Review

Animal models of Sjögren's syndrome: an update

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Received on May 29, 2019; accepted in revised form on July 9, 2019.

Clin Exp Rheumatol 2019; 37 (Suppl. 118): S209-S216.

Key words: Sjögren's syndrome, animal models, pathogenesis, therapies

Funding: see page 214.

Competing interests: none declared.

ABSTRACT

Sjögren's syndrome (SS) is a chronic autoimmune disease characterised by lymphocytic infiltration in exocrine glands with secretory dysfunction. Although both environmental triggers and genetic predisposition have been recognised as important factors in the initiation and development of SS, the pathogenesis of SS is complex and still largely unclear. Animal models have served as useful tools for studying SS pathogenesis with several advantages. A number of animal models recapitulating key characteristics of primary SS patients including secretory dysfunction, glandular inflammation and presence of autoantibodies were developed in the past years. The studies based on the animal models of SS have provided significant insight in SS pathogenesis and therapeutic intervention. This review summarises current animal models with primary SS-like symptoms including spontaneous models, genetically modified models, induced models and humanised models, and discusses their contribution to the understanding of SS aetiology and therapies.

Introduction

Sjögren's syndrome (SS) is a heterogeneous autoimmune disease characterised by lymphocytic infiltration in exocrine glands, predominantly salivary and lachrymal glands (LG), resulting in dry mouth and dry eyes (1). SS is also a systemic disease with the involvement of multiple extraglandular organs including lung, kidney, and skin (1, 2). SS may either occur alone as primary SS or exist in the presence of other autoimmune diseases as secondary SS (1). Glandular infiltration of lymphocytes and the presence of anti-SSA autoantibodies are key evidence for the diagnosis of SS while ocular problems and salivary hypofunction are also important criteria (3, 4).

Although SS has been studied for decades, the pathogenesis is still largely unclear. Both B cells and T cells activation as well as disturbed cytokine network in SS pathogenesis were demonstrated in clinical research and animal models studies (5-7). The predominant infiltration of CD4 T cells and B cells in salivary gland (SG) tissues of both SS patients and animal models with SS-like symptoms strongly suggested the involvement of dysregulated B and T cell responses in SS pathogenesis (6, 8). However, the exact roles of the immune populations in initiation and maintenance of SS are illusive. Increasing evidence suggests that both genetic predisposition and environmental triggers including virus infection are significant mediators in SS pathogenesis (5, 9). Clinical observations have provided important information on disease manifestations but can hardly delineate immunological and pathogenic changes before the occurrence of overt clinical signs (10). The studies based on SS animal models have the advantages of illustrating the whole disease spectrum before and after the appearance of disease symptoms, and bridging basic research and clinical observation. During recent years, a number of animal models with primary SS-like symptoms have been developed and those studies have provided new insight in the understanding of SS aetiologies (11-13).

This review summarises and discusses recent studies on animal models that resemble key features of primary SS patients, including spontaneous models, genetically modified models, induced models and humanised models. Current understanding and future perspectives of SS animal models studies are also discussed.

Spontaneous models

A number of mouse strains spontane-

ously develop SS-like phenotypes. The lupus-prone mice such as MRL/lpr and NZB/NZW F1 mice exhibited lymphocytic infiltration in SG tissues and were considered as secondary SS models (14, 15). Non-obese diabetic (NOD) mice with insulin-dependent diabetes also showed SS-like symptoms (16). Moreover, the NOD derivatives with only SS but not diabetic symptoms were developed. Other spontaneous models include NFS/sld model, IQI/Jic model and Aly/aly model. Although the spontaneous models are useful tools for studying SS pathogenesis, the accompanying phenotypes of other diseases have limited their applications.

NOD and derivative mice

The NOD model is widely used to study the immune-pathogenesis and develop potential therapeutics for human SS. The NOD mice spontaneously develop both diabetic and SS-like symptoms, which serves as a typical secondary SS model. Lymphocytic infiltration was observed in exocrine glands including SG and LG, resulting in sialadenitis and dacryoadenitis (17). The autoantibody signature in NOD model resembles human SS patients with the presence of anti-SSA, anti-SSB and anti-muscarinic receptor type III (M3R) autoantibodies but usually with low levels (13, 18-20). Moreover, a number of NOD derivative models including NOD.B10-H2^{b} and NOD.H-2h4 mice recapitulated key symptoms of SS patients without the occurrence of diabetes, indicating the independent development of glandular dysfunction and diabetic symptoms (21, 22). Multiple insulin dependent diabetes (idd) loci were identified in NOD mice for diabetes development while two of them Idd3 and Idd5 were found to be critical for SS-like phenotypes (23). C57BL/6 mice with congenic loci of Idd3 and Idd5 from NOD mice termed as C57BL/6.NOD-Aec1Aec2 also mirrored human SS characteristics without diabetic symptoms, thus serving as another primary SS model (24).

Recent studies on NOD and derivative models have indicated key features of SS pathogenesis and provided strategies for developing novel therapies. Recently, it's reported that blocking CD40-CD40L interactions markedly reduced lymphocytic infiltration and glandular ectopic lymphoid structures (ELS) in NOD model (25). Even a single treatment of anti-CD40L significantly decreased ELS formation and serum autoantibodies levels in NOD.H-2h4 mice (26). Consistently, clinical studies also indicated the benefits of anti-CD40 monoclonal antibody CFZ533 in SS patients (27). Together, these results demonstrated the involvement of CD40–CD40L pathway in SS pathogenesis and suggested the therapeutic potential of targeting CD40/CD40L for treating SS.

NFS/sld mice

NFS/sld mutant mice bear defects of salivary glands differentiation. The mice with thymectomy at 3 days after birth (3d-Tx NFS/sld) exhibited significant inflammatory lesions in SG and LG with secretory dysfunctions (28). Aging-associated CD4 T cells dysregulation and Fas-mediated epithelial cell apoptosis were suggested to be involved in autoimmune development in this model (29). Moreover, α-fodrin appeared to be an important autoantigen. Neonatal immunisation with recombinant 120-kDa α-fodrin decreased inflammatory lesions in 3d-Tx NFS/sld mice (30) while immunisation in 4-week old normal NFS/lsld mice induced autoimmune SS symptoms (31). However, anti-α-fodrin antibodies are less specific and sensitive when compared with anti-SSA autoantibodies in SS patients (32), suggesting that anti-α-fodrin antibodies may not be suitable for SS diagnosis.

Aly/aly mice

The alymphoplasia mutated (aly/aly) mice possess a spontaneous mutation which causes a systemic lack of Peyer's patches and lymph nodes (33). Aly/aly mice developed inflammatory infiltration in exocrine glands including SG, LG and pancreas (34). Inflammatory lesions in liver and lung were also observed but autoantibodies were not detected in aly/aly mice. Transfer of T cells from aly/aly mice into RAG2 knockout (KO) mice induced inflammation in exocrine organs, suggesting that autoreactive T cells are critical for disease initiation and progression in this model.

IQI/Jic mice

IQI/Jic mice spontaneously develop lymphocytic inflammation in SG and LG with increased incidence and severity in aged mice (35). Female IQI/Jic mice exhibit severer tissue damage when compared with male mice. CD4 T cells were found to be the dominant population in small foci while the frequencies of B cells were elevated in accordance with increased disease severity, which was consistent with B and T cells quantification in minor salivary glands of SS patients (35, 36). However, anti-SSA autoantibodies were not detected (35). Notably, inflammatory lesions within multiple organs including pancreas, lung and kidney were observed in IQI/Jic mice , resembling systemic manifestation in SS patients (37). Increased expression of kallikrein (Klk)-13 in salivary tissues and elevated levels of antibodies against Klk-13 in diseased mice were detected, suggesting that Klk-13 may function as an autoantigen in the disease development (38).

Genetically modified models

Genetic factors play critical roles in SS development. Various genetically modified models were established in the past decades. Some genetically modified mice such as BAFF transgenic mice exhibited secondary SS phenotypes (39). Moreover, genetically modified models recapitulating primary SS symptoms were also studied. The gene editing technologies will further elucidate new pathogenic pathways in SS pathogenesis.

Inhibitor of differentiation 3(Id3) KO mice

Id3 is a critical transcriptional regulator in cell proliferation and differentiation of various cell types, including B and T cells (40, 41). The Id3 KO mice developed glandular lymphocytic infiltration and secretory dysfunction at early stages while the presence of autoantibodies was detected at late stage (42). Adoptive transfer of Id3 KO T cells induced SS-like secretory dysfunction in recipi-

ent mice, suggesting a T cell-intrinsic role of Id3. Furthermore, mice with Id3 deficiency in T cell lineage also exhibited comparable SS-like phenotypes with Id3 germline KO mice (43), further demonstrating the critical roles of T cells in driving disease development. However, B cells depletion ameliorated glandular inflammation with improved secretory functions (44), suggesting differential roles of B and T cells at different stages of disease progression. The clinical relevance of Id3 in SS patients has not been confirmed as available studies suggested no obvious predisposition of Id3-related SNPs in SS patients (45).

Aromatase KO mice

The higher incidence of SS in females has suggested the involvement of oestrogen in disease pathogenesis (2). Ovariectomy of the normal mice led to SS-like disease symptoms while administration of oestrogen prevented apoptosis of SG epithelial cells in oestrogen-deficient mice, indicating the protective effects of oestrogen in SS (46,47). Aromatase is an enzyme that controls a key step in the biosynthesis of oestrogens. Aromatase KO mice developed severe inflammatory infiltrates in SG with glandular dysfunction, which was possibly related to adipose tissue-associated macrophages (48, 49).

Autoimmune regulator (Aire) KO mice

Aire is a transcription factor that regulates self-tolerance by promoting ectopic expression of autoantigens in thymus and controlling peripheral autoreactive B cells (50, 51). Aire is not only expressed in thymic medullary epithelial cell but also in peripheral lymphoid organs (52). Previous clinical observations revealed that Aire deficient patients harboured unique autoantibodies profiles with loss of B cell tolerance (53). Aire deficient mice exhibited spontaneous development of autoimmune profiles and served as an animal model for SS (54). The Aire KO mice developed SS-like lymphocytic infiltration in lacrimal glands, parotid glands and submandibular glands together with severe dry eyes (54–56). It was found that autoimmunity against α -fodrin and odorant binding protein 1a were associated with disease development while both the autoantigens were identified in thymus (54, 57). Moreover, mouse genetic background markedly affected SS progression in Aire KO mice because disease development differed in C57/BL6, BALB/c and NOD background (54, 55). Recently, neuropathic changes were found to be associated with chronic lacrimal inflammation in Aire KO mice (58), suggesting disturbed neuronal regulation in SS pathogenesis. Additionally, gene expression analysis in Aire KO mice revealed the involvement of multiple signalling pathways in early regulation of inflammation, innervation, and cell survival during autoimmune SS development (55).

T cell-specific phosphoinositide 3-kinase (PI3K) KO mice

PI3K functions as a second messenger downstream of multiple receptors and has key roles in regulating immune cell functions (59). Mice with T cell-specific PI3K deficiency showed autoimmune development with SS-like phenotypes. Glandular lymphocytic infiltration, increased antinuclear antibodies (ANA) and anti-SSA antibodies were detected (60). A recent study reported that *in vivo* blockade of PI3Kδ activity ameliorated disease symptoms in a SS-like sialoadenitis model, suggesting that PI3K pathway might be a novel therapeutic target for SS treatments (61).

IκBα$^{M/M}$ mice

NF-κB represents a family of transcription factors with diverse roles. Defective NF-κB signalling substantially contributed to the development of autoimmunity (62). IκBα is induced by NF-κB activation and in turn inhibits NF-κB activity with a feedback loop. Polymorphisms in IκBα promoter region were suggested to be related with SS susceptibility (63). IκBα$^{M/M}$ mice with mutated κB enhancers in IκBα promoter developed autoimmune symptoms which were very similar to SS patients (64). The IκBα$^{M/M}$ mice exhibited inflammatory infiltrates in SG, LG and lung tissues. Moreover, autoantibodies against SSA and SSB were detected.

Osteopontin (OPN) transgenic mice

OPN is a multifunctional cytokine with diverse sources (65). Previous studies suggested that aberrant expression and function of OPN were associated with a number of autoimmune diseases, including systemic lupus erythematosus (SLE), rheumatoid arthritis and multiple sclerosis (66-68). The association between OPN and SS pathogenesis was further revealed by the SS-like phenotypes in OPN transgenic mice which served as another SS model (69). OPN transgenic mice recapitulated SS characteristics in terms of exocrine histopathology, saliva hypofunction, increased anti-SSA antibodies and female predilection.

Overexpression of retinoblastoma-associated protein 48 (RbAp48) in SG

RbAp48 is a histone binding protein with multiple functions. Previous studies reported that RbAp48 induced apoptosis in the exocrine glands which was dependent on oestrogen deficiency (70). Moreover, transgenic expression of RbAp48 in SG tissues resulted in autoimmune exocrinopathy (71). Inflammatory infiltrates with CD4 T cells in SG and LG tissues and reduced saliva and tear secretion were observed. In addition, increased anti-SSA/SSB autoantibodies levels were detected. SG epithelial cells may serve as antigen-presenting cells and promote disease progression in this model.

Overexpression of TNF-α in SG

TNF-α is an important cytokine in autoimmunity. Increased TNF-α expression was observed in patients with autoimmune diseases, including SS (72). Moreover, TNF-α levels were implicated to be associated with secretory dysfunctions and inflammation in SS (73). A recent study showed that overexpression of TNF-α within salivary glands induced SS-like sialadenitis symptoms, including lymphocytes aggregation in SG tissues and secretory dysfunction (74). However, autoantibodies were not observed in this model, suggesting the autoantibody-independent induction of SG hypofunction in the model.

Induced models

In addition to genetic background,

extrinsic triggers are also important factors involved in SS pathogenesis. Immunisation with specific autoantigens can induce breakdown of the immune-tolerance and result in glandular inflammation and hypofunction, which resembles the symptoms of SS patients. Currently, the antigens used for SS induction include Ro peptides, M3R peptides, carbonic anhydrise 2 (CA2) and SG protein extracts. Moreover, adenovirus infection in SG tissues also induced SS-like symptoms. The induced models serve as powerful tools for translational studies and have the advantage of exploring the whole disease development spectrum from a precise point of disease onset.

Ro immunisation

The presence of anti-SSA/Ro autoantibody is important for the diagnosis and classification of SS patients. Repeated immunisation with short peptide derived from Ro 60 induced profound lymphocytic infiltrates in SG tissues with glandular hypofunction in BALB/c mice (75). Moreover, the immunised mice exhibited anti-SSA/Ro autoantibodies while oral feeding of Ro 60 peptides prevented disease progress through induction of immune tolerance (76). Recent studies reported that immunisation of mRo60_316-335 peptide antigen with a predominant T cell epitope induced several major SS-like symptoms in mice, including glandular dysfunction and tissue inflammation as well as the increase of autoantibodies and inflammatory cytokines (77). An indispensable role of B cells was demonstrated in this model when B cell depletion prevented the development of SS-like disease. Genetic predisposition was also important because immunisation with Ro 60 peptides induced different degrees of preclinical autoimmunity with diverse phenotypes in different strains of mice (78).

Autoantibodies against SSA/Ro recognise two types of ribonucleoprotein antigens with 52 kDa and 60 kDa, respectively. Not only Ro 60 but also Ro 52 peptides immunisation induced SS-like phenotypes in mice. NZM2758 mice with immunisation of Ro52 exhibited symptoms resembling those of SS patients(79). Moreover, Ro52-induced antibodies were capable of inducing SG hypofunction, which was dependent on activation of innate immunity (79).

M3R peptide immunisation

Anti-M3R autoantibodies detected in SS patients are suggested to be involved in SS pathogenesis (80). M3R is located on the surface of SG acinar cells and plays key roles in saliva secretion. The predominant role of M3R in regulating saliva production was revealed by findings that M3R KO mice showed 20% reduction of saliva secretion when compared with wild type (WT) mice (81). Previous studies suggested that anti-M3R autoantibodies bound to M3R in SG tissues and contributed secretory dysfunction (82). Adoptive transfer of splenocytes from the M3R KO mice which received immunisation with M3R-derived peptides into Rag KO immunodeficient mice resulted in profound hyposalivation accompanied with severe glandular inflammation (83). The immune pathogenesis in this model was dependent on T cells because the transfer of $CD3^+$ T cells but not $CD3^-$ cell population conferred development of SS-like phenotypes in recipient mice. M3R-specific effector T cells especially Th17 cells were critically involved in M3R-induced SS development. RORγt antagonist treatment significantly improved SG secretory functions with suppressed IFN-γ and IL-17 production (84), indicating that RORγt antagonism might be a potential therapeutic strategy for SS patients. However, immunisation with second extracellular loop of M3R in BALB/c mice induced neither secretory hypofunction nor histological abnormality though the presence of high levels of anti-M3R autoantibodies (85), suggesting that anti-M3R autoantibodies for the second extracellular loop may not exert any pathogenic function in SS development.

SG protein immunisation

Early studies reported the induction of salivary gland inflammation in SMA mice with repeated immunisation of salivary gland extract with Klebsiella O3 Lipopolysaccharide as adjuvant (86). Moreover, SS-like keratoconjunctivitis sicca symptoms were also observed in Lewis rats with immunisation of a mixture of lacrimal and salivary gland extract (87), suggesting that salivary and lacrimal glands-derived proteins may contain autoantigens for the induction of SS-like symptoms. Our recent work has established an experimental SS (ESS) model induced in C57BL/6 mice, which may serve as a powerful tool for studying SS pathogenesis and screening potential therapeutic candidates (88). The proteins were prepared from homogenised SG tissues in normal mice. Upon immunisation with the SG-derived proteins, the mice displayed decreased saliva production, increased anti-SSA and anti-M3R autoantibodies, profound glandular inflammation with the infiltration of both T and B cells. Pulmonary and renal inflammation were also observed in some mice at chronic disease stage (unpublished data), suggesting that the ESS mice also mimicked systemic manifestation with multiple organs-injury in SS patients. Using this ESS model, we demonstrated a critical role of Th17 cells in SS development (88). IL-17 KO mice were resistant to ESS induction while adoptive transfer of polarised Th17 cells into IL-17 KO recipient mice induced hyposalivation and focal sialadenitis (88). Moreover, the proteasome inhibitor Bortezomib suppressed Th17 but not Th1 responses in ESS development accompanied with ameliorated disease pathology, suggesting that targeting Th17 cells might be a promising therapeutic strategy for treating SS patients (89). In addition, IL-25 pathway was demonstrated to be involved in human primary SS patients and ESS model (90). Furthermore, our recent work revealed the regulatory roles of IL-10-producing B cells and myeloid-derived suppressor cells in SS pathogenesis (91, 92).

CA2 immunisation

CA2 is a metalloenzyme that catalyses the reversible hydration of carbon dioxide. Antibodies against CA2 were detected and associated with renal damage in a subset of SS patients (93). PL/J(H-2u) mice immunised with human CA2 exhibited lymphocytic infiltration

Table I. Animal models of Sjögren's syndrome.

Models	Glandular infiltration	Impaired fluids secretion	Autoantibodies	Other organs involved	References
			Spontaneous models		
NOD	SG, LG	saliva, tear	anti-SSA, anti-SSB, anti-M3R, ANA	pancreas (T1D)	17-19
NOD.B10-H2^{b}	SG, LG	saliva, tear	anti-SSA, anti-SSB, anti-M3R, ANA	not determined	21
C57BL/6.NOD-Aec1Aec2	SG, LG	saliva, tear	anti-SSA, anti-SSB, anti-M3R, ANA	not determined	24
NFS/sld	SG, LG	saliva	anti-SSA, anti-SSB, anti-α fodrin	not determined	28-31
Aly/aly	SG, LG	not determined	Negative for ANA	pancreas, liver, lung	34
IQI/Jic	SG, LG	not determined	ANA	pancreas, kidney, lung	35, 37, 38
			Genetically modified models		
Id3 KO	SG, LG	saliva, tear	anti-SSA, anti-SSB	not determined	42, 43
Aromatase KO	SG	not determined	anti-α fodrin	kidney	48, 49
Aire KO	SG, LG	tear	anti-α fodrin	liver, lung, pancreas prostate, stomach	54-58
T cell-specific PI3K KO	SG, LG	not determined	anti-SSA, anti-SSB, ANA	lung, liver, intestines	60
IκBα$^{M/M}$	SG, LG	not determined	anti-SSA, anti-SSB	lung	64
OPN transgenic	SG, LG	saliva	anti-SSA, ANA	not determined	69
Overexpression of RbAp48 in SG	SG, LG	saliva, tear	anti-SSA, anti-SSB	not determined	71
Overexpression of TNF-α in SG	SG	saliva	Negative for anti-SSA/SSB	not determined	74
			Induced models		
Ro immunisation (hRo60-480-494/274-290/273-289)	SG	saliva	anti-SSA, anti-SSB, ANA	not determined	75
Ro immunisation (mRo60-316-335)	SG, LG	tear	anti-SSA	not determined	77
Ro immunisation (mRo52)	SG	saliva	anti-SSA	not determined	79
M3R immunisation	SG, LG	saliva	anti-M3R	not determined	83-85
Salivary gland protein immunisation	SG, LG	saliva, tear	anti-SSA, anti-M3R	lung, kidney	88-92
CA2 immunisation	SG, LG	not determined	not determined	not determined	94, 95
SG infection of adenovirus 5	SG	saliva	ANA	not determined	99
SG cannulation of Ad5-IL17 vectors	SG	saliva	ANA	not determined	103
			Humanised model		
Chimeric human–mouse model	SG, LG	saliva	negative for ANA	not determined	106

in SG tissues with the presence of anti-CA2 antibodies (94, 95). Moreover, impaired renal functions were also observed in immunised mice.

Virus-induced model

Environmental triggers including virus infections have been suggested to be important for SS initiation and progression. Several viruses such as Epstein-Barr virus (EBV) and cytomegalovirus (CMV) were associated with SS development (96). Previous studies showed that murine CMV (MCMV)-infected autoimmune-prone mice including B6-lpr/lpr and NZM2328 mice exhibited SS-like disease symptoms and served as secondary SS models (97, 98). Notably, SG administration of a replication-defective adenovirus 5 in WT C57BL/6 mice reproduced several phenotypic and functional features of SS patients including lymphocytic infiltration in SG tissues, decreased saliva secretion and functional B cell activation with increased ANA levels (99). Ectopic lymphoid structures with germinal centres were observed in the majority of infected mice. Therefore, the adenovirus-infected mice may also serve as a SS model for studying cellular and molecular mechanisms.

SG cannulation of Ad5-IL17 vectors

A number of studies strongly suggested the involvement of IL-17 in SS pathogenesis (100-103). Our previous studies also showed the critical roles of Th17 cells in driving SS progression in a murine model (88). Moreover, overexpression of IL-17 in SG tissues directly induced SS-like disease profiles, serving as another SS model. The mice with retrograde salivary gland cannulation of adenovirus serotype 5 vectors expressing IL-17 (Ad5-IL-17) exhibited increased IL-17 production accompanied with elevated inflammatory cytokines, glandular lymphocytic infiltration, presence of autoantibodies, and reduction of saliva secretion (103). In addition, blocking IL-17 reduced SS pathology in C57BL/6.NOD-Aec1Aec2 model (104, 105), further demonstrating that IL-17 might be a promising therapeutic target for treating SS.

Humanised model

Animal models are proved to be useful tools for studying human diseases, but the differences between animals and human biology limit the translation of knowledge from animal models to clinical outputs. In current research, humanised mouse models have been increasingly recognised as important pre-clinical tools to fill the gap between mouse and human. The humanised SS model was developed by adoptive transfer

of peripheral blood mononuclear cells (PBMCs) from SS patients into immunodeficient NOD-scid IL-2rγ(null) recipient mice (NSG mice) (106). The chimeric mice with PBMCs from SS patients exhibited inflammation in SG and LG tissues together with reduced saliva production. Further histological analysis revealed primarily CD4 T cells infiltration with minimal CD8 T cells and B cells. This chimeric humanised model represents an important platform for future translational studies.

Conclusions and future perspectives

SS is a heterogeneous disease with complex pathogenesis. Both external triggers and intrinsic factors contribute to SS development. Clinical research has provided important evidence for the understanding of SS aetiology. However, the pathological changes before the clinical diagnosis can hardly be studied from clinical observations. Animal models, especially murine models with the advantages of genetic consistency, short life span and sufficient sample size, have provided a myriad of information regarding disease initiation, progression and treatment. During recent decades, a number of animal models recapitulating the key characteristics of SS patients have been developed (Table I). Those animal models of SS serve as excellent tools for studying full disease spectrum. The advancement and applications of genetically modified mice in SS models will identify the direct roles of target genes in disease pathogenesis. In addition, pre-clinical studies based on animal models will benefit the potential development of novel therapies for SS patients.

Although there are still discrepancies between SS animal models and patients, numerous studies on SS models have contributed substantially to the current understanding of SS pathogenesis. Notably, the humanised mouse model has markedly narrowed the gap between animal models and SS patients, allowing the in vivo study of human immune cells under SS disease condition. Moreover, the humanised mouse model is usually patient-specific, which may benefit the advancement of clinical applications of personalised therapies. Further research in animal models is needed for a comprehensive understanding of SS pathogenesis. The future translational studies from animal models to clinical research will certainly provide new insight in understanding SS pathogenesis and further developing effective therapies for patients.

Funding

This work was supported by the National Natural Science Foundation of China (no. 91842304 and 81771761), General Research Fund, Hong Kong Research Grants Council (17114515 and 17149716), Chinese National Key Technology R&D Program, Ministry of Science and Technology (2017YFC0907601, 2017YFC0907605 and 2018YFC1705200), Hong Kong Croucher Foundation (260960116) and HKU Seed Funding for Strategic Interdisciplinary Research Scheme (2018/19).

References

1. FOX RI: Sjögren's syndrome. *Lancet* 2005; 366: 321-31.
2. MARIETTE X, CRISWELL LA: Primary Sjögren's Syndrome. *N Engl J Med* 2018; 378: 931-9.
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* 2016; 69: 35-45.
4. FRANCESCHINI F, CAVAZZANA I, ANDREOLI L, TINCANI A: The 2016 classification criteria for primary Sjögren's syndrome: what's new? *BMC Med* 2017; 15: 69-71.
5. NOCTURNE G, MARIETTE X: B cells in the pathogenesis of primary Sjögren's syndrome. *Nat Rev Rheumatol* 2018; 14: 133-45.
6. VOULGARELIS M, TZIOUFAS AG: Pathogenetic mechanisms in the initiation and perpetuation of Sjögren's syndrome. *Nat Rev Rheumatol* 2010; 6: 529-37.
7. YOUINOU P, PERS J-O: Disturbance of cytokine networks in Sjögren's syndrome. *Arthritis Res Ther* 2011; 13: 227.
8. ARGYROPOULOU OD, VALENTINI E, FERRO F *et al*.: One year in review 2018: Sjögren's syndrome. *Clin Exp Rheumatol* 2018; 36 (Suppl. 112): S14-26.
9. NOCTURNE G, MARIETTE X: Advances in understanding the pathogenesis of primary Sjögren's syndrome. *Nat Rev Rheumatol* 2013; 9: 544-56.
10. DELALEU N, NGUYEN CQ, PECK AB, JONSSON R: Sjögren's syndrome: studying the disease in mice. *Arthritis Res Ther* 2011; 13: 217.
11. LEE BH, GAUNA AE, PAULEY KM, PARK Y-J, CHA S: Animal models in autoimmune diseases: lessons learned from mouse models for Sjögren's syndrome. *Clin Rev Allergy Immunol* 2012; 42: 35-44.
12. MARIA NI, VOGELSANG P, VERSNEL MA: The clinical relevance of animal models in Sjögren's syndrome: the interferon signature from mouse to man. *Arthritis Res Ther* 2015; 17: 172-82.
13. LAVOIE TN, LEE BH, NGUYEN CQ: Current Concepts: Mouse Models of Sjögren's Syndrome. *J Biomed Biotechnol* 2011; 2011: 549107-20.
14. HOFFMAN RW, ALSPAUGH MA, WAGGIE KS, DURHAM JB, WALKER SE: Sjögren's syndrome in MRL/l and MRL/n mice. *Arthritis Rheum* 1984; 27: 157-65.
15. KESSLER HS: A laboratory model for Sjögren's syndrome. *Am J Pathol* 1968; 52: 671-85.
16. MIYAGAWA J, HANAFUSA T, MIYAZAKI A *et al*.: Ultrastructural and immunocytochemical aspects of lymphocytic submandibulitis in the non-obese diabetic NOD mouse. *Virchows Archiv B Cell Pathol* 1986; 51: 215.
17. HU Y, NAKAGAWA Y, PURUSHOTHAM KR, HUMPHREYS-BEHER MG: Functional changes in salivary glands of autoimmune disease-prone NOD mice. *Am J Physiol* 1992; 263: E607-614.
18. HUMPHREYS-BEHER MG, BRINKLEY L, PURUSHOTHAM KR *et al*.: Characterization of antinuclear autoantibodies present in the serum from nonobese diabetic (NOD) mice. *Clin Immunol Immunopathol* 1993; 68: 350-6.
19. SKARSTEIN K, WAHREN M, ZAURA E, HATTORI M, JONSSON R: Characterization of T cell receptor repertoire and anti-Ro/SSA autoantibodies in relation to sialadenitis of NOD mice. *Autoimmunity* 1995; 22: 9-16.
20. KERN J, DRUTEL R, LEANHART S, BOGACZ M, PACHOLCZYK R: Reduction of T cell receptor diversity in NOD mice prevents development of type 1 diabetes but not Sjögren's syndrome. *PLoS One* 2014; 9: e112467-77.
21. ROBINSON CP, YAMACHIKA S, BOUNOUS DI *et al*.: A novel NOD-derived murine model of primary Sjögren's syndrome. *Arthritis Rheum* 1998; 41: 150-6.
22. BRALEY-MULLEN H, YU S: NOD.H-2h4 mice: an important and underutilized animal model of autoimmune thyroiditis and Sjögren's syndrome. *Adv Immunol* 2015; 126: 1-43.
23. BRAYER J, LOWRY J, CHA S *et al*.: Alleles from chromosomes 1 and 3 of NOD mice combine to influence Sjögren's syndrome-like autoimmune exocrinopathy. *J Rheumatol* 2000; 27: 1896-904.
24. CHA S, NAGASHIMA H, BROWN VB, PECK AB, HUMPHREYS-BEHER MG: Two NOD Idd-associated intervals contribute synergistically to the development of autoimmune exocrinopathy (Sjögren's syndrome) on a healthy murine background. *Arthritis Rheum* 2002; 46: 1390-8.
25. WIECZOREK G, BIGAUD M, PFISTER S *et al*.: Blockade of CD40–CD154 pathway interactions suppresses ectopic lymphoid structures and inhibits pathology in the

NOD/ShiLtJ mouse model of Sjögren's syndrome. *Ann Rheum Dis* 2019; 78: 974-8.
26. MAHMOUD TI, WANG J, KARNELL JL *et al*.: Autoimmune manifestations in aged mice arise from early-life immune dysregulation. *Sci Transl Med* 2016; 8: 361ra137.
27. JOBLING K, NG WF: CD40 as a therapeutic target in Sjögren's syndrome. *Expert Rev Clin Immunol* 2018; 14: 535-7.
28. HANEJI N, HAMANO H, YANAGI K, HAYASHI Y: A new animal model for primary Sjögren's syndrome in NFS/sld mutant mice. *J Immunol* 1994; 153: 2769-77.
29. ISHIMARU N, YONEDA T, SAEGUSA K *et al*.: Severe destructive autoimmune lesions with aging in murine Sjögren's syndrome through Fas-mediated apoptosis. *Am J Pathol* 2000; 156: 1557-64.
30. HANEJI N, NAKAMURA T, TAKIO K *et al*.: Identification of alpha-fodrin as a candidate autoantigen in primary Sjögren's syndrome. *Science* 1997; 276: 604-7.
31. SAEGUSA K, ISHIMARU N, YANAGI K *et al*.: Prevention and Induction of Autoimmune Exocrinopathy Is Dependent on Pathogenic Autoantigen Cleavage in Murine Sjögren's Syndrome. *J Immunol* 2002; 169: 1050-7.
32. ZANDBELT MM, VOGELZANGS J, VAN DE PUTTE LB, VAN VENROOIJ WJ, VAN DEN HOOGEN FH: Anti-alpha-fodrin antibodies do not add much to the diagnosis of Sjögren's syndrome. *Arthritis Res Ther* 2004; 6: R33-8.
33. MACPHERSON AJ, UHR T: The donor splice site mutation in NFkappaB-inducing kinase of alymphoplasia (aly/aly) mice. *Immunogenetics* 2003; 54: 693-8.
34. TSUBATA R, TSUBATA T, HIAI H *et al*.: Autoimmune disease of exocrine organs in immunodeficient alymphoplasia mice: a spontaneous model for Sjögren's syndrome. *Eur J Immunol* 1996; 26: 2742-8.
35. SAEGUSA J, KUBOTA H: Sialadenitis in IQI/Jic mice: a new animal model of Sjögren's syndrome. *J Vet Med Sci* 1997; 59: 897-903.
36. COSTA S, SCHUTZ S, CORNEC D *et al*.: B-cell and T-cell quantification in minor salivary glands in primary Sjögren's syndrome: development and validation of a pixel-based digital procedure. *Arthritis Res Ther* 2016; 18: 21.
37. TAKADA K, TAKIGUCHI M, KONNO A, INABA M: Spontaneous development of multiple glandular and extraglandular lesions in aged IQI/Jic mice: a model for primary Sjögren's syndrome. *Rheumatology* (Oxford) 2004; 43: 858-62.
38. TAKADA K, TAKIGUCHI M, KONNO A, INABA M: Autoimmunity against a tissue kallikrein in IQI/Jic Mice: a model for Sjögren's syndrome. *J Biol Chem* 2005; 280: 3982-8.
39. GROOM J, KALLED SL, CUTLER AH *et al*.: Association of BAFF/BLyS overexpression and altered B cell differentiation with Sjögren's syndrome. *J Clin Invest* 2002; 109: 59-68.
40. PAN L, SATO S, FREDERICK JP, SUN X-H, ZHUANG Y: Impaired Immune Responses and B-Cell Proliferation in Mice Lacking the Id3 Gene. *Mol Cell Biol* 1999; 19: 5969-80.
41. JI Y, POS Z, RAO M *et al*.: Repression of the DNA-binding inhibitor Id3 by Blimp-1 limits the formation of memory CD8+ T cells. *Nat Immunol* 2011; 12: 1230-7.
42. LI H, DAI M, ZHUANG Y: A T cell intrinsic role of Id3 in a mouse model for primary Sjögren's syndrome. *Immunity* 2004; 21: 551-60.
43. GUO Z, LI H, HAN M, XU T, WU X, ZHUANG Y: Modeling Sjögren's syndrome with Id3 conditional knockout mice. *Immunol Lett* 2011; 135: 34-42.
44. HAYAKAWA I, TEDDER TF, ZHUANG Y: B-lymphocyte depletion ameliorates Sjögren's syndrome in Id3 knockout mice. *Immunology* 2007; 122: 73-9.
45. SELLAM J, MICELI-RICHARD C, GOTTENBERG J-E *et al*.: Is Inhibitor of differentiation 3 involved in human primary Sjögren's syndrome? *Rheumatology* (Oxford) 2008; 47: 437-41.
46. ISHIMARU N, ARAKAKI R, WATANABE M, KOBAYASHI M, MIYAZAKI K, HAYASHI Y: Development of autoimmune exocrinopathy resembling Sjögren's syndrome in estrogen-deficient mice of healthy background. *Am J Pathol* 2003; 163: 1481-90.
47. ISHIMARU N, SAEGUSA K, YANAGI K, HANEJI N, SAITO I, HAYASHI Y: Estrogen deficiency accelerates autoimmune exocrinopathy in murine Sjögren's syndrome through fas-mediated apoptosis. *Am J Pathol* 1999; 155: 173-81.
48. SHIM G-J, WARNER M, KIM H-J *et al*.: Aromatase-deficient mice spontaneously develop a lymphoproliferative autoimmune disease resembling Sjögren's syndrome. *Proc Natl Acad Sci USA* 2004; 101: 12628-33.
49. IWASA A, ARAKAKI R, HONMA N *et al*.: Aromatase controls Sjögren syndrome-like lesions through monocyte chemotactic protein-1 in target organ and adipose tissue-associated macrophages. *Am J Pathol* 2015; 185: 151-61.
50. ANDERSON MS, VENANZI ES, KLEIN L *et al*.: Projection of an immunological self shadow within the thymus by the aire protein. *Science* 2002; 298: 1395-401.
51. SNG J, AYOGLU B, CHEN JW *et al*.: AIRE expression controls the peripheral selection of autoreactive B cells. *Sci Immunol* 2019; 4: eaav6778-91.
52. ELDERSHAW SA, SANSOM DM, NARENDRAN P: Expression and function of the autoimmune regulator (Aire) gene in non-thymic tissue. *Clin Exp Immunol* 2011; 163: 296-308.
53. MEYER S, WOODWARD M, HERTEL C *et al*.: AIRE-deficient patients harbor unique high-affinity disease-ameliorating autoantibodies. *Cell* 2016; 166: 582-95.
54. KURODA N, MITANI T, TAKEDA N *et al*.: Development of autoimmunity against transcriptionally unrepressed target antigen in the thymus of Aire-deficient mice. *J Immunol* 2005; 174: 1862-70.
55. CHEN FY, GAYLORD E, MCNAMARA N, KNOX S: Deciphering molecular and phenotypic changes associated with early autoimmune disease in the aire-deficient mouse model of Sjögren's syndrome. *Int J Mol Sci* 2018; 19: E3628.
56. CHAN MF, DEVOSS J, LECLAIR N *et al*.: Mechanisms of autoimmunity in the aire-deficient mouse model of sjögren's syndrome. *Invest Ophthalmol Vis Sci* 2007; 48: 2833-2833.
57. DEVOSS JJ, LECLAIR NP, HOU Y *et al*.: An autoimmune response to odorant binding protein 1a is associated with dry eye in the aire-deficient Mouse. *J Immunol* 2010; 184: 4236-46.
58. CHEN FY, LEE A, GE S, NATHAN S, KNOX SM, MCNAMARA NA: Aire-deficient mice provide a model of corneal and lacrimal gland neuropathy in Sjögren's syndrome. *PLoS One* 2017; 12: e0184916.
59. KOYASU S: The role of PI3K in immune cells. *Nat Immunol* 2003; 4: 313-9.
60. OAK JS, DEANE JA, KHARAS MG *et al*.: Sjögren's syndrome-like disease in mice with T cells lacking class 1A phosphoinositide-3-kinase. *Proc Natl Acad Sci USA* 2006; 103: 16882-7.
61. NAYAR S, CAMPOS J, SMITH CG *et al*.: Phosphatidylinositol 3-kinase delta pathway: a novel therapeutic target for Sjögren's syndrome. *Ann Rheum Dis* 2019; 78: 249-60.
62. SUN S-C, CHANG J-H, JIN J: Regulation of nuclear factor-κB in autoimmunity. *Trends Immunol* 2013; 34: 282-9.
63. OU T-T, LIN C-H, LIN Y-C *et al*.: IkappaB-alpha promoter polymorphisms in patients with primary Sjögren's syndrome. *J Clin Immunol* 2008; 28: 440-4.
64. PENG B, LING J, LEE AJ *et al*.: Defective feedback regulation of NF-κB underlies Sjögren's syndrome in mice with mutated κB enhancers of the IκBα promoter. *Proc Natl Acad Sci USA* 2010; 107: 15193-8.
65. DENHARDT DT, GIACHELLI CM, RITTLING SR: Role of osteopontin in cellular signaling and toxicant injury. *Annu Rev Pharmacol Toxicol* 2001; 41: 723-49.
66. D'ALFONSO S, BARIZZONE N, GIORDANO M *et al*.: Two single-nucleotide polymorphisms in the 5′ and 3′ ends of the osteopontin gene contribute to susceptibility to systemic lupus erythematosus. *Arthritis Rheum* 2005; 52: 539-47.
67. GAZAL S, SACRE K, ALLANORE Y *et al*.: Identification of secreted phosphoprotein 1 gene as a new rheumatoid arthritis susceptibility gene. *Ann Rheum Dis* 2015; 74: e19-e19.
68. SHIMIZU Y, OTA K, IKEGUCHI R, KUBO S, KABASAWA C, UCHIYAMA S: Plasma osteopontin levels are associated with disease activity in the patients with multiple sclerosis and neuromyelitis optica. *J Neuroimmunol* 2013; 263: 148-51.
69. HUSAIN-KRAUTTER S, KRAMER JM, LI W, GUO B, ROTHSTEIN TL: The osteopontin transgenic mouse is a new model for sjögren's syndrome. *Clin Immunol* 2015; 157: 30-42.
70. ISHIMARU N, ARAKAKI R, OMOTEHARA F *et al*.: Novel role for RbAp48 in tissue-specific, estrogen deficiency-dependent apoptosis in the exocrine glands. *Mol Cell Biol* 2006; 26: 2924-35.
71. ISHIMARU N, ARAKAKI R, YOSHIDA S, YAMADA A, NOJI S, HAYASHI Y: Expression of the retinoblastoma protein RbAp48 in exocrine glands leads to Sjögren's syn-

drome-like autoimmune exocrinopathy. *J Exp Med* 2008; 205: 2915-27.
72. KANG EH, LEE YJ, HYON JY, YUN PY, SONG YW: Salivary cytokine profiles in primary Sjögren's syndrome differ from those in non-Sjögren sicca in terms of TNF-α levels and Th-1/Th-2 ratios. *Clin Exp Rheumatol* 2011; 29: 970-6.
73. ZHOU J, KAWAI T, YU Q: Pathogenic role of endogenous TNF-α in the development of Sjögren's-like sialadenitis and secretory dysfunction in non-obese diabetic mice. *Lab Invest* 2017; 97: 458-67.
74. LIMAYE A, HALL BE, ZHANG L *et al*.: Targeted TNF-α overexpression drives salivary gland inflammation. *J Dent Res* 2019: 713-9.
75. SCOFIELD RH, ASFA S, OBESO D, JONSSON R, KURIEN BT: Immunization with short peptides from the 60-kDa Ro antigen recapitulates the serological and pathological findings as well as the salivary gland dysfunction of Sjögren's syndrome. *J Immunol* 2005; 175: 8409-14.
76. KURIEN BT, ASFA S, LI C, DORRI Y, JONSSON R, SCOFIELD RH: Induction of oral tolerance in experimental Sjögren's syndrome autoimmunity. *Scand J Immunol* 2005; 61: 418-25.
77. ZHENG J, HUANG Q, HUANG R *et al*.: B cells are indispensable for a novel mouse model of primary Sjögren's syndrome. *Front Immunol* 2017; 8: 1384-92.
78. KURIEN BT, DSOUZA A, IGOE A *et al*.: Immunization with 60 kD Ro peptide produces different stages of preclinical autoimmunity in a Sjögren's syndrome model among multiple strains of inbred mice. *Clin Exp Immunol* 2013; 173: 67-75.
79. SZCZERBA BM, KAPLONEK P, WOLSKA N *et al*.: Interaction between innate immunity and Ro52-induced antibody causes Sjögren's syndrome-like disorder in mice. *Ann Rheum Dis* 2016; 75: 617-22.
80. SUMIDA T, TSUBOI H, IIZUKA M, ASASHIMA H, MATSUMOTO I: Anti-M3 muscarinic acetylcholine receptor antibodies in patients with Sjögren's syndrome. *Mod Rheumatol* 2013; 23: 841-5.
81. BYMASTER FP, MCKINZIE DL, FELDER CC, WESS J: Use of M1-M5 muscarinic receptor knockout mice as novel tools to delineate the physiological roles of the muscarinic cholinergic system. *Neurochem Res* 2003; 28: 437-42.
82. DAWSON LJ, STANBURY J, VENN N, HASDIMIR B, ROGERS SN, SMITH PM: Anti-muscarinic antibodies in primary Sjögren's syndrome reversibly inhibit the mechanism of fluid secretion by human submandibular salivary acinar cells. *Arthritis Rheum* 2006; 54: 1165-73.
83. IIZUKA M, WAKAMATSU E, TSUBOI H *et al*.: Pathogenic role of immune response to M3 muscarinic acetylcholine receptor in Sjögren's syndrome-like sialoadenitis. *J Autoimmun* 2010; 35: 383-9.
84. TAHARA M, TSUBOI H, SEGAWA S *et al*.: RORγt antagonist suppresses M3 muscarinic acetylcholine receptor-induced Sjögren's syndrome-like sialadenitis. *Clin Exp Immunol* 2017; 187: 213-24.
85. CHEN Y, ZHENG J, HUANG Q *et al*.: Autoantibodies against the second extracellular loop of M3R do neither induce nor indicate primary Sjögren's syndrome. *PLoS One* 2016; 11: e0149485.
86. MU MM, CHAKRAVORTTY D, TAKAHASHI K *et al*.: Production of experimental autoimmune sialadenitis in mice immunized with homologous salivary gland extract and Klebsiella O3 lipopolysaccharide. *J Autoimmun* 2001; 16: 29-36.
87. JIANG G, KE Y, SUN D *et al*.: A new model of experimental autoimmune keratoconjunctivitis sicca (KCS) induced in Lewis rat by the autoantigen Klk1b22. *Invest Ophthalmol Vis Sci* 2009; 50: 2245-54.
88 LIN X, RUI K, DENG J *et al*.: Th17 cells play a critical role in the development of experimental Sjögren's syndrome. *Ann Rheum Dis* 2015; 74: 1302-10.
89. XIAO F, LIN X, TIAN J *et al*.: Proteasome inhibition suppresses Th17 cell generation and ameliorates autoimmune development in experimental Sjögren's syndrome. *Cell Mol Immunol* 2017; 14: 924-34.
90. GUGGINO G, LIN X, RIZZO A *et al*.: Interleukin-25 axis is involved in the pathogenesis of human primary and experimental murine sjögren's syndrome. *Arthritis Rheumatol* 2018; 70: 1265-75.
91. LIN X, WANG X, XIAO F *et al*.: IL-10-producing regulatory B cells restrain the T follicular helper cell response in primary Sjögren's syndrome. *Cell Mol Immunol* 2019; [Epub ahead of print].
92. TIAN J, RUI K, HONG Y *et al*.: Increased GITRL impairs the function of myeloid-derived suppressor cells and exacerbates primary Sjögren syndrome. *J Immunol* 2019; 202: 1693–703.
93. PERTOVAARA M, BOOTORABI F, KUUSLAHTI M, PASTERNACK A, PARKKILA S: Novel carbonic anhydrase autoantibodies and renal manifestations in patients with primary Sjogren's syndrome. *Rheumatology* (Oxford) 2011; 50: 1453-7.
94. NISHIMORI I, BRATANOVA T, TOSHKOV I *et al*.: Induction of experimental autoimmune sialoadenitis by immunization of PL/J mice with carbonic anhydrase II. *J Immunol* 1995; 154: 4865-73.
95. TAKEMOTO F, KATORI H, SAWA N *et al*.: Induction of anti-carbonic-anhydrase-II antibody causes renal tubular acidosis in a mouse model of Sjögren's syndrome. *Nephron Physiol* 2007; 106: 63-8.
96. IGOE A, SCOFIELD RH: Autoimmunity and infection in Sjögren's syndrome. *Curr Opin Rheumatol* 2013; 25: 480-7.
97. FLECK M, KERN ER, ZHOU T, LANG B, MOUNTZ JD: Murine cytomegalovirus induces a Sjögren's syndrome-like disease in C57Bl/6-lpr/lpr mice. *Arthritis Rheum* 1998; 41: 2175-84.
98. OHYAMA Y, CARROLL VA, DESHMUKH U, GASKIN F, BROWN MG, FU SM: Severe focal sialadenitis and dacryoadenitis in NZM2328 mice induced by MCMV: a novel model for human Sjögren's syndrome. *J Immunol* 2006; 177: 7391-7.
99. BOMBARDIERI M, BARONE F, LUCCHESI D *et al*.: Inducible tertiary lymphoid structures, autoimmunity, and exocrine dysfunction in a novel model of salivary gland inflammation in C57BL/6 mice. *J Immunol* 2012; 189: 3767-76.
100. VERSTAPPEN GM, CORNETH OBJ, BOOTSMA H, KROESE FGM: Th17 cells in primary Sjögren's syndrome: pathogenicity and plasticity. *J Autoimmun* 2018; 87: 16-25.
101. MIELIAUSKAITE D, DUMALAKIENE I, RUGIENE R, MACKIEWICZ Z: Expression of IL-17, IL-23 and their receptors in minor salivary glands of patients with primary Sjögren's syndrome. *Clin Dev Immunol* 2012; 2012: 187258.
102. SAKAI A, SUGAWARA Y, KUROISHI T, SASANO T, SUGAWARA S: Identification of IL-18 and Th17 cells in salivary glands of patients with Sjögren's syndrome, and amplification of IL-17-mediated secretion of inflammatory cytokines from salivary gland cells by IL-18. *J Immunol* 2008; 181: 2898-906.
103. NGUYEN CQ, YIN H, LEE BH, CARCAMO WC, CHIORINI JA, PECK AB: Pathogenic effect of interleukin-17A in induction of Sjögren's syndrome-like disease using adenovirus-mediated gene transfer. *Arthritis Res Ther* 2010; 12: R220.
104. NGUYEN CQ, YIN H, LEE BH, CHIORINI JA, PECK AB: IL17: potential therapeutic target in Sjögren's syndrome using adenovirus-mediated gene transfer. *Lab Invest* 2011; 91: 54-62.
105. WU C, WANG Z, ZOURELIAS L, THAKKER H, PASSINEAU MJ: IL-17 sequestration via salivary gland gene therapy in a mouse model of Sjogren's syndrome suppresses disease-associated expression of the putative autoantigen Klk1b22. *Arthritis Res Ther* 2015; 17: 198-207.
106 YOUNG NA, WU L-C, BRUSS M *et al*.: A chimeric human-mouse model of Sjögren's syndrome. *Clin Immunol* 2015; 156: 1-8.