Primary Sjögren’s syndrome (pSS) is a complex and systemic autoimmune disease, displaying specific features amongst the other autoimmune disorders. First, pSS as opposed to other autoimmune diseases such as systemic lupus erythematosus (SLE) or rheumatoid arthritis (RA), is not characterised by a relapsing-remitting course but follows a rather slowly, stable and progressive course, leading to cumulative tissue damage and production of mild symptoms that may be present many years before patients seek medical advice (1). As a consequence, the majority of pSS patients at diagnosis, have almost complete clinical phenotype and immunologic profile, remaining with no further progression or organ involvement during follow-up. Second, pSS is the only autoimmune disease that seems to combine organ specific and systemic features at the same time. Almost all patients experience oral and eyes dryness along with immunopathologic findings, strongly supporting that the autoimmune response begins within the salivary and lachrymal glands. Interestingly, even though the initial immune response seems to be confined to the periductal lining epithelium that plays an active role in initiation, maintenance and perpetuation of the inflammatory response, in some patients the periepithelial lesions expand to other tissues beyond the exocrine glands (2). In addition, pSS patients with B cell symptoms and the systemic form of the disease, are considered to develop immune complex mediated manifestations accompanied by increased morbidity and mortality. Therefore, it is obvious that in pSS, salivary and lachrymal tissue represent the initial site of autoimmune response that has the capacity to orchestrate an extended response, involving also other organs and support B cell expansion mediating systemic manifestations. Thus, the composition and dynamic nature of the periductal lymphocytic infiltrate within the minor salivary glands, seems to define the wide clinical spectrum of pSS that begins from a mild and benign exocrinopathy (T cell predominant infiltrate) and ends to systemic complications and lymphoma (B cell predominant infiltrate) (3). Third, pSS carries the highest risk for B cell derived lymphomas among other autoimmune disease, pointing out the dynamic continuum of the B cell component that follows a longstanding and multistep transition process from non-specific B cell polyclonality to malignant B cell transformation (4).

In the past 15 years, several new biologic treatments including TNFa inhibitors, B cell depletion agents and IL-1 blockade, have been administered to improve sicca symptoms in pSS and modify disease progression, without much of success (5). Those attempts were mainly based on the experience from other autoimmune diseases rather than on a mechanistically driven rationale. The reasons for this limited efficacy have been extensively discussed in the literature (6). On the one hand, the short duration of clinical trials along with the inefficiency of the current metric tools reflecting overall disease activity such as ESSPRI or ESSDAI to capture changes in significant parameters of pSS, especially tissue/organ specific manifestations. On the other hand, the unique features of the disease mentioned previously were not taken into consideration in study design including the chronic and slow nature of pSS, the diversity of endotypes and phenotypes and the yet unrevealed molecular and cellular mechanisms that govern the effector components of the
peripheral inflammatory infiltrate such as B and T cells. In the era of biotechnologic revolution, the necessity to discover novel biomarkers for pSS and define clinically useful endpoints, remains a great challenge for both clinicians and researchers.

Lately, newly proposed biomarkers have drawn much of attention within the scientific community (7). Ectopic germinal centre (eGC)-like structures have been implicated in the pathogenesis of pSS and are considered immunologically active, representing also a possible site of lymphomagenesis, since they have been proposed as an independent predictor of lymphoma (8). Up to 25% of pSS patients have been reported to enclose eGC within the minor salivary gland biopsy at the time of diagnosis, with intact functional capacity as suggested by expression of activation induced cytidine deaminase (AID) that mediates class switch and somatic hypermutation (9, 10). The eGC-like structures in pSS are thought to reflect high degree of lymphoid organisation as a result of enlargement of the inflammatory foci, mediated by specific lymphoepoietic chemokines such as CXCL13, CCL21 and CXCL12. Interestingly, CXCL13 and CCL21 expression is increased at the protein and mRNA level within the eGC of minor salivary glands of pSS patients as opposed to CXCL12 which is only expressed by infiltrated epithelia and marginal zone (MZ) malignant B cells (11). In addition, serum levels of CXCL13 have been found increased in pSS patients with lymphoma and correlate with disease activity (12). Thus, CXCL13 appears an attractive biomarker at the serological and molecular level to monitor both disease progression and lymphoma development. Studies in minor salivary glands (MSG) of pSS patients, regarding the microRNA (miRNA) family 200 with major regulatory properties upon epithelial to mesenchymal transition, revealed a specific member miRNA-A200b-5p as a potential biomarker (13). After total RNA extraction and real time PCR from MSG of pSS patients with established lymphoma and sequential prelymphoma state, it was clearly shown that miRNA200b-5p levels were significantly reduced compared to pSS without lymphoma and this reduction did not seem to change during completion of lymphomagenesis process. Multivariate analysis also showed that reduced miRNA200b-5p levels could be identified in pre-lymphoma pSS patients, years before the occurrence of lymphoma and this reduction was proven to be the strongest, independent predictor of lymphoma among traditional risk factors. Interestingly, miRNA200b-5p levels were also found to reflect response to treatment among pSS patients with MALT lymphomas. Although the exact pathogenetic role of miR200b-5p in pSS associated lymphomas remains to be addressed, it could be used as surrogate marker in MSG biopsy to predict lymphoma development and response to MALT treatment. Another promising molecule is the thymic stromal lymphopoietin (TSLP) which exerts either proinflammatory or regulatory functions depending on the isoform (long or short form respectively), the stimulus, the cytokine milieu and the tissue (14). Recent data showed that levels of the inducible long form of TSLP are detected in a progressively increasing manner, from pSS patients with benign lesion towards those with NHLs. Similarly, TSLP expressing B cells in the minor salivary glands of pSS patients, are also increasing in frequency following the transition towards lymphoma, implying a possible pathogenetic role. On the contrary TSLP appears to be down regulated by epithelial cells both at the protein and mRNA level in pSS patients compared to controls, not as a consequence of epithelial damage as supported by quantification of TSLP producing cells in intact regions of salivary gland tissue (15). Finally, the role of salivary ultrasound is being examined as a potential biomarker in the context of pSS. In the past years, it has been shown that parotid or submandibular ultrasonography may improve the diagnostic classification of pSS patients and the performance of the currently used criteria for Sjögren’s syndrome (16). Abnormal ultrasound findings have been correlated to autoantibody positivity, higher overall disease activity and some adverse predictors of lymphoma (17, 18). Furthermore, vascularisation and echostructural changes of salivary glands have been proposed as a measure to monitor response to treatment among pSS patients (19).

More sophisticated bioinformatics tools (20) and in-depth basic and translational research is expected to enrich the pathogenetic landscape of the disease and allow the identification of useful biomarkers with the prospective to better diagnose, stratify, treat and follow up pSS patients covering the whole clinical spectrum of the disease.

References