HSG (High symptom burden); DDF (dryness dominant with fatigue); and PDF (Pain dominant with fatigue). Critically, these newly defined clinical subsets of SS were associated with distinct transcriptional profiles and were mostly stable over time, suggesting that they reflect largely separate disease entities underlined by different pathogenic mechanisms.

The possible use of novel biomarkers as indicators for therapeutic response has been shown by B. Fisher (Birmingham, UK) who reported the results of the CFZ533 trial (NCT02291029, Novartis). CFZ533 is a novel monoclonal antibody that potently and selectively blocks CD40, a co-stimulatory pathway receptor essential for germinal centre reactions and other immune mediated functions implicated in SS pathogenesis. In a recently completed randomised, double-blind, placebo-controlled, multi-centric trial, patients treated with CFZ533 displayed improvement in EULAR Sjögren's Syndrome Disease Activity Index (ESSDAI), as well as in other clinical indices, such as EULAR Sjögren's Syndrome Patient Reported Index (ESSPRI), and physician and patient Global Assessments. Additionally, he reported that CFZ533 may also mediate changes in soluble, cellular, and genomic biomarkers relevant to disease pathology and CD40 pathway inhibition, including reduction in the percentage of ICAM1+ B cells. At the soluble level, a decrease in the germinal centre-related serum biomarker, CXCL13, was reported in CFZ533-treated patients together with a trend for reduction in anti-Ro (but not anti-La) auto-antibodies, despite large variability in the response. At the genomic level, a decrease in the expression of pro-inflammatory genes in CFZ533-treated patients was also observed.

Another approach to precision medicine was presented by van J.A.G. Roon (Utrecht, The Nederlands). His research team used epigenetic cell counting, a promising novel tool, to reproducibly and easily quantify immune cells in the inflamed labial salivary gland of sicca patients. Relatively low amounts of tissue were needed. Considering the potential of this technique to include a huge number of cell-specific biomarkers, this technique may open up new standardised ways for salivary gland analysis with high relevance for patient classification, understanding of immunopathology and clinical trials. The feasibility of a large-scale use of this approach remains to be investigated in larger cohorts.

At the end of this session, G.E. Thorlacius (Stockholm, Sweden) presented some of the most recent findings from a Scandinavian research project called "DISSECT (*i.e.* dissecting disease mechanisms in three systemic inflammatory autoimmune diseases with an interferon signature, one of which was SS). Targeted sequencing identified 79 000 novel SNPs. In a case-control logistic regression analysis of the 920 SS cases and 1264 controls, the strongest associations were with the HLA locus and IRF5. Associations with the MAP kinase MAP2K2 on chromosome 19 and with variants in the GOT-1 – NKX2.3 locus were also detected, the latter having been associated previously with inflammatory bowel disease. Considering SS patient subtypes, targeted sequencing revealed three independent signals in HLA I and II that associate strongly with the presence of anti-SSA/SSB antibodies and correlate significantly with a distinct subset of clinical manifestations.

Third plenary session: Oral and ocular manifestations of SS

In this session we learned that SS oral and ocular manifestations include much more than dry eye and dry mouth. M. Brennan (Charlotte, USA) highlighted that around 12% of patients with pSS may present oral lesions of autoimmune origins (OLAIE) including lichen planus; aphthous stomatitis; pemphigoid; pemphigus; linear IgA disease; and chronic ulcerative stomatitis. Moreover, burning mouth may be detected in up to 45% of patients. These conditions should be taken into account in patients' treatment. He. recommended also

to routinely evaluate residual salivary function and to consider the use of sialogogues especially when stimulated flow is greater than unstimulated. Given the high rate of SS-related dental decay and loss of teeth, dental implants are an important therapeutic approach to consider. At one-year follow-up of a prospective clinical trial, M. Schiodt (Copenhagen, Denmark) reported that dental implants have a similar survival and success rate in patients with SS as compared to healthy controls.

Similarly, ocular manifestations of SS apparently included not just the dryness and ocular discomfort: non SS dry eye patients had even more subjective symptoms of ocular dryness in comparison to SS dry eye patients. By contrast, the vision related symptoms seem more common and more severe in patients with SS dry eye. In this regard, S. Koh (Osaka, Japan) demonstrated that instability of a disrupted tear film over the irregular ocular surface of the dry eye can impair quality of vision and result in fluctuating vision with blinks, glare, blurriness and eye fatigue. Therefore, diagnostic and therapeutic management of dry eye is essential in improving not only the dryness but also patients' quality of vision and of life. In addition, E. Akpek (Baltimore, USA) highlighted, vision-threatening ocular findingsin patients with SS including corneal ulcerations and melt. These patients with extraglandular ocular findings were 3.9 times more likely to have serious systemic involvement including neuropathy, interstitial nephritis, and vasculitis. Finally, men with primary SS have a higher frequency of serious ocular and systemic manifestations. Although pSS is typically considered a disease of middle-aged women, it may be underdiagnosed and consequentially can be more severe in men. Physicians should have a lower threshold to test for SS in men with dry eye.

D. Hammenfors (Bergen, Norway) presented the results of a multicentre study of juvenile SS. The study was conducted in Europe (Norway, Spain, The Netherlands), USA (Florida) and Brazil (Rio de Janeiro, Sao Paulo, Vitoria) and had an enrolment of 67 patients (mean age at diagnosis 12.1 (4–18) yrs). Interestingly, despite regional differences, salivary gland enlargement and abnormalities on salivary gland ultrasonography (SGUS) were common in these patients (41/67). Patients with SGUS abnormalities presented a higher frequency of non-organ specific autoantibodies. The ESSPRI for dryness correlated with disease duration. Similar to juvenile SS patients, adult SS patients with subclinical SGUS abnormalities but without overt salivary gland enlargement, presented a higher prevalence of extraglandular manifestations and auto-antibodies as compared with pSS with normal SGUS. Regarding histology parameters (*i.e.* focus score, number of foci, number of germinal centre (GC)-like structures), again pSS patients with subclinical ultrasonographic abnormalities presented a greater complexity in the infiltration of their minor salivary glands that was comparable to that observed in patients with clinically detectable salivary gland swelling. Finally, the presence of GC-like structures was significantly associated with the measure of the biggest hypo/anechoic area observed with ultrasonography.

Fourth plenary session: SS aetiopathogenesis

SS pathophysiology includes concomitant dysregulation of innate and adaptive immune responses involving both cell-mediated and humoral disease pathways that are incompletely understood. K. Sivils (Oklahoma City, USA) opened this session highlighting the potential

usefulness of genetics in defining SS subsets. She presented the results of the genome-wide association and large-scale replication studies performed by the Sjögren's Genetics Network (SGENE), a collaborative research effort comprised of multiple international sites. In addition to strong association within the HLA region at 6p21, the group has also established significant associations with several genes involved in both innate and adaptive immunity including: IRF5-TNPO3, STAT4, IL12A, FAM167A-BLK, DDX6-CXCR5, and TNIP1. Suggestive associations were also observed with 29 regions including TNFAIP3, PTTG1, PRDM1, DGKQ, FCGR2A, IRAK1BP1, ITSN2, and PHIP amongst others. Regarding the usefulness of genetics in SS phenotyping, the association between germline and somatic abnormalities of TNFAIP3 and transformation from autoimmunity to lymphoma was highlighted. In addition, Sivils reported recent results establishing an association for the SS risk allele, rs10774671, with reduced OAS1 enzymatic activity and ability to clear viral infections, as well as reduced responsiveness to IFN treatment. These results support a potential role for defective viral clearance due to altered IFN response as a genetic pathophysiological basis of SS.

M. Manoussakis (Athens, Greece) discussed the role of innate autoimmunity in SS pathogenesis focusing on the activation of inflammasomes in SS. Inflammasomes are multiprotein oligomers that promote the maturation and secretion of pro-inflammatory cytokines, Interleukin 1β (IL-1β) and Interleukin 18 (IL-18). In his updated and comprehensive review, Manoussakis showed that patients with severe SS manifest systemic activation of inflammasomes in the peripheral blood (PBMC, monocytes and serum), in the salivary gland-infiltrating macrophages (induction of pyroptosis) and in the salivary ductal epithelia. He also suggested that inflammasome activation in SS patients may be caused by aberrant widespread accumulation of inflammagenic DNA present due to deficient degradation mechanisms. Several lines of evidence also seem to indicate that inflammasomes may participate in the pathogenesis of adverse clinical outcomes, such as lymphoma development, rendering inflammasomes potential novel biomarkers for the disorder and for its more severe subsets.

Finally, S. De Vita (Udine, Italy) discussed the pathogenesis of lymphoma in SS and its relationship with SS disease activity. He extensively analysed whether a high ESSDAI score might represent a risk factor for lymphoma development. Based on a review of the literature (14–17) and on a prospective evaluation of a cohort of 255 pSS patients from Udine, Italy, including 30 pSS patients with B-cell lymphoma, parotid swelling and mixed cryoglobulinaemia were shown to be sensitive early and late predictors of lymphoma in pSS, reflecting the degree of glandular inflammation and lymphoproliferation. By contrast, ESSDAI was not an adequate predictor, being low at baseline in about one third of patients developing lymphoma, and not being able to adequately mirror glandular disease activity in SS.

M. Voulgarelis (Athens, Greece) analysed risk factors and pathogenetic mechanisms of B cell lymphomagenesis in pSS. More specifically, he discussed the dysfunction of critical checkpoints that could drive autoimmune B cells towards malignant transformation (*i.e.* increased production of B cell growth factors, such as BAFF; formation of germinal centre (GC)-like structures and/or marginal zone (MZ) equivalents; large amounts of IgG

complexed to (self-) antigens produced in the salivary gland and over-activation of the NFκB pathway). He highlighted how autoimmunity and lymphomagenesis represent a continuum of the same antigen-driven process whereby continuous stimulation of RF-producing B cells by immune-complexes engaging TLR9 and BCR on B cells infiltrating the SS salivary glands promotes clonal selection, clonal escape and malignant transformation via genetic instability. In this regard, sustained activation of NFκB can also be favoured by genetic susceptibility as indicated by the BAFFHis159Tyr polymorphism and somatic genetic variations of TNFAIP3, a key negative regulator of NFκB activation, which can be acquired within the inflamed salivary gland microenvironment. A better understanding of the molecular mechanisms underlying the step-by-step process leading to B cell lymphoma in pSS would lead to the identification of early predictors and key therapeutic targets for lymphoma prevention at the early stage of poly- or oligo-clonal B cell activation.

Concurrent session C: Systemic manifestations, including lymphoma

This session included invited and selected oral presentations ranging from basic discoveries to clinical management. V. Valim (Vitoria, Brazil) gave a comprehensive review of the cardiovascular manifestations commonly associated with pSS with presentation of clinical cases of pericarditis, valvular disease and myocarditis in pSS patients. The importance of state-of-the-art diagnostic tools such as cardiac MRI but also pulse-wave velocity and arterial tonometry was highlighted, again stressing the importance of a multidisciplinary approach in the diverse manifestations of pSS. She concluded with a focus on subclinical atherosclerosis, its underlying mechanisms such as inflammation-dependent endothelial dysfunction and the recent findings of new soluble biomarkers associated with atherosclerosis in pSS including calprotectin, tumour necrosis factor receptor 2, hepatocyte growth factor and MCP-1. J. Mofors (Stockholm, Sweden), reported the results of a case-control study of the rate of infections preceding the diagnosis of pSS by at least one year in almost 1,000 Scandinavian pSS patients and 9,000 controls. She reported that preceding infections had a prevalence almost double in pSS cases compared to controls and were more strongly associated with the seropositive (*i.e.* anti-Ro/SSA and anti-La/SSB) subset of pSS. Interestingly, respiratory tract and skin infections but not gastrointestinal infections were associated with pSS. Overall, these data reinforce the current views that the onset of autoimmunity and clinical manifestations in pSS are favoured by external triggers of immunity which act on a genetically determined background of disease susceptibility. E. Corsiero (London, UK) then presented data obtained from single-cell VH and VL immunoglobulin gene analyses of different B cell subsets (*i.e.* neoplastic B cells and plasmablasts) isolated from parotid MALT-lymphoma in pSS. She confirmed that unswitched neoplastic IgM-memory B cells display evidence of intraclonal diversification in keeping with their post-germinal centre phenotype and demonstrated that these cells can differentiate into IgM plasmablasts and then diversify further following rounds of somatic hypermutation. Conversely, class-switched IgA and IgG plasmablasts were not clonally related to neoplastic IgM-memory B cells suggesting that Ig hypermutation, class switching and B cell differentiation become uncoupled during lymphomagenesis in pSS. The recognition that the prevalent neoplastic B cell and plasmablast population utilise VH1–69/D3–22/JH4 segments preferentially, as do rheumatoid-factor producing memory B cells,

highlights the close association between autoimmunity and lymphomagenesis in pSS. Remaining within the topic of lymphoma, E.K. Kapsogeorgou (Athens, Greece), reported novel findings which indicate that low levels of the microRNA miR200b-5p in the salivary glands are an independent predictor of lymphoma development. Specifically, she and her colleagues observed a 50 to 80% reduction in the levels of miR200b-5p in minor salivary gland biopsies of pSS prior to the onset of lymphoma or with concomitant lymphoma compared to pSS with no future lymphoma development. Multivariate analysis confirmed miR200b-5p as an independent predictor of lymphoma development together with the known associated risk factors. Overall, these findings are of significant interest both in terms of pathogenesis given the critical role of the miR-200 family in the regulation of oncogenes and, if confirmed in larger longitudinal studies, as putative early predictors of subsequent evolutoin to lymphoma. The final talk of this session was from D. Cornec (Brest, France) who presented a very detailed report on the hospitalisation rates among patients with pSS in a retrospective population-based study spanning over 20 years. His analysis showed that patients with pSS experienced higher rates of hospitalisation than the general population. Of interest, endocrine, nutritional, metabolic diseases and as predicted immunity and musculoskeletal disorders were the main reasons for the observed increase in hospitalisation while cardiovascular complications were a cause for increased hospitalisation only in pSS patients aged ≥75 years.

Concurrent session D: Glandular outcome measures

K. Nichols (Birmingham, USA) opened the session focusing on the unmet need for validated biomarkers for dry eye in clinical trials. Even though the pathogenesis of dry eye disease is not fully understood, it is widely accepted that immune-mediated inflammation has a key role in its development and progression. Therefore, a great interest in inflammatory biomarkers has recently arisen. More specifically, among them mucins and several cytokines (IL-1, IL-6 and TNF-alpha) seem to be useful to monitor therapeutic response. Tear osmolarity (cutoff value 308 mOsm/L) has been also proposed as an objective biomarker for use in clinical trials. Finally, besides ocular surface staining and methods assessing tear film stability (break up time) other proposed biomarkers are represented by patient-reported outcomes, evaluation of the meibomian glands and alterations in the lipid layer thickness.

Saliva and salivary glands may also represent potential outcome measures as A. Vissink, E. Haacke and Mossel (Groningen, The Netherlands) have shown. Sialometry, sialochemistry and salivary proteomics can differentiate patients with primary and secondary SS from healthy controls and patients with systemic lupus erythematosus. Moreover, SS patients with ectopic GC-like structures are characterised by a distinct salivary proteome. Minor salivary gland biopsy and parotid biopsy provide not only important diagnostic/ prognostic biomarkers for SS, but also therapeutic biomarkers. Baseline number of $CD20^{+}$B-cells/mm^2 represented a prognostic biomarker for efficacy of rituximab. In turn, rituximab has been described as able to reduce the number of B-cells in parotid gland parenchyma, to ameliorate several other parameters (*i.e.* focus score, size of infiltrates, lympho-epithelial lesions and GC) and to promote the redifferentation of lymphoepithelial duct lesions to normal striated ducts. Similarly, abatacept therapy was associated with a decline in the number of GC in parotid gland tissue. With respect to salivary gland ultrasonography, a good correlation

between ultrasonography, histology and sialometry has been reported. Recent clinical trials have also provided preliminary evidence that the salivary gland ultrasonography score may change after biological treatment.

Fifth plenary session: Outcome measures for clinical trials

The first part of this session was a debate on the pro and cons of the existing ESSDAI and ESSPRI indices. X. Mariette (Paris, France) provided a review of the state of the art in the use of the ESSDAI and ESSPRI in the most recent clinical trials in SS. In open label studies ESSDAI and ESSPRI have been found sensitive to change. Similar results were obtained in the phase IIa trial with CFZ533 monoclonal antibodies against CD 40. The vast majority of the other RCTs used ESSDAI and ESSPRI as primary end-points, but solely as secondary endpoints. Moreover, for ethical reasons in all the trials, more active patients that might have been more prone to improve were excluded. In TEARS and TRACTISS, ESSDAI was calculated retrospectively. ESSDAI was prospectively assessed in the baminercept trial but still as a secondary endpoint. To improve ESSDAI and ESSPRI a number of suggestions were provided. First, the need for ameliorating the educational training of physicians when using the ESSDAI in trials to avoid scoring damage. Second, the importance of determining the ESSDAI domains that are the more prone to change. Third, the possibility of elaborating composite indices. From this perspective, the responder index by Cornec *et al.* derived from the TEAR study was mentioned. End-points of the Necessity project are 1) to develop a new composite responder index (CRISS) that incorporates systemic disease activity, objective measures of dryness, and possibly PROs, and 2) redefining trial entry criteria in order to include patient subsets having the most chance to improve with treatment.

D. Wallace (Los Angeles, USA) made a critical reappraisal of the requirements to bring a new SS drug to the market. Before focusing on disease activity and potential limitations of the existing indices, he highlighted some of the major flaws of the ACR/EULAR 2016 criteria for patients' enrolment. More specifically, he pointed out that less than 5% of international SS patients have had a biopsy; outside of a few centres and commented on misinterpretation of the biopsy itself, concluding that patients who were anti-SSA negative could never fulfill criteria and be enrolled. Regarding the ESSDAI, Wallace emphasised that ESSDAI weighting was based on the lupus (SLE) SLEDAI, which is now obsolete and is being replaced by a new composite index, since 20 SLE drugs in Phase II/ III trials since 2005 have failed to meet their primary endpoint using the SLEDAI as an outcome measure. He also cited some SS trials to point out potential limitations of the ESSDAI. In the hydroxychloroquine (HCQ) trial for example, HCQ at 48 weeks decreased inflammation (ESR, IgM) which suggested some efficacy, but neither ESSPRI nor ESSDAI demonstrated it, indicating that mild to moderate disease might not be picked up by the ESSDAI. In the belimumab trial (18) and in the rituximab trial (19) only a limited number of the domains included in the ESSDAI (*i.e.* biological, haematological, constitutional, articular and glandular) showed some potential for substantial change from baseline and appeared to be under-represented in SS patients, making it difficult to recruit patients. In fact, Wallace showed that in US 90% of SS patients have "benign glandular manifestations" (dry eyes or mouth, arthralgia, myalgia, fatigue, vague cognitive changes) and solely 10% "extraglandular" features (vasculitis, lymphoma, cytopenias, interstitial lung) concluding

that these subsets should be studied separately. Regarding the ESSPRI, possible limitations relate to the fact that it is highly subjective, did not received cross cultural validation and does not take into account medications such as steroids, and other co-morbidities including fibromyalgia. Wallace concluded that we may need a ACR 20/50/70 for SS derived from completed controlled trials focusing on inflammatory biomarkers and a PROMIS derived patient-reported outcome (20) to assess the efficacy of a candidate drug. Regarding the outcome measures for clinical trials in SS, N. Nikolov (Rockville, USA) presented the FDA perspective on the expectations of how an ideal clinical outcome measure should be developed, and discussed some of the properties important for ascertaining the validity of the outcome as well as some of the considerations on the interpretation of a particular instrument. He discussed how ESSDAI and ESSPRI content validity has been sufficiently established through a rigorous consensus process and additional consultation with an expert steering committee. He added that evidence presented in the literature suggested that the ESSDAI was a reliable and valid measure that was able to detect change over time. However, the threshold for meaningful within-patient change on both the ESSDAI and ESSPRI have been proposed based on anchor-based methods. The interpretability of changes on the total score remained, however, to be characterised prospectively in a clinical trial setting. Finally, since ESSDAI and ESSPRI are complementary but assess different concepts, he concluded that the determination of whether the ESSDAI and ESSPRI are fit-for-purpose and yield meaningful results needs to be evaluated within each specific context of use, considering the evidence presented for a specific drug development program.

At the end of the session, R. Weiss (Rockville, USA) discussed the Industry perspective on current outcome measures and development in SS. It was recognised that current primary outcome measure (ESSDAI) is good in expert hands, but might not be translated successfully to large multinational phase 3 studies, reinforcing the concept of the necessity of training to score the ESSDAI properly. Most importantly, it was pointed out the need for a better definition of SS population candidates for systemic therapy in order not to miss important populations and to prevent damage accrual even at the glandular level.

Six plenary session: Novel therapeutic targets

The session was kicked off by M. Bombardieri (London, UK) who focused his lecture on the key cellular and molecular mechanisms underlying the formation and function of ectopic germinal centres in the salivary glands of pSS patients and their exploitation as potential targets with novel therapeutics. The classical view of a positive feedback loop between lymphotoxin-β and lymphoid chemokines CXCL13, CCL19 and CCL21 was briefly discussed before highlighting the emerging role of cytokines as novel positive (*i.e.* IL-17, IL-21, IL-22) and negative (IL-27) regulators of the lymphoid neogenesis process in the salivary glands. The importance of specialised CD4 Th cell subsets in the maintenance and resolution of ectopic germinal centres was also discussed, with particular focus on the dichotomic role of T follicular helper and T follicular regulatory cells. Next, the importance of ectopic lymphoid structures in the response and resistance to B cell depletion with rituximab in pSS was discussed, before closing with novel therapeutics currently tested in ongoing clinical trials in pSS targeting key costimulatory pathways critically implicated in T/B cell interactions, such as the CD40/CD40L and the ICOS/ ICOSL pathways.

The session continued exploring novel therapeutic targets in SS-related dry eye. Lack of inclusion of the vision-related symptoms of dry eye in the ESSPRI and lack of inclusion of serious extraglandular ocular findings including corneal melting or ulceration, scleritis, and uveitis in ESSDAI tools were criticised. S.C. Pflugfelder (Houston, USA) gave a state-of-the-art lecture on the immune pathways underlying ocular surface inflammation in pSS patients and their relevance as targets for therapeutic intervention. He introduced the topic with a clear explanation of the “dry eye cycle”, highlighting the interactions between cells of the innate and the adaptive immune system with resident cells which exert a key role in local homeostasis and are lost during pSS inflammation, such as goblet cells and the corneal epithelial barrier. The role of important innate immunity pathways which are directly activated by the increased osmolarity such as the JNK and the NFκB signalling cascades was also discussed. Accordingly, animal models with gene targeting of JNK2 or NFκB display a less severe ocular dryness phenotype. Finally, the talk concluded with the importance of T cell-derived cytokines, such as IFNγ in the loss of globlet cells typically seen in pSS patients. Of note, high levels of IFNγ are associated with clinically significant dry eye disease. While administration of IFNγ directly promotes the loss of goblet cells, neutralisation of IFNγ almost completely suppresses goblet cell loss.

The final two selected abstract presentations were from the Birmingham (UK) group and focused on preclinical therapeutic intervention in an inducible model of sialadenitis and germinal centres triggered by local viral infection (also discussed elsewhere). J. Campos presented data on the therapeutic effects of PEPITEM, a B cell-derived peptide which is secreted in response to adiponectin and regulates T-cell trafficking during inflammation via modulation of sphingosine 1 phosphate activity. Animals treated with PEPITEM displayed reduced levels of $CD4^+$ and $CD8^+$ cell in the salivary glands and decreased mRNA transcripts for lymphotoxin beta, IL-7 and lymphoid chemokines CCL19 and CXCL13. Human studies will be required to address the importance of these pathways in modulating T cell trafficking in patients with pSS. Finally, S. Najar raised stromal cells in the spotlight by presenting extensive animal data in support of a critical role for resident stromal cells in orchestrating the inflammatory responses and the organisation of the infiltrating immune cells in the salivary glands. In elegant studies using KO mice for different cytokines and receptors, she demonstrated that the acquisition of a lymphoid phenotype by resident stromal cells requires a multistep process which is initially dependent upon IL-4Rα engagement by IL-13; this is followed by an expansion phase regulated by IL-22 signalling which in turn is followed by a maintenance phase which requires LTβR and the cross-talk with infiltrating lymphocytes to maintain highly organised lymphoid structures in the inflamed salivary glands. The reproducibility of such findings in the human counterpart remains to be fully demonstrated but could pave the way for the exploitation of the above stromal-cell related pathways for therapeutic intervention in pSS patients.

Seventh plenary session: Clinical trial design and emerging treatments for SS

S. Bowman (Birmingham, UK) opened the session summarising the experience gained with Rituximab in open and randomised clinical trials. He specifically focused on the lessons

learned over time from the use of rituximab. The first lesson was the awareness of the possibility of conducting randomised clinical trials in SS. The second lesson concerned the clinical outcomes selected in the trials and the discordant results obtained suggesting the unmet need of better defining outcome measures. The third lesson came from the ultrasonographic assessment of salivary gland response to rituximab. Both in the TEARS study and in the TRAC-TISS study, ultrasonography showed an improvement of salivary gland echostructure in patients with pSS receiving rituximab. In addition, patients with higher sonographic scores at baseline were more prone to be rituximab non-responders compared to those with lower sonographic scores. Lesson four was the role of the biopsy of the minor salivary glands as an endpoint in clinical trials. Biopsy seemed also useful as a therapeutic biomarker since patients with higher focus scores were more refractory to rituximab. Finally, the experience gained with rituximab gave us important clues on how to design novel clinical trials, highlighting the importance of recruitment eligibility, outcome assessment, composite measures, patient stratification and combination therapy.

H. Bootsma (Groningen, The Netherlands) summarised the status of the ongoing clinical trials in SS. She mentioned, in particular the following strategies: the blockade of the IFN-BAFF-B lymphocyte axis (*i.e.* hydroxychloroquine/leflunomide phase II; belimumab/rituximab phase II, VAY736 early phase II, tocilizumab phase II/III trial); the inhibition of the formation of germinal centres (*i.e.* anti-IgG2k ICOS ligand blocker and baminercept phase II trial); the inhibition of B and T lymphocytes; the inhibition of costimulation (abatacept, lulizumab, B7RP-1 and human iG1 anti CD40 trial). The leit motif of the current trials is represented by the attempt of improving treatment of SS through a tissue based approach, combination therapy, targeted therapy and precision medicine.

Among novel therapeutic strategies, two trials were specifically presented. A.S. Papas (Boston, USA) presented data on a phase IIa double-blind, placebo-controlled randomised trial using a novel anti-CD40 monoclonal antibody CFZ533. In this proof of concept study active SS patients were randomised to 10 mg/kg i.v. CFZ533 or placebo over 12 weeks in Period 1. Four additional doses 10 mg/kg i.v. CFZ533, respectively, were administered in an open label extension for 12 weeks. Thirty-two patients were enrolled, 21 received 10 mg/kg i.v. CFZ533 and 11 placebo. Overall, CFZ533 was safe and well tolerated, and the majority of AEs were mild or moderate. Improvements in ESSPRI, ESSDAI, Multi-dimensional Fatigue Inventory, Physicians's VAS, and Patient's Global Assessment were observed.

J. He (Beijing, china) presented data on a low-dose IL-2 randomised, double-blinded, placebo-controlled clinical trial performed in 60 SS patients randomised at 1:1 ratio to receive either IL-2 (n=30) or placebo group (n=30) and followed up for 24 weeks. The authors reported that that low-dose rhIL-2 administration was associated with selective expansion of Treg and Breg cells and decreasing Th17 and Tfh cells. At week 12, resolution of clinical activity present at baseline was observed in multiple manifestations in patients with IL-2 treatment, including fatigue (12/22), leukopenia (18/18) and arthritis (5/8). Laboratory parameters showed reductions of anti-SSA and anti-SSB titres as well as reduction in IgG levels and ESR.

Eighth plenary session: Novel insights

In this session novel insights into lachrymal and salivary dysfunction were presented indicating novel potential targets for future intervention in SS.

Edman (Los Angeles, USA) demonstrated in human and animal models of SS an imbalance between Cathepsin S (CTSS) and its inhibitor, suggesting that reduced levels of Cystatin C may contribute to increased CTSS activity. This in turn may contribute to the degradation of other tear proteins including cystatin C itself, lactoferrin and possibly salivary IgA.

S.L.M. Blokland (Utrecht, The Netherlands) indicated mTOR inhibition as a novel therapeutic strategy. The presented results showed that SS patients display decreased mTORC1 activity in peripheral blood B cells correlating with B cell hyperactivity and increased mTORC1 activity in salivary gland T and B cells. Importantly, stimulated T and B cell activity associated with increased mTOR activity was however robustly inhibited by rapamycin *in vitro*, thus suggesting possible new treatment approaches.

S.-I. Jang (Bethesda, USA) described the role of the EBV microRNA ebv-miR-BART13–3p as a potential link between salivary hypofunction and IFN activation. Ebv-microRNA ebv-miR-BART13–3p was shown as significantly elevated in the salivary glands of SS patients and able to target both the stromal interacting molecule, STIM1, a primary regulator of the store-operated $Ca2^{+}$ entry (SOCE) pathway and the water channel AQP5, both critical components of saliva formation. Moreover, ebv-miR-BART13–3p appeared able to induce IFN-β expression in primary salivary epithelial cell by directly binding to RIG-I and through canonical miRNA functions by associating with AGO2.

Finally, I.J. Saldanha (Baltimore, USA) highlighted the importance of identifying what matters to patients with SS related dry eye all over the world. This process will feed into core outcome set development, a much-needed step to promote consistency in outcome measurement and reporting in research for SS.

Ninth plenary session: International collaboration in SS and late-breaking abstracts

This session provided a broad overview on the ongoing international research collaborative projects.

R. Seror (Paris, France) described “NECESSITY”, a project of the innovative medicines initiative for the development of sensitive and validated clinical endpoints in pSS. She explained the three objectives of the project: a) to develop and assess sensitive clinical end-points for use in clinical trials to evaluate response to drugs; b) to identify and evaluate discriminative biomarkers for SS stratification; c) to set-up and perform a clinical trial to validate the newly defined SS endpoints and the identified biomarkers.

A.G. Tzioufas (Athens, Greece) presented “HARMONICSS” the ongoing research project that received funding from the European’s Union Horizon 2020 Research and Innovation Programme and is aimed at creating an International Network and Alliance of partners and

cohorts, entrusted with the mission of addressing the unmet needs in primary SS. Starting from a conceptual step-wise categorisation of SS clinical, histologic, and molecular stratification, the vision of HARMONICSS was presented highlighting the key point of data harmonisation as a tool to eliminate the discrepancies between centres in terms of ontology and content, and create a platform with open standards and tools, designed to enable secure storage, governance, analytics, access control and controlled sharing of information at multiple levels along with methods to make results of analyses and outcomes comparable across centres and sustainable through Rheumatology scientific associations. Two final late-breaking abstracts closed this session. The first was presented by I.L.A. Bodewes (Rotterdam, The Netherlands). She and her research team explored whether stratification of patients in the JOQUER study [hydroxychloroquine (HCQ) versus placebo for pSS] based upon their expression of IFN signature genes may result in an improvement on ESSDAI and ESSPRI with HCQ in the IFN positive patient group compared to the IFN negative patients and the placebo group. The results demonstrated that the mentioned stratification did not reveal an improvement of ESSPRI or ESSDAI scores with HCQ in either subgroup. However, treatment with HCQ for 24 weeks decreased systemic IFN activation and reduced expression of IFN-inducible RNA and DNA sensors in the cytosol showing that HCQ affected the known pathways in the pSS patients. These data suggested the involvement of other pathways than the IFN pathway in the induction of dryness, pain and fatigue in pSS.

The second was presented by B.M. Warner (Baltimore, USA). He described a large cohort of 16 patients treated with immune checkpoint inhibitors (ICI; *e.g.* pembrolizumab, nivolumab, ipilimumab) for neoplastic disease who developed salivary gland hypofunction. Results from multiple avenues of analysis suggested that ICIs may elicit profound negative effects on salivary secretion potentially breaking immune tolerance locally leading to activation of cytotoxic T cells, cytolysis, and cytokine secretion, in a non-classic autoimmune fashion, at least like the one observed in SS.

Conclusions

In brief, this exciting meeting offered the possibility to share a considerable amount of novel data both in basic and clinical science including therapeutic aspects proposing novel approaches on the future research in SS.

References

1. BRITO-ZERON P, BALDINI C, BOOTSMA H et al.: Sjögren syndrome. Nat Rev Dis Primers 2016; 2: 16047. [PubMed: 27383445]
2. BARONE F, COLAFRANCESCO S: Sjögren's syndrome: from pathogenesis to novel therapeutic targets. Clin Exp Rheumatol 2016; 34 (Suppl. 98): S58–62.
3. SHIBOSKI CH, SHIBOSKI SC, SEROR R et al.: 2016 American College of Rheumatology/ European League Against Rheumatism classification criteria for primary Sjögren's syndrome A consensus and data-driven methodology involving three international patient cohorts. Ann Rheum Dis 2017; 76: 9–16. [PubMed: 27789466]
4. SHIBOSKI CH, BAER AN, SHIBOSKI SC et al.: Natural history and Predictors of Progression to Sjögren's Syndrome Among Participants of the SICCA registry. Arthritis Care Res (Hoboken) 2018; 70: 284–94. [PubMed: 28437595]

5. MINGUENEAU M, BOUDAOUD S, HASKETT S et al.: Cytometry by time-of-flight immunophenotyping identifies a blood Sjögren's signature correlating with disease activity and glandular inflammation. J Allergy Clin Immunol 2016; 137: 1809–21 e12. [PubMed: 27045581]
6. FONSECA VR, ROMAO VC, FONSECA JE, AGUA-DOCE A, GRACA L: Reply. Arthritis Rheumatol 2018.
7. TOBON GJ, RENAUDINEAU Y, HILLION S et al.: The Fms-like tyrosine kinase 3 ligand, a mediator of B cell survival, is also a marker of lymphoma in primary Sjögren's syndrome. Arthritis Rheum 2010; 62: 3447–56. [PubMed: 20556820]
8. BRKIC Z, MARIA NI, VAN HELDEN-MEEUWSEN CG et al.: Prevalence of interferon type I signature in CD14 monocytes of patients with Sjögren's syndrome and association with disease activity and BAFF gene expression. Ann Rheum Dis 2013; 72: 728–35. [PubMed: 22736090]
9. NOCTURNE G, SEROR R, FOGEL O et al.: CXCL13 and CCL11 Serum Levels and Lymphoma and Disease Activity in Primary Sjögren's Syndrome. Arthritis Rheumatol 2015; 67: 3226–33. [PubMed: 26359802]
10. MARGIOTTA DP, NAVARINI L, VADACCA M et al.: The IL33/ST2 axis in Sjögren syndrome in relation to disease activity. Eur Rev Med Pharmacol Sci 2016; 20: 1295–9. [PubMed: 27097949]
11. LEE KE, KANG JH, YIM YR et al.: Predictive significance of CCL21 and CXCL13 levels in the minor salivary glands of patients with Sjögren's syndrome. Clin Exp Rheumatol 2017; 35: 234–40. [PubMed: 27782867]
12. AKIYAMA M, SASAKI T, KANEKO Y et al.: Serum soluble interleukin-2 receptor is a useful biomarker for disease activity but not for differential diagnosis in IgG4-related disease and primary Sjögren's syndrome adults from a defined population. Clin Exp Rheumatol 2018; 36 (Suppl. 112) S157–64.
13. NISHIKAWA A, SUZUKI K, KASSAI Y et al.: Identification of definitive serum biomarkers associated with disease activity in primary Sjögren's syndrome. Arthritis Res Ther 2016; 18: 106. [PubMed: 27180164]
14. QUARTUCCIO L, ISOLA M, BALDINI C et al.: Biomarkers of lymphoma in Sjögren's syndrome and evaluation of the lymphoma risk in prelymphomatous conditions: results of a multicenter study. J Autoimmun 2014; 51: 75–80. [PubMed: 24231556]
15. PAPAGEORGIOU A, MAVRAGANI CP, NEZOS A et al.: A BAFF receptor His159Tyr mutation in Sjögren's syndrome-related lymphoproliferation. Arthritis Rheumatol 2015; 67: 2732–41. [PubMed: 26097183]
16. NOCTURNE G, VIRONE A, NG WF et al.: Rheumatoid factor and disease activity are independent predictors of lymphoma in primary Sjögren's syndrome. Arthritis Rheumatol 2016; 68: 977–85. [PubMed: 26606524]
17. BRITO-ZERON P, KOSTOV B, FRAILE G et al.: Characterization and risk estimate of cancer in patients with primary Sjögren syndrome. J Hematol Oncol 2017; 10: 90. [PubMed: 28416003]
18. MARIETTE X, SEROR R, QUARTUCCIO L et al.: Efficacy and safety of belimumab in primary Sjögren's syndrome: results of the BELISS open-label phase II study. Ann Rheum Dis 2015; 74: 526–31. [PubMed: 24347569]
19. MEINERS PM, ARENDS S, BROUWER E, SPIJKERVET FK, VISSINK A, BOOTSMA H: Responsiveness of disease activity indices ESSPRI and ESSDAI in patients with primary Sjögren's syndrome treated with rituximab. Ann Rheum Dis 2012; 71: 1297–302. [PubMed: 22258489]
20. KASTURI S, SZYMONIFKA J, BURKET JC et al.: Feasibility, validity, and reliability of the 10-item Patient Reported Outcomes Measurement Information System Global Health Short Form in outpatients with systemic lupus erythematosus. J Rheumatol 2018; 45: 397–404. [PubMed: 29419473]